UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

June 22, 2005

EPA-SAB-CASAC-05-010

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

Subject: Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel's Peer Review of the Agency's *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)

Dear Administrator Johnson:

EPA's Clean Air Scientific Advisory Committee (CASAC), supplemented by subject-matter-expert Panelists — collectively referred to as the CASAC Ozone Review Panel ("Panel") — met in a public meeting held in Research Triangle Park (RTP), NC, on May 4-5, 2005, to conduct its initial peer review of the Agency's revised *Air Quality Criteria for Ozone and Related Photochemical Oxidants (First External Review Draft)*, *Volumes I, II, and III*, (January 2005), also known simply as the first draft Ozone Air Quality Criteria Document (AQCD). The current Panel roster is found in Appendix A of this report. The charge questions provided to the Panel by EPA are found in Appendix B to this report. The individual review comments of Panel members are provided in Appendix C of this report.

The members of the CASAC Ozone Review Panel were generally pleased with the high quality of this first draft Ozone AQCD and compliment the Agency staff on their efforts. The Panel was appreciative of the new format, in which the information in the previous Ozone Air Quality Criteria Document was briefly summarized at the beginning of the chapters while the remainder of each chapter was devoted to new information that had been acquired since the last criteria document. This approach constitutes a significant improvement over prior ozone criteria documents and should allow the main part of the chapters to focus on integrating study results around major issues related to ozone effects on public health and the environment, with detailed supporting information described in the annexes. The Panel encourages EPA to extend this new format, which was restricted to the first eight chapters, to the chapters on welfare effects (*i.e.*, Chapters 9-11). The Panel also identified a number of critical areas that need to be addressed, and provided general and specific suggestions for strengthening the draft Ozone AQCD.

1. Background

The CASAC, comprised of 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 comprises 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. Section 109(d)(1) of the Clean Air Act (CAA) requires that EPA carry out a periodic review and revision, as appropriate, of the air quality criteria and the NAAQS for the "criteria" air pollutants, currently six in number, one of which is 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). 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.

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

The peer review of the EPA's first external review draft air quality criteria document for ozone and related photochemical oxidants took place in a public meeting held in RTP, NC, on May 4-5, 2005. The members of the CASAC Ozone Review Panel (the current roster for which is found in Appendix A of this report) were generally pleased with the high quality of this first draft Ozone AQCD and compliment the Agency staff on their efforts.

The Panel was appreciative of the new format, in which the information in the previous Ozone Air Quality Criteria Document was briefly summarized at the beginning of the chapters while the remainder of each chapter was devoted to new information that had been acquired since the last criteria document. This approach constitutes a significant improvement over prior criteria documents and should allow the main part of the chapters to focus on integrating study results around major issues related to ozone effects on public health and the environment, with detailed supporting information described in the annexes. The Panel encourages EPA to extend this new format, which was restricted to the first eight chapters, to the chapters on welfare effects (*i.e.*, Chapters 9-11). Despite the fine overall quality of the draft document, the Panel also identified a number of critical areas that need to be addressed and/or improved, and provided general and specific suggestions for strengthening the draft Ozone AQCD. For example, an

important limitation identified by the Panel was that the "related photochemical oxidants" topic was not well-covered. Ozone was chosen as the indicator for the NAAQS because of its ease of measurement and its independent effects, but it was also thought to serve as a surrogate for the suite of airborne oxidants, gaseous and particulate, that may produce adverse health and welfare effects. However, the additional evaluation of the validity of ozone as a surrogate should be a key aspect of the continuing review of science to support the NAAQS for ozone and other photochemical oxidants.

Many constructive recommendations were made for each chapter of the draft document. The following paragraphs contain a brief summaries of comments on each chapter that represent the Panel's advice and recommendations in response to the charge questions provided by the Agency (and presented in Appendix B to this report). More detailed responses to these charge questions are provided in the Panel members' individual review comments that are included in Appendix C to this report.

Atmospheric Chemistry Physics and Air Quality (Chapters 2 and 3): These chapters were considered well-written, with some Panel members commenting on the extraordinary job the Agency did in synthesizing the large body of new literature on ozone chemistry. Currently, ozone serves as a surrogate for all photochemical oxidants that could generate health and welfare effects. However, there were insufficient details on the pathways leading to formation of other photochemical oxidants. A summary of what is known about the quantitative relationships between ozone and the other oxidizing species in both the gas and particle phases is needed. CASAC Ozone Review Panel members made suggestions to include more extensive discussion of ozone-related photochemical oxidants and the problems associated both with monitoring such compounds and determining their separate and combined potential health effects.

Human Health Effects: (Chapters 4-8): Chapter 4 was considered to be well-written in its summary of the new information on the respiratory tract dosimetry of inhaled ozone published since the 1996 Ozone Air Quality Criteria Document. The Panel noted that non-human primate data on lung structure, enzymes and repair mechanisms are now available and that these should be included in order to strengthen the species comparison discussion.

Chapter 5 discussed animal and *in vitro* toxicity studies. Panelists noted that the chapter was not consistent in its presentation of exposure information, which should always include the exposure concentration, the exposure duration, and the species of animal exposed. In addition, several Panel members noted that this chapter did not take advantage of the new format to discuss major studies and issues in the chapter while delegating detailed descriptions of all studies to the annex. There was a great deal of overlap between the narrative in the chapter and the annex; therefore, the chapter should be revised to discuss overarching issues rather than to describe details on specific studies already detailed in the annex. Studies using exposure concentrations above 1 ppm ozone should be deleted from the text of the chapter. There needs to be a clear discussion of the relevance of the studies that examine only the exposure of animals to ozone in the absence of other oxidants that could be present in the atmosphere in conjunction with discussion of studies of the health effects of other oxidants, such as hydrogen peroxide. The focus has shifted from the multiple oxidizing species that are present in both the gas and particle

phases to only ozone and that may potentially underestimate the health effects of atmospheric mixture of oxidants.

Chapter 6 was well-written; the chapter captures current scientific knowledge regarding acute ozone health effects based on controlled human exposure studies. As in Chapter 5, the reviewers felt that the chapter should be revised to address major issues rather than duplicate the detailed descriptions of studies as presented in the annex. The section on genetics was weak and needs revision. The same problem exists here in using only ozone to reflect the complex mixture of oxidants that is present in the atmosphere and could contribute to health effects observed in the epidemiological studies.

Chapter 7 describes epidemiological studies on the health effects of ozone. The chapter was considered to be a good first draft with a fair presentation of findings. However, members of the Panel judged that the chapter was uneven in quality. There was also a lack of consistency in the presentation of effect estimates. Besides the point estimate, the standard error or 95% confidence interval should be given whenever possible. Enhancements of details in the appendix tables will further promote interpretation and synthesis of research results. Some reviewers also felt the chapter was too long and repetitive of information that is already well-known (for example, the description of Hill's postulates). Again it needs to be noted that ozone is the measured quantity, but the underlying causal agents may include a wider variety of oxidants in both the gaseous and particulate phases.

Chapter 8 provides an integrative synthesis of the human health effects chapters. The conclusion of this chapter is that, while there has been a downward trend in ambient air ozone concentrations in the United States, the available health risk data coming from a wide variety of study designs continue to indicate adverse health effects in human subjects, particularly sensitive populations, at exposure levels that are below the current air quality standards for ozone. This important conclusion needs to be accompanied by a more comprehensive synthesis of the experimental and observational findings on which this conclusion is based. Certain topics, such as ozone-allergen interactions, cardiovascular mortality and chronic effects of ozone, need expanded discussions.

Environmental or Welfare Effects (Chapters 9-11): Chapter 9 is a comprehensive summary of the effects of ozone on vegetation and ecosystems. The text was considered to be a good start but needed extensive editorial revision not only to remove repetitive sections but to ensure that the information/conclusions presented in the text are consistent as well as balanced from beginning to end. The review of the various potential measures that have been used to evaluate the ecosystem and crop damage effects of ozone, for example, must be more carefully written. The numerous references to potential secondary standards are inappropriate for the Ozone AQCD and should be removed from the text. The Panel felt that Chapters 9-11 would greatly benefit by the use of the new format which has been used for Chapters 2-8. Additional, consensus comments by four members of the Panel who reviewed Chapters 9 and 10 are provided in Appendix D of this report.

Chapter 10 provides a succinct and instructive summary of the influence of tropospheric ozone on the penetration of UV-B flux to the earth's surface, as well as the contribution of

anthropogenic ozone as a greenhouse gas to climate change. The chapter then becomes vague in its conclusions, and would benefit from a clear summarization, indicating, if warranted, that there is not currently a strong basis to make quantitative estimates of the relatively minor effects that changes in U.S. tropospheric ozone might have on these global radiation and climate issues. The Agency was also encouraged to work toward future evaluations of the effects that changing global climate or UV radiation might have on, as well as from, tropospheric ozone. Chapter 11 on the effects of ozone on man-made materials is brief but effectively presents the limited data available in the peer-reviewed literature.

In conclusion, the CASAC Ozone Review Panel was pleased to review this first draft of the air quality criteria document for ozone and related photochemical oxidants. NCEA-RTP has stated that it intends to issue a revision to this draft Ozone AQCD. The Panel looks forward to reviewing this updated draft document and wishes the EPA staff well in this important endeavor.

Sincerely,

/signed/

Dr. Rogene Henderson, Chair
Clean Air Scientific Advisory Committee

Appendix A – Roster of the CASAC Ozone Review Panel

Appendix B – Charge to the CASAC Ozone Review Panel

Appendix C – Review Comments from Individual CASAC Ozone Review Panelists

Appendix D – Additional, Consensus Review Comments from Selected CASAC Ozone Review Panelists on Chapters 9-11

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

**Immediate past CASAC Chair

Appendix B – Charge to the CASAC Ozone Review Panel

A. Format and Structure of the Draft O_3 AQCD

In developing the January 2005 First Draft O_3 AQCD, NCEA followed past advice from the CASAC to streamline the format of the document to facilitate timely CASAC and public review by focusing more clearly on those issues most relevant to the policy assessment to be provided in the Staff Paper. As described in Chapter 1 of the draft Ozone AQCD, emphasis is placed on interpretative evaluation and integration of evidence in the main body of the document, with more detailed descriptions of individual studies being presented in a series of accompanying annexes. Key information from historical ozone-related literature is only succinctly summarized (usually without citation) in the opening paragraphs of each section or subsection, to provide a very brief overview of previous work. For more detailed discussion of pre-1996 work, readers are referred to EPA's 1996 O_3 AQCD. This revised format is intended to make each chapter a more manageable length, to focus on interpretation and synthesis of relevant new research, and to avoid redundancy with the previous O_3 AQCD. Because this revised format only started to be put into place in later phases of preparation of the First Draft O_3 AQCD, the current draft does not fully embody the revised format, especially in those chapters dealing with welfare effects. EPA intends, following the CASAC review in May 2005, to use the revised format throughout a subsequent draft.

As for overall structure and content, after an introductory chapter (Chapter 1), the First Draft O_3 AQCD presents chapters addressing three main topic areas:

- Characterization of ambient O_3, including the physics and chemistry of O_3 in the atmosphere (Chapter 2) and environmental concentrations, patterns, and exposure estimates of O_3 (Chapter 3);
- O_3-related health effects, including dosimetry and extrapolation (Chapter 4), toxicological effects in animals and in vitro test systems (Chapter 5), controlled human exposure studies (Chapter 6), epidemiology studies (Chapter 7), and an integrative synthesis of O_3 health effects (Chapter 8); and
- O_3-related welfare effects, including environmental effects on vegetation and ecosystems (Chapter 9), tropospheric O_3 effects on UV-B flux and climate change processes (Chapter 10), and effects of O_3 on man-made materials (Chapter 11).

Charge Question A1. To what extent is the document format restructuring *(i.e.*, main chapters of the draft Ozone AQCD focused on evaluative/interpretive aspects, with descriptive materials presented in annexes) useful and desirable? Can the restructuring be further improved? If so, how?

B. Characterization of Ozone-Related Atmospheric Processes, Measurement Methods, Air Quality Patterns and Exposure

1. Policy Relevant Background (PRB) Ozone. PRB ozone concentrations will ultimately be taken into account by OAQPS in analyses to be included in the Ozone Staff Paper that attempt to

estimate risks to human health and environmental effects associated with exposures to ozone concentrations attributable to anthropogenic sources of precursors emitted in the United States, Canada and Mexico (*i.e.*, to ozone levels above PRB concentrations). The estimation of PRB ozone concentrations precludes the use of observational data alone because of substantial production and transport from anthropogenic sources in the United States and bordering countries . Contributions to PRB ozone arise from intrusions of stratospheric ozone, biogenic and other natural sources of ozone precursors, and anthropogenic sources outside of the U.S., Canada and Mexico. The modeling approach that has been adopted for estimation of PRB concentrations is based on peer reviewed journal articles describing the GEOS-CHEM model, its evaluation and application to the calculation of PRB ozone values.

> **Charge Question B1.** Does Chapter 3 appropriately and sufficiently characterize the science supporting the basis for estimates of policy relevant background? In particular, is the approach for determining PRB ozone concentrations outlined in Section 3.7 and in AX3.9 based on the best available methodology?

2. Ozone Spatial and Temporal Variability. The characterization of spatial variability in Chapter 3 follows essentially the same methodology as was used in the latest PM AQCD, which provides information about: (a) the representativeness of community monitors or spatial averaging of monitoring results; and (b) the potential for exposure misclassification in urban areas. The characterization of temporal variability of ozone allows for judgments to be made regarding the timing of potential human exposures. Both spatial and temporal variability aspects are of considerable importance in understanding and interpreting epidemiologic (observational) studies and relating their results to those of human and/or laboratory animal controlled exposure studies.

> **Charge Question B2.** Does the discussion of ground-level O_3 concentrations adequately describe the variability attributed to diurnal patterns, seasonal patterns, and spatial differences in both urban and non-urban locations? Also, to what extent do the characterizations of temporal and spatial variability of O_3 in urban areas provide support for better understanding and interpreting epidemiologic studies discussed later? How might these characterizations be modified to help enhance such understanding and/or would other characterizations (as time permits) be useful in relation to later evaluation of various welfare effects? Is the summary of the effect of elevation on ozone concentrations sufficient to inform later evaluation of the representativeness of elevated ozone monitors (*e.g.*, rooftop) in relation to ozone levels in the breathing zones in children?

3. Ozone Exposures in Various Microenvironments. An extremely important element of analysis to be included in the OAQPS Ozone Staff Paper is the characterization of factors affecting human exposures to ambient ozone. Such analyses will include: (a) estimation of typical ranges of ambient ozone encountered in different important microenvironments (*e.g.*, outdoors, indoors while in motor vehicles, or indoors while at work or in home residence); (b) delineation of time/activity patterns that assist in estimating patterns of movements between the different classes of microenvironments by various population groups; and, hence, (c) estimation of likely periods of exposure of various potentially susceptible groups (*e.g.*, highly-active healthy children, asthmatic children) to different ambient ozone levels typically encountered in the selected microenvironments.

Charge Question B3. Does Chapter 3 provide a sufficiently discussion of concepts and issues related to human exposures, applicable microenvironments, and modeling of O_3 exposure to serve as a foundation for quantitative exposure analyses to be done in conjunction with the Ozone Staff Paper. How might these discussions be improved?

4. Measurement Methods and Potential Ozone Measurement Bias. Chapter 2 describes measurement methods for ozone and other important oxidant precursor or atmospheric reaction products. Ozone is measured routinely by the UV photometry and chemiluminescence techniques in monitoring networks operated by the EPA, and State and Tribal agencies. Available evidence suggests that there may be small positive interferences in O_3 measurement by the UV photometric technique in some very limited areas, *i.e.*, in areas having high concentrations of products of the oxidation of aromatic hydrocarbons and in situations where there are very high PM concentrations (as in traffic with high PM emitters).

Charge Question B4. Have the techniques for measuring O_3 and its precursor molecules been adequately described? To what extent do monitoring-related uncertainties raise issues with regard to utilization of the ozone monitoring data, *e.g.*, in estimating potential health risks in epidemiologic analyses?

5. Relationships of Ozone to Other Atmospheric Species. Data for other oxidants such as hydrogen peroxide are sparse and have been obtained only as part of specialized field investigations designed to study atmospheric chemistry. Co-occurrence data is more widely available for the other criteria pollutants.

Charge Question B5. Do the discussions in Section 2.2 discussions on ozone photochemistry and Sections 3.6 and AX3.7 on relationships between ozone and other species reflect well the current state of the science? Do they provide useful background information on "related" oxidants that may be toxic? Does the information given in Sections 3.6 and in AX3.8 on the co-occurrence of ozone with other criteria pollutants usefully inform judgments related to later discussions of epidemiologic analyses? Is the use of threshold values for calculating co-occurrences appropriate?

C. Characterization of Ozone-Related Dosimetry and Health Effects

1. Theoretical Ozone Dosimetry Models. Chapter 4 states that the high degree of consistency in O_3 uptake studies provides increased confidence in the use of theoretical dosimetry models. The chapter further discusses refinements in modeling utilizing advancements in physiological, anatomical, and biochemical data inputs.

Charge Question C1. Does the Panel agree that the newer O_3 dosimetry models better predict respiratory tract distribution and uptake of O_3 and foci of injury from O_3? Are the strengths and weaknesses of the models appropriately characterized? Have any new models been missed that should be included in the discussion?

2. Interspecies Extrapolations. Chapter 4 discusses comparisons between O_3 respiratory tract distribution and uptake in humans with varying demographic characteristics (*e.g.*, age, sex) and

health status (*e.g.*, healthy, compromised respiratory health, etc.) and various laboratory animal test species, as well as interspecies similarities and differences in pathophysiological responses to O_3.

Charge Question C2. Is the information in Chapter 4 sufficiently complete in terms of discussion of both qualitative and quantitative extrapolation and of interspecies similarities and differences in O_3 dosimetry and in responses to O_3? Do the relatively high O_3 exposure concentrations/doses used in animals studies and in vitro studies allow valid comparisons to human "real-world" exposure scenarios? New animal uptake studies have not been performed. Thus, the Ozone AQCD is relying on the information presented in the 1996 AQCD which estimated that exercising humans received a 4- to 5-fold higher dose of 0.4 ppm O_3 than resting rats. Does the Panel still consider this a valid comparison? Also, to what extent does the Panel consider evaluations of rodent responses to O_3 as being a valuable tool for predicting human responses to O_3? What about other species (*e.g.*, monkeys) used in laboratory animal studies and the use of resting animals versus exercising humans?

3. Characterization of Short-Term Exposure Effects in Experimental Studies. Chapters 5 and 6 discuss the health effects of short-term O_3 exposures, as delineated by controlled laboratory exposures of human subjects or various laboratory animal species (rodents and primate strains with varying susceptibility to O_3) and *in vitro* systems. For present purposes, it is useful to highlight certain key aspects and to pose charge questions in relation to several main subcategories of types of *in vivo* effects evaluated in those chapters: (a) pulmonary mechanical function effects (indexed by spirometrically-determined lung function measures, *e.g.*, FEV_1, Sh_{aw}, etc.), respiratory symptoms (indexed by self-reported cough, wheezing, substernal pain, etc.), airway hyperreactivity, or AHR (indexed by pulmonary function response to metacholine or other challenge); (b) inflammation, effects on lung defense mechanisms (*e.g.*, alterations of respiratory tract clearance or immune system components or function) or other injury to lung tissue; (c) cardiovascular effects (indexed by alterations in electrocardiogram readings, thermoregulatory control, etc.); and/or (d) other types of systemic effects (*e.g.*, neurobehavioral).

(a) Acute Pulmonary Function/Respiratory Symptom Effects. Overall, as assessed in Chapter 6, the findings of the relatively few newly available controlled human exposure studies of effects of single or repeated acute exposures (of 1 h or 6-8 h duration) do not appear to provide any basis for altering previous conclusions stated in the 1996 O_3 AQCD with regard to dose-response relationships for short-term O_3 exposure induction of pulmonary function changes (*e.g.*, decreased FEV_1) indicative of acute brochoconstriction in healthy or asthmatic children or adults under light to moderate exercise conditions. The new human exposure studies also verify and extend findings related to attenuation of the acute respiratory function effects after several days of repeated daily O_3 exposures, but tend to indicate less notable increases in respiratory symptoms at lowest acute exposure/exercise levels producing significant pulmonary function decrements. Of much importance are new findings expanding our knowledge of O_3 effects on airway responsiveness in healthy and asthmatic adults and in asthmatic animal models.

Charge Question C3a(i). Have any important new human or laboratory animal controlled exposure studies been missed in Chapter 5 or 6 discussions of short-term O_3 exposure effects on pulmonary function and/or respiratory symptoms? Are the discussions on mouse strains

with genetically determined differential susceptibility to O_3 sufficiently clear and useful? Do the chapters adequately discuss newly available controlled exposure studies of airway responsiveness in humans and/or laboratory animal models, and what are CASAC Panel member views on the discussion of new insights into the mechanisms related to airway hyperreactivity? Are the discussions in both Chapters 5 and 6 (as well as in Chapter 8, Integrative Synthesis) adequate to help 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 or respiratory disease status)?

Charge Question C3a(ii). Controlled human and animal exposure studies show that O_3-induced deficits in pulmonary function typically resolve quickly (within a few hours) to baseline when exposure ceases in normal individuals. However, asthmatics can have an extended period (up to 24h) of recovery from lung function decline and airway hyperresponsiveness. To what extent do such findings help to explain the increase in emergency room visits, hospital admissions, and use of asthma medication in asthmatics observed in new epidemiology studies?

(b) Acute Lung Defense/Other Lung Injury Effects. The discussions in Chapters 5 and 6 of the few new studies of short-term O_3 exposure effects on lung clearance and immune system components do not appear to substantially alter key findings and conclusions stated in the 1996 Ozone AQCD concerning such endpoints. However, the newly-available research does notably expand our knowledge about mechanisms underlying O_3-induced lung injury. That is, deleterious health effects of O_3 appear to begin with injury to lung tissue, followed by a cascade of events including inflammation, altered permeability of the epithelial barrier, altered clearance, and (over time) chronic alterations of pulmonary structure. Preexisting respiratory disease may exacerbate of some of these events. New information on the roles of monooxygenases, antioxidants, and alveolar macrophages is discussed in Chapters 5 and 6.

Charge Question C3b(i). Do these discussions, including possible exacerbation of listed effects by preexisting respiratory disease, adequately cover new research in this area?

Charge Question C3b(ii). A large component of Chapter 5 is presentation of data from studies of mice strains with differing genetically-determined sensitivities to O_3. These mouse strains differ in O_3-induced inflammatory responses, lung permeability, and pulmonary responses. NCEA staff consider these studies important as a possible explanation for differing human sensitivities to O_3, though the links between the mouse and human have not yet been established. Does the Panel agree with the inclusion and emphasis placed on this area of research? Do these discussions adequately cover the important new research in this area or were any important studies missed? How might the discussion be improved?

Charge Question C3b(iii). Some preliminary data from acute O_3 exposure animal toxicology and some controlled human exposure studies support epidemiological studies suggesting that asthmatics are a potentially sensitive sub-population. To what extent are the animals models of asthma using rodents sensitized to ovalbumin useful in modeling human asthma? Do these animal models provide useful information in modeling human asthma?

To what extent do they provide credible support for the plausibility of the epidemiologic findings?

(c) Cardiovascular Effects. As noted later, there is some lack of consistency among findings from epidemiologic, human exposure and animal controlled studies evaluating possible associations between ambient O_3 exposures and cardiovascular effects in human populations. Also, available controlled human exposure studies have not found any compelling evidence linking O_3 exposure to indicators of altered cardiovascular function. However, some new controlled exposure animal studies have found that short-term exposures to near-ambient O_3 levels can cause certain cardiovascular-related effects (*e.g.* the hypothermic response consisting of decreased core temperature, heart rate, and blood pressure).

Charge Question C3c. Can the Panel suggest further inputs that may allow a more complete evaluation of potential cardiovascular effects of O_3?

(d) Other Types of Systemic Effects. There is limited information available from controlled exposure studies on systemic effects in humans or laboratory animals. Most of these short-term exposures used much higher than ambient O_3 concentrations.

Charge Question C3d. Is the existing discussion of such systemic effects adequate? Should it be expanded to take into account any pertinent studies that may have been missed that show such effects at more relevant O_3 exposure levels? Or, alternatively, should this section be dropped entirely as irrelevant for current purposes?

4. Characterization of Long-term Exposure Effects in Controlled Exposure Studies. Chapter 5 also discusses results of controlled human and animal exposure studies that help to elucidate the effects of long-term O_3 exposures, including extended periods of months or years of regularly repeated 1, 4, or 6-8 h per day exposures, continuous low level, or other long-term exposure patterns. The effects of such exposures have been evaluated in animals using various endpoints, *e.g.*, chronic alterations to lung structure or function. No comparable data are available from controlled human exposures.

Charge Question C4a. The issue of differing health risks of continuous versus intermittent daily exposure is discussed in the Ozone AQCD. A series of studies evaluating the long-term morphological effects of simulated, seasonal O_3 in rhesus monkeys is given considerable emphasis. Does the Panel consider these studies to be important in lending biologic plausibility to the causal relationship observed in epidemiology studies between seasonal O_3 exposure and adverse health effects such as lung function decline? Is the discussion of season-specific O_3 health effect estimates adequate?

Charge Question C4b. The weight of evidence from toxicology studies does not support ambient O_3 as a carcinogen in animal models, but a few epidemiologic studies from Mexico City suggest a link between ambient O_3 exposure and genotoxic effects. The Ozone AQCD attributes this inconsistency to possible interspecies differences in this health point and inadequate exposure characterization. Do the present O_3 AQCD discussions adequately cover the state of knowledge regarding the possible genotoxicity/carcinogenicity of O_3?

5. Observational Studies of Short and Long-Term O_3 Exposure Effects. Chapter 7 discusses methodological issues attendant to the use of epidemiologic approaches to study air pollution effects and assesses evidence derived from observational of associations between both short-term (< 24 h average) and long-term (typically annual average) ambient O_3 exposures and various health endpoints. Such endpoints include mortality and morbidity indicators, *e.g.*, hospital admissions, respiratory-related emergency department (ERD) visits, school absences, respiratory symptoms, pulmonary function decrements, etc.? Important new findings from numerous studies published since the 1996 O_3 AQCD — including, perhaps most notably, new evidence for associations between exposures to ambient O_3 and increased risk not only of asthma-related symptoms and ERD visits but also of premature mortality. Numerous issues are discussed in Chapter 7 with regard to assessing the credibility of newly reported findings being attributable to O_3 acting alone or in combination with other ambient co-pollutants and with regard to the extent that experimental (controlled exposure) study findings lend support to the plausibility of reported epidemiologic associations being causal.

Charge Question C5a. The Ozone AQCD discussions of observational and field studies mainly focus on studies of potential O_3 effects among the general population, school-aged children, the elderly, asthmatics, and outdoor workers. Do the studies and the document discussions adequately cover the key populations that should be considered? Are discussions of differences in individual vulnerability and susceptibility adequate?

Charge Question C5b. Chapter 7 highlights the evaluation of two large multi-city studies that examined ambient O_3 effects on mortality, *i.e.*, the study of 95 U.S. communities and the study of 23 European cities. These studies show positive and significant O_3 effect estimates for all cause (non-accidental) mortality. Does the discussion of those studies adequately address questions regarding possible confounding by co-occurring PM, *i.e.*, indicating that the O_3 effect on mortality is independent of PM? Also, is the issue of the seasonality of O_3-mortality effects adequately addressed?

Charge Question C5c. The temporal relationship between O_3 exposure and the occurrence of health effects is important in animal toxicology studies, controlled human studies, and epidemiology studies. Most epidemiology studies find an immediate O_3 effect, with health effects having the strongest associations with acute exposure on the same day and/or previous day. What are the views of the Panel on the adequacy of the discussion on choice of lag period between ozone exposure and the observed health effect? Are sensitivity analyses appropriately considered to address model specification for adjustment of potential confounding by temporal trends in epidemiologic studies?

Charge Question C5d. Given our experience during the past several years in dealing with GAM-related statistical issues in the recently issued PM AQCD (October 2004), NCEA staff has generally excluded epidemiology studies using GAM with default convergence criteria from consideration in the current draft O_3 AQCD. Is the CASAC Panel in agreement with this choice?

Charge Question C5e. The O_3 AQCD evaluates the appropriateness of O_3 exposure assessments used in the epidemiological studies. Does the Panel consider the discussion of ambient versus personal monitoring and choice of exposure indices to be adequate? How might it be further strengthened?

6. Integrative Synthesis of Exposure, Dosimetry, and Health Effects Information. Chapter 8 of the O_3 AQCD aims to provide an overall interpretive synthesis of the most important and pertinent findings and conclusions derived from the evaluations contained in the earlier chapters, especially with regard to typical levels and patterns of human exposure to ambient O_3 in the United States, dosimetric considerations, and health effects information derived from both human observational and controlled human and laboratory animal studies.

Charge Question C6a. Are the topics chosen for discussion in Chapter 8 appropriate ones and are they sufficiently clearly addressed? Are there any other important topics or issues that need to be added in the Chapter 8 Integrative Synthesis? In particular, NCEA staff consider the following health endpoints associated with short-term exposure to be important in evaluating adverse health outcomes from O_3 exposure: premature mortality, hospital admissions for respiratory illness, emergency department visits for respiratory illness, lung function decrements, and respiratory symptoms. Is this list sufficiently comprehensive or should other health endpoints be considered?

Charge Question C6b. Myriad health effects described in both epidemiology and controlled exposure human and animal studies (including decreased pulmonary function and various respiratory symptoms) are highlighted as being of possible health significance in Chapter 8 and elsewhere. Are the earlier discussions in Chapters 5 and 6 adequate to help 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)? How much short-term or reversible impairment is necessary to be considered a "biologically significant adverse effect?" for adults, children or adults with varying severity of asthma, etc.)? Does Table 8-2, brought forward largely intact from the 1996 O_3 AQCD, still accurately characterize mild through severe functional and symptomatic responses? Also, is Table 8-3 still relevant for characterizing gradations of individual responses to short-term O_3 exposure in individuals with impaired respiratory systems?

D. Characterization of Ozone-Related Welfare Effects

1. Methodologies Used in Vegetation Research. Section 9.2 notes that, to date, most data on exposure-response relationships for crop yield and tree growth have been derived from open-top chamber (OTC) studies. However, numerous chamber effects have been documented and the limited ability to extrapolate chamber data to the field has been recognized. Some recent studies, however, have employed an alternative methodology, the Free Air Control Exposure systems (FACE)[1]. Another method for characterizing exposures in the field is the use of passive

[1]Recent studies on the effects of ozone on soybean using the FACE methodology will be included in the next draft of the AQCD.

monitoring. Additionally, there has been an increasing reliance on air quality models to fill in the gaps in rural and remote U.S. regions where there is inadequate monitoring.

> **Charge Question D1.** Is the discussion of methodologies used in vegetation research sufficiently clear and adequate to allow comparisons between methodologies and to allow characterization of the uncertainties associated with estimating exposures to vegetation with each system? In particular, is the new FACE technology adequately characterized, and to what extent has it overcome the limitations of the OTC method? What are the uncertainties associated with the FACE data that would apply if trying to extrapolate to other regions of the country with different ozone exposure regimes and vegetation growing conditions? Given that the results from FACE studies are similar to findings from earlier OTC studies, does this increase our confidence in the results from studies using the OTC methodology? Lastly, would it be useful to move Section 9.2 to an Annex?

2. Mode of Action Underlying O_3 Vegetation Effects. Processes involved in ozone uptake and toxicity are better understood today than in 1996, based largely on advances gained through use of molecular techniques in following rapid O_3-induced changes within the leaf, as discussed in Chapter 9, Section 9.3. O_3 entrance into the leaf via stomata is a critical step in sensitivity. Initial O_3 reactions within the leaf remain unclear except for involvement of hydrogen peroxide. Also, reactions of ozone or its products with ascorbate and other antioxidants in the apoplastic space of mesophyll cells serve to lower the amount of O_3 or products available to alter plasma membranes of the cell. A primary trigger of O_3-induced cell responses appears to be changes in internal Ca levels; and the primary set of metabolic reactions triggered by O_3 comprise "wounding" responses like those generated by cutting the leaf or insect attack. Longer-term responses under low concentrations over long time periods, are linked to senescence or some physiological response very closely linked to senescence (*i.e.*, translocation, reallocation, reabsorption of nutrients and carbon).

> **Charge Question D2.** Has any important new information been missed on mode-of-action for O_3-induced vegetation effects? Also, to what extent does the new information on the mode of action of ozone at the cellular, molecular or biochemical level significantly alter our understanding of plant effects?

3. Modification of Growth Response. Chapter 9 notes that none of the few new studies since the 1996 review significantly alter our understanding of how other biotic and abiotic factors modify plant response to O_3. As for biotic interactions, new evidence on insect pests and diseases has not reduced uncertainties noted in the 1996 O_3 AQCD; we still cannot predict the nature of any particular O_3-plant-insect interaction, its likelihood or its severity or of O_3-disease interactions. Nor does new evidence improve our understanding of interactions between O_3 and root symbionts. The few new studies of O_3 effects of plant competition suggest that grasses frequently show greater resilience than other types of plants; but there are insufficient bases to predict specific plant competition situations, *e.g.*, successional plant communities or crop-weed interaction. Temperature is an important variable affecting plant response to O_3, but available data quantifying this interaction are limited and often contradictory. Evidence does suggest that O_3 exposure sensitizes plants to low temperatures by reducing important belowground carbohydrate reserves (which impairs grown in the following seasons). Both increased ambient

air relative humidity and/or soil water availability appear to enhance plant sensitivity to O_3. Information on O_3 interactions with specific nutrients is still contradictory; but some experimental data suggests that low fertility increases O_3 sensitivity, while model simulations of tree growth suggest nutrient deficiency and O_3 interact less than additively. There is emerging information regarding potential interactions of O_3 exposure and global change factors, including concurrent elevated CO_2, elevated temperature, altered nutrient and water availability, as well as increased surface UV-B radiation. Studies using elevated O_3 in the presence of high CO_2 without elevated temperature are of limited value for assessing impacts of climate change on response to O_3.

> **Charge Question D3**. Was any important pertinent information missed in the Chapter 9 discussions of factors that modify plant growth response to O_3 exposure? Also, is there sufficient information in the literature and has it been discussed adequately to predict how elevated CO_2, temperature, drought and/or other climate change factors may modify plant response to ozone?

4. Exposure Indices. One of the most important continuing challenges faced in the 1996 O_3 AQCD — and again addressed in Chapter 9 of the current draft Ozone AQCD — is how to incorporate plant biology and interacting physical, site, and meteorological processes into air quality indices reflective of exposure- or dose-response relationships for O_3-induced vegetation effects. The few pertinent new studies since 1996 appear to substantiate earlier conclusions on the role of exposure components (*e.g.*, concentration, duration, and seasonal exposure patterns) in determining effects of O_3 on plant growth responses; and ambient exposure indices (*e.g.*, SUM06) continue to be seen by some as good surrogates for actual O_3 exposures affecting plant target tissues. New studies also demonstrate potential disconnects between peak O_3 events and maximal stomatal conductance periods, either due to site and meteorological factors or day/night differences in conductance. The lack of coincidence in temporal patterns of conductance and peak concentrations introduces uncertainty into regional and national scale assessments because of climate and site factors that modify response to O_3. A large amount of literature regarding a flux-based approach, in contrast to the ambient exposure approach for an index, is bolstered by much progress in developing and testing stomatal models that may be generally applicable across certain vegetation types and landscapes.

> **Charge Question D4.** Are there ways that the Chapter 9 discussion of exposure indices can be improved? For example, are there any published data not appropriately considered in the Chapter 9 discussions? To what extent are the conclusions from this section consistent with our current capabilities to address spatial and temporal factors in exposure and effects on plants? Are there new experimental data that would call into question the conclusions of 1996 that a best available exposure index is one that cumulates hourly concentrations over a three-month period and weights concentration and daylight hours? Are there sufficient data on the relationship between ozone flux and plant response to move away from an ambient exposure-based approach to developing an index at this time? Also, are there adequate experimental exposure-response data for relevant crop species, annual and perennial plants species, and tree species as seedlings to support Chapter 9 conclusions regarding concentration levels of an exposure index that is protective of vegetation?

5. Exposure-Response Relationships for Individual Plant species. Newly available information supports the 1996 O_3 AQCD conclusions that ambient O_3 concentrations are reducing the yield of major crops. New FACE studies support findings from earlier open-top chamber studies of deciduous tree species and crop species. New studies support earlier generalizations: woody plants (*i.e.*, seedling tree species) are less sensitive than are most annual plant species (including agronomic crops), with the exception of a few deciduous tree species. Current ambient O_3 concentrations in the U.S. are sufficient to reduce growth in seedlings of these sensitive species. Coniferous species are generally less sensitive than most deciduous species in the U.S., and slow-growing species are less sensitive than fast-growing ones. Long-lived species present difficult problems in assessing O_3 impacts, because even multiple-year exposures do not expose trees to O_3 for more than a small fraction of their lives and because competition may exacerbate O_3 effects on individuals (thus making it difficult to determine effects on mature trees).

> **Charge Question D5.** Does the discussion in Chapter 9 of exposure-response relationships for O_3 effects on individual types of plants accurately and adequately characterize the most pertinent available information on the subject? Was any important relevant information missed? How might the discussion be improved? Are multiple species mixes and/or multi-year studies adequately covered? Also, are there adequate experimental exposure-response data for relevant crop species, annual and perennial plant species, and tree species as seedlings to support conclusions regarding concentration levels that might be judged to be protective of vegetation?

6. Ecosystem Response. Despite growing recognition of possible O_3 ecosystem effects, the database demonstrating and quantifying the degree to which O_3 is altering natural ecosystems is very limited, as discussed in Chapter 9. Much of the impact is speculative and based on several case studies of forest plot field-based data reporting on a number of different species. Little is known about O_3 effects on water, carbon and nutrient cycling, especially at the stand and community levels; and little is known about O_3 effects on structural or functional components of soil food webs or how these impacts may affect plant species diversity. Also, little is known about feedbacks between O_3 exposures and climate change effects on ecosystem productivity, given the lack of interaction studies with other components of climate change (*e.g.*, warming, water availability, N deposition). Most of the available data is from seedling studies and annual plants, thus limiting use of these data in developing an understanding of O_3 impacts on natural ecosystems and services derived from them. In general, methodologies to determine the important services and benefits derived from natural ecosystems are lacking, making it difficult to identify and quantify factors that could be used in quantitatively assessing O_3 -related ecosystem effects.

> **Charge Question D6.** How can the Chapter 9 assessment of existing literature on ecosystem response to O_3 be improved? Is the information discussed sufficient to evaluate whether current air quality is damaging natural or managed ecosystems? For example, does new information regarding the role of N in the San Bernardino forests alter our previous understanding of how O_3 affects the ponderosa pine ecosystem? Was any new information missed by which to identify other useful endpoints or measures for assessing ecosystem response to O_3? Also, are there appropriate measures of ecosystem services supported by published literature that would provide better linkages to economic or societal valuation of

these services? Is the discussion of ecosystem services adequate for the available information at this time?

7. UV-B Flux and Climate Change. Chapter 10 provides a concise overview of key information regarding tropospheric O_3 effects on UV-B flux at the earth's surface. It also briefly discusses factors governing human exposures to ultraviolet radiation and potential impacts on human health (both deleterious and possibly beneficial effects) that may result from such exposure. In addition, the chapter discusses the role of tropospheric O_3 in climate change processes, including both direct and indirect climate forcing due to O_3. Overall, the chapter concludes that, due to a variety of factors, quantification of tropospheric O_3 effects on surface-level UV-B flux or to climate change processes (as well as consequent contributions to health or welfare effects) would be highly uncertain at this time.

Charge Question D7. What are the views of the Panel on the adequacy and clarity of the presentation of the evidence on the role of tropospheric ozone in ground-level UV-B flux and UV-related health and environmental effects? In general, have the factors governing UV radiation flux at the earth's surface and human exposure to UV radiation been appropriately addressed? In particular, is the discussion of the influence of ozone on ground-level UV radiation flux adequate? Are potential human health impacts due to UV radiation addressed adequately for present purposes? In particular, has the possibility of UV-related deleterious or beneficial health effects from changes in tropospheric ozone levels been suitably discussed? What are the views of the Panel on the scientific soundness and usefulness of the discussion in Chapter 10 of O_3 interactions with global climate change components, *e.g.*, increased atmospheric CO_2, increased mean global temperatures?

Appendix C – Review Comments from Individual CASAC Ozone Review Panelists

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.

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Dr. John Balmes

Individual Review Comments from John R. Balmes, MD, for Chapter 6, "Controlled Human Exposure Studies of Ozone and Related Photochemical Oxidants," U.S. EPA Ozone AQCD (first draft), 4/30/05

GENERAL COMMENTS:

The approach of including both a main chapter and annex is potentially helpful to a reader, but, in my opinion, the current draft has too much overlap of these two components to be really useful. If the point is to provide a focused summary of the most important data in the main chapter and more detailed information in the annex, then the main chapter appears overly long and too duplicative of the annex.

In the hope that a more focused main chapter will be provided in future drafts, I will only provide comments on the main chapter at this time. Overall, it captures the scientific knowledge regarding acute ozone health effects based on controlled human exposure studies in a well-organized and comprehensive way. That said, little judgment was exercised about the relative importance of the information presented for any potential change in the air quality standard (i.e., is the forest lost in the trees). Perhaps less weight could be given to explaining details of ozone-induced lung function responses at concentrations of ozone above the current air quality standard and more weight to the studies showing adverse health effects (both lung function decrements and markers of airway inflammation or injury) after exposures to 0.08 ppm ozone for less than 8 hours.

SPECIFIC COMMENTS

Page 6-2, line 4 Should be "repeatedly" rather than "repeated."

Page 6-2 The first full paragraph describing the limitations of controlled human exposure studies is good.

Page 6-2 The second full paragraph indicates that the focus of the chapter is on new literature since the 1996 AQCD was published. While this is appropriate, it does not diminish the importance of earlier studies that showed adverse health effects (both lung function decrements and markers of airway inflammation or injury) after exposures to 0.08 ppm ozone for less than 8 hours.

Page 6-2, line 26 Should be "filtered."

Page 6-3, line 20 Should be "exposures."

Page 6-5 Section 6.2.3 contains highly relevant information regarding adverse health effects at ozone exposure levels near or below the current air quality standard.

Page 6-8, lines 20-22 The symptoms and lung function changes are accompanied by increased airway responsiveness and airway inflammation in grouped data, but not necessarily at the individual level, as pointed out later in the chapter. This sentence is misleading as currently written and should be changed.

Page 6-9 The last paragraph on airway inflammation is not necessary here and should be deleted.

Page 6-12, line 30 Should be "the C-fiber-associated tachykinin, substance P, in human…"

Page 6-13, line 5 Would delete "generally" and substitute "innate."

Page 6-15, line 21 "QCE" should be explained.

Page 6-20, line 22 Should be "a 20 year old."

Page 6-21, line 24 V_T and f_B should be explained.

Page 6-21, lines 26-27 Should be "seems to have minimal effect. In general, the lung function response…"

Page 6-22, lines 2-3 Cite references at end of sentence.

Page 6-23, line 4 Would substitute "agents" for "admixtures."

Page 6-23, line 27 Should be "still significant ($p<0.05$) at both temperatures."

Page 6-24, line 14 Delete "a" before "release."

Page 6-24 Section 6.5.7 needs to be rewritten. First, since the section starts with a mention of "several studies," more than just the Bergamaschi et al. should be cited. I suggest citing both the Corradi et al and Romieu et al. studies. Second, I would substitute "acute responses" for "pulmonary function and airway inflammatory response." Third, I would spell out NQO1 and GSTM1 here and then on page 6-32 abbreviations can be used instead of the fully spelled out names. Fourth and most importantly, the last sentence of this section substantially undervalues the potential importance of these genetic markers of susceptibility to ozone. GSTM1 null status has also recently been shown to a major risk factor for enhancement of specific responses to nasal allergen challenge in humans with allergic rhinitis after exposure to another oxidant pollutant, diesel exhaust particles. In addition, there is evidence based on inbred mouse model data that polymorphisms of genes involved in innate immune responses (e.g., TNFα and TLR4) may affect susceptibility to acute ozone-induced effects. When this section is rewritten, the last sentence should be deleted.

Page 6-25, line 15 "PDI" should be explained.

Page 6-27, line 13 The second half of this sentence is somewhat illogical and should be deleted. I would revise the sentence as follows: "Although inflammation could play a role in the

increase in airway responsiveness, animal studies in which neutrophils have been depleted have still shown increases in airway responsiveness after ozone exposure."

Page 6-28, lines 7-9 This statement needs references.

Page 6-31, lines 5-6 I disagree with this sentence and think it should be deleted. Differences in experimental protocol are probably not even the main reason for the relative lack of correlation among acute effects of ozone. There is strong evidence from inbred mouse studies that airway inflammatory, lung injury, and epithelial permeability effects are regulated by separate genetic loci on different chromosomes.

Page 6-32, line 28 This sentence should be changed to "one study" because the increased IL-8 in BAL in asthmatic subjects in the Scannell study (of which I am a co-author) was not statistically significant at the $p<0.05$ level.

Page 6-33 The first paragraph on this page needs to be rewritten to reflect the fact that the Bosson et al. paper and the Stenfors et al. paper both used data collected from the same subjects in a single experiment. Even though there was a failure to find differences between the early inflammatory cell responses to ozone between normal, healthy and asthmatic subjects, this team of investigators did in fact find imunohistochemical evidence of increased pro-inflammatory cytokine expression in bronchial biopsies in the asthmatic subjects. In addition the last sentence of this paragraph should be referenced.

Page 6-35, lines 5-8 This sentence should be revised as follows: "The continued presence of markers of cell injury indicates a persistent effect of ozone that is not necessarily clinically recognizable due to attenuation of spirometric and symptom responses."

Page 6-35, line 10 Should be "after 4-consecutive-day exposure" instead of "at day 4" since the BAL was obtained 18h after the day 4 exposure.

Page 6-35, line 11 I would add a sentence here as follows: "The lack of decrease in total protein and LDH concentrations in the BAL fluid after 4-consecutive-day exposure suggests persistence of airway injury.

Page 6-35, line 2 I would revise this sentence as follows: "Following a similar study design and exposure parameters, <u>except for addition of a single-day FA exposure</u>,…"

Page 6-35, line 15 Add "compared to FA" at end of this sentence.

Page 6-36, line 15 Add "but does not inhibit ozone-induced airway responsiveness (Ying et al. 1990)" to end of sentence.

Pages 6-36 to 6-37 The first paragraph of Section 6.9.6 is largely duplicative of other sections of the chapter and should be largely deleted.

Page 6-39, line s 9-11 Should be "controlled human exposure studies of either healthy or more susceptible subjects."

Page 6-39, line 12 Delete "Regarding the latter."

Page 6-41, line 7 Substitute "physiological pulmonary" with "lung function."

Page 6-41, line 19 Substitute "physiological" with "lung function."

Page 6-42, line 4 Should be "…assessed by persistent decrement…"

Page 6-42, line 20 Should be "do" instead of "did."

Dr. Ellis Cowling

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

General Comments on the Need for a (Public Wefare Based) Secondary Standard for Ozone Different in Form from the Primary Standard

Being a student of history, my attention was naturally drawn to the "Summary of Past O_3 NAAQS Reviews" contained in the March 2005 "Plan for Review of the National Ambient Air Quality Standards for Ozone."

In the light of EPA's presently strong emphasis on effects of ozone and related photochemical oxidants on human health, how interesting it is to realize that the injurious effects of ozone and other photochemical oxidants were first discovered on vegetable crops and forest trees and only later were discovered also to be injurious to human health and to be the principal cause of eye irritation in photochemical smog!

Since the time of initial adoption of the "photochemical oxidants" standard in 1971, EPA's principal focus of concern has been on public health. In fact, the Secondary (public welfare-based) National Ambient Air Quality Standard for Ozone and Related Photochemical Oxidants has always been defined and administered in the same way as the Primary (public health based) National Ambient Air Quality Standard for Ozone and Related Photochemical Oxidants.

In this connection, it is also interesting that the European regionally distinct "critical levels" approach to ozone management makes the general assumption that decreases in emissions of ozone precursors aimed at decreasing damage to plants and natural ecosystems in specific localities will provide a good way also to protect the health of people. In the US, by contrast, EPA's National Ambient Air Quality Standards approach to management of ozone and related photochemical oxidants makes the general assumption that decreases in emissions of chemical precursors aimed at achieving a public-health based nationally-uniform ozone air quality standard will provide a good way also to protect the health and productivity of vegetation and natural ecosystems.

Since my special competence is in the sciences of plant physiology and ecology, my attention in this review has focused primarily on the injurious effects of photochemical oxidants (and especially of ozone) on the myriad of plants, animals, insects, and microorganisms that make up the natural and managed ecosystems that provide our food and sustain The Nature in which we live.

Ozone is a general metabolic poison. Ozone and other oxidants enter plants mainly through the stomata of leaves. Here these pollutants interfere with photosynthesis, respiration, and many other growth and developmental processes. Surprisingly, exposure to high concentrations of

ozone frequently leads to decreases in the rate of root development even more than to decreases in the growth of leaves and shoots.

Ozone and other oxidants also cause stress in plants and thus predispose both individual plants and whole ecosystems to attack by natural enemies that include disease- and injury-inducing bacteria, fungi, nematodes, viruses, and insects. In some cases, exposure to high concentrations of ozone also decreases the resistance of plants to injury and damage by abiotic stress factors such as drought and frost.

Different species and varieties of plants vary widely in susceptibility to ozone and other oxidants. Many species of crop plants, forest and shade trees, and some of the multiple-species of plants in natural ecosystems are more sensitive to injury and damage by ozone than most people. That is, many plants show visible symptoms of injury at concentrations of ozone that are considerably lower (40 to 60 ppb of ozone) than the 80 to 120 ppb of ozone that are generally recognized to cause ill-health in people.

The injurious effects of ozone and other oxidants on plants and ecosystems are cumulative in their effects rather than acute in their effects as is often suggested for most health effects of ozone on people. Thus, many plant physiologists and ecologists like me are prone to assert, somewhat factiously, that:

"Plants do not worry about a bad Tuesday, but they do worry about a bad ozone season."

For this reason, plant pathologists, physiologists, and ecologists concerned with the injurious effects of ozone and other photochemical oxidants on plants recommend that the "averaging time" of exposure necessary to avoid or decrease injury to crop plants, trees, and natural ecosystems should extend over the whole growing season rather than just a few hours. Hence the "ozone indices" recommended to avoid or decrease injury to plants have usually been of a cumulative form – such as SUM 06, which is based on the number of hours the ozone concentration is greater than 60 ppb during an average 3-month-long growing season (as was recommended by CASAC and EPA Staff in 1997), or the European AOT 40 objective, which is based on Accumulated Ozone concentrations above an assumed Threshold of 40 ppb over a growing season (as is now commonly used in the European Union).

On March 21, 1996, I presented the attached statement [pages C-9 through C-13 below] to the CASAC of that time regarding the need for a secondary standard for ozone that is different in form from the primary standard. That statement was titled "Avoiding the Necessity for a Second NRC Report on 'Rethinking the Ozone Problem in Urban and Regional Air Pollution' during the Years Between 2002 and 2017." After careful study of Chapter 9 in the 2005 Criteria Document on Ozone, rereading again the 1991 NRC "Rethinking" report, and finally rereading my 1996 statement to CASAC, I am even more convinced (and for the same general and specific reasons outlined on pages 3-7 of this summary of my comments on the 2005 Criteria Document for Ozone) that the time has come for EPA Staff to do all within their powers of persuasion to convince the Administrator of the USEPA that a secondary standard for ozone that is different in form from the primary standard should be promulgated and implements by the Agency in 2007.

Avoiding the Necessity for a Second NRC Report on "Rethinking the Ozone Problem in Urban and Regional Air Pollution" during the Years Between 2002 and 2017

Statement by Ellis B. Cowling
University Distinguished Professor At-Large and
Professor of Plant Pathology and Forest Resources at
North Carolina State University
to the
Clean Air Act Scientific Advisory Committee (CASAC)
EPA Auditorium
Research Triangle Park, North Carolina
March 21, 1996

The objective of this written statement is to provide additional justification to CASAC for recommending to the Administrator of EPA, that a secondary standard for ozone clearly different in form from the primary standard should be promulgated in 1997. This justification is based on three fundamental premises:

1) As discussed in the EPA Staff Paper on the secondary standard for ozone, a longer term seasonal standard, which is cumulative in form will provide an addition measure of protection against the harmful effects of ozone on the many different species of crop plants, forest trees, shade trees, ornamental plants, and the thousands of other plant, animal, insect, and microbial species that make up the living components of all the natural and managed ecosystems on which the quality of American life depends.

2) A secondary standard different in form from the primary standard will also accelerate and improve the processes of public education about many aspects of the tropospheric ozone problem. These aspects include, among others, the following general ideas:

-- Contemporary ozone pollution causes significant harm to crops, forests, ornamental plants, and natural ecosystems in many parts of the United States.

-- Ozone pollution is a serious threat to the welfare of people and ecosystems in many rural as well as urban areas of our country.

-- Ozone and its chemical precursors are frequently transported from rural areas to urban areas and from urban areas to rural areas in many parts of the United States.

-- The air concentrations of ozone and other oxidants that cause harm to crop plants, forests, and natural ecosystems are appreciably lower than the concentrations of ozone and other oxidants that cause harm to most people.

-- Ozone pollution is not just an urban problem associated with high peak concentrations of ozone during exceptional weather episodes but also a problem of longer-term chronic exposures of plants to much lower, but still toxic, concentrations under persistent weather conditions.

3) A secondary standard clearly different in form from the primary standard will also have significant and pronounced effects on the <u>nature, quality, and policy relevancy of ozone-related scientific research that will be undertaken during 1997 and beyond</u>. A very important objective of that research should be to:
-- fill the persistent gaps in available knowledge, and
-- decrease the continuing scientific uncertainties
that have plagued ozone decision making in the past and,
<u>if we do not change the way we think about the ozone problem, will continue to plague the periodic updates and CASAC reviews of the Ozone Criteria Documents</u> that are now scheduled to occur in 2002, 2007, 2012, 2017, etc.

Every CASAC member is aware of the 10 principal findings of the 1991 NRC report entitled "<u>Rethinking the Ozone Problem in Urban and Regional Air Pollution</u>" and the call for reform of the precepts for decision making about tropospheric ozone that were advanced in Milton Russell's classic paper: <u>Ozone Pollution: The Hard Choices</u> (Science 241:1275-1276, 1988) -- see attached reprint.

The title-words <u>Rethinking</u> in the NRC report and <u>Hard Choices</u> in Milton Russell's paper were chosen very deliberately. The intent in both cases was to encourage a significant change in <u>the way American scientists, regulatory officials in industry and government, and the public at large think about ozone pollution and its management</u>. Without a radical change in the quality of scientific, regulatory, and public thinking, both the NRC committee, and Milton Russell, former Assistant Administrator of EPA, were convinced, the United States will continue to fall short of its own objective -- to develop robust, scientifically sound, and cost effective strategies and tactics by which to manage ozone pollution during the remainder of this century and beyond.

The NRC report of 1991 indicated that despite 20 years of expensive and well-intentioned attempts, America's efforts to manage ozone near the ground "largely have failed". These attempts failed for two primary reasons:

1) Because the identical primary and secondary ozone standards established in 1970-71 and in 1978-79 were neither statistically robust nor founded on an adequate scientific understanding of the biological, chemical, and meteorological processes that lead to ozone accumulation near the ground, and

2) Because previous decisions about the kinds and quality of ozone-relevant biological-effects research and atmospheric-science research that was done were too often driven primarily by short-term regulatory deadlines, and, frequently, by incomplete scientific perceptions and policy assumptions.

The time has come for American scientists, leaders in industry and government, and people in general to understand that the problem of ozone pollution can not be managed by continuing to believe that the people in metropolitan areas like Atlanta, Chicago, New

York, and other urban and regional ozone non-attainment areas can "solve the problem" of urban smog and regional ozone exposures without understanding <u>the regionality and the seasonality of both the ozone problem itself</u> and <u>the regionality and seasonality of the management approaches that must be used</u> if the nation is to learn how to manage ozone and other oxidants at reasonable cost.

This deficiency in understanding of the regionality and seasonality of the ozone problem was one of the most important points made in the NRC report and in Russell's "Hard Choices" paper. But these same deficiencies were driven home even more forcefully in November 1994, when 26 of the 29 states that were required to submit a State Implementation Plan for Ozone were unable to make an attainment demonstration following available guidelines.

As a result:

-- Mary Nichols issued her now-famous "Memo of March 2, 1995,"

-- The Environmental Commissioners of States (ECOS) joined together with EPA in creating the Ozone Transport Assessment Group (OTAG) involving more than 30 states east and some west of the Mississippi River, and

-- The Federal Advisory Committee Act Subcommittee on Ozone, Fine Particulate Matter, and Regional Haze Implementation was created to look at at least three of the five or six air-pollution problems that are related to the general oxidative capacity of the atmosphere (the other problems being acidification of soils and surface and ground waters, nitrogen saturation of forest soils, and airborne-nitrogen-induced eutrophication of surface waters).

But even these more recent initiatives are driven by unrealistically short-term regulatory deadlines, and, frequently, by incomplete scientific perceptions and policy assumptions. Examples include:

-- Use of specific exceptional ozone episodes rather than by <u>both</u> episodic <u>and</u> season-long ozone time periods of interest,

-- Use of local and regional emissions inventories for natural and anthropogenic emissions that are of uneven quality for both rural and urban/suburban sources of ozone precursors,

-- Use of emissions-based mathematical models rather than <u>both</u> emissions-based <u>and</u> observation-based air quality models, and

-- Use of models that may "get the ozone peaks right" but are not skillful enough to "get the peaks, <u>and</u> the low ozone concentrations, <u>and</u> the natural and anthropogenic ozone precursors right" at the same time.

As CASAC makes its decisions about the closure letter that must now be written about the secondary standard for ozone, I hope all committee members will think very carefully about the nature, quality, pace, and intensity of research interactions that will occur as the result of the two choices you will help make today:

1) To recommend, once again, that identical primary and secondary standards be established for ozone in 1997, as was done in 1970-71 and in 1977-79, albeit, an 8-hour primary standard for which CASAC already has prepared a closure letter; or, alternatively,

2) To recommend that a secondary standard clearly different in form from the primary standard be established -- an 8-hour primary standard of simple form, and a separate 3-month-long standard of cumulative form as recommended in the EPA Staff Paper.

I hope CASAC will reflect very carefully on the extent and thoroughness of <u>rethinking</u> of the ozone problem that will occur under these two alternative choices. How differently will the thinking and nature of communications be -- both between and among the following kinds of expert- and non-expert persons who are interested in or have responsibilities for research and management decisions about ozone pollution:

-- air pollution biologists,
-- atmospheric chemists and physicists,
-- air pollution meteorologists,
-- air quality modelers,
-- state and federal air-quality officials,
-- air-quality leaders in industry and commerce including those in:
-- the utility industry,
-- the automobile industry,
-- the petroleum industry,
-- the printing, painting, solvents, and forest products industries,
-- etc.

and, perhaps most important of all,
-- the public at large who will ultimately pay the bills for whatever decisions are made about ozone management during the years ahead?

<u>In Summary</u>:

Promulgation of a secondary standard for ozone that is clearly distinct in form from the primary standard will accomplish five important things:

1) It will <u>provide an addition measure of protection</u> against the harmful effects of ozone on the many different species of crop plants, forest trees, shade trees, ornamental plants, and the thousands of other plant, animal, insect, and microbial species that make up the living components of all the natural and managed ecosystems on which the quality of American life depends.

2) It will <u>accelerate and improve the processes of public education</u> about many aspects of the tropospheric ozone problem and its management.

3) It will <u>enhance and improve the nature, quality, and policy relevancy of the scientific research</u> that will be undertaken during 1997 and beyond.

4) It will <u>enhance the quality and intensity of interactions</u> that will occur between air pollution biologists concerned with the impact of ozone on crops and forests and atmospheric scientists who are interested in the chemical, meteorological, biological, energy use, transportation, and industrial-development processes that undergird our future air-quality management policies; and

5) It will <u>avoid the necessity for another NRC report on "rethinking the ozone problem in urban and regional air pollution</u>" sometime during the years between 1997, 2002, 2007, 2012, and 2017 because we failed, once again in 1996 and 1997, to recognize the need for still further <u>rethinking</u> of the tropospheric ozone problem.

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

In general, I find the organization and presentation of the current state of scientific knowledge of ozone effects on vegetation and ecosystems to be well organized, well written, and thoroughly documented. The principle issues of concern have been addressed and references to research findings since the last Criteria Document for Ozone in 1997 have left few if any important gaps -- at least gaps that are essential to establishing a secondary standard for ozone.

This is not to say that there are not important uncertainties – for example, about the biochemical mechanisms and rate of repair by ozone damaged cells, the ability of relatively ozone resistant species and genotypes in mixed forest stands to compensate for ozone damage and injuries in more ozone sensitive species and genotypes, and the continuing nagging issues of ozone-plant disease interactions and the impact of mixtures of air pollutants. Thus many of us look forward to the recommendations for additional research that will be produced at the conclusion of the present Criteria Document revision cycle.

Most of my specific comments are focused on the specific CASAC "Charge Questions" raised in Lester Grant's letter to Fred Butterfield dated April 21, 2005. Please note in the paragraphs below, that my suggested responses to Les Grant's questions are written in indented paragraphs, whereas the background statements by Les Grant and his specific Charge Questions are written in non-indented paragraphs.

D. Characterization of Ozone-Related Welfare Effects

1. Methodologies Used in Vegetation Research. Section 9.2 notes that, to date, most data on exposure-response relationships for crop yield and tree growth have been derived from open-top chamber (OTC) studies. However, numerous chamber effects have been documented and the limited ability to extrapolate chamber data to the field, has been recognized. Some recent studies, however, have employed an alternative methodology, the Free Air Control Exposure systems (FACE). Another method for characterizing exposures in the field is the use of passive monitoring. Additionally, there has been an increasing reliance on air quality models to fill in the gaps in rural and remote U.S. regions where there is inadequate monitoring.

Charge Questions D1.
Is the discussion [in the 2005 CD on ozone] of methodologies used in [ozone-effects] vegetation research sufficiently clear and adequate to allow comparisons between methodologies and to allow characterization of the uncertainties associated with estimating exposures to vegetation with each system?

Yes, I think so.

In particular, is the new FACE technology adequately characterized, and to what extent has it overcome the limitations of the OTC method?

Section 9.2.2 of the 2005 ozone CD takes up this question in some detail and offers the general conclusion that "Although FACE systems have increased our understanding in some areas, in most cases results from FACE systems have confirmed what we already knew or hypothesized about how plants and plant assemblages respond to ozone." This

conclusion is consistent with my understanding of the recent published literature and thus leads me to not to worry very much about many of the sometimes conjectural or purely theoretical "limitations" of OTC systems.

What are the uncertainties associated with the FACE data that would apply if trying to extrapolate to other regions of the country with different ozone exposure regimes and vegetation growing conditions?

I'm not sure that the uncertainties associated with extrapolation from results with FACE systems are any more problematical than extrapolating from results with OTC studies – especially since OTC systems have been used in many more parts of the US and abroad.

Given that the results from FACE studies are similar to findings from earlier OTC studies, does this increase our confidence in the results from studies using the OTC methodology?

I think that similarity in results from these two systems is very reassuring and should increase our confidence in results from the more widely used OTC systems.

Lastly, would it be useful to move Section 9.2 to an Annex?

I see no great advantage in moving section 9.2 to an Annex. I'd leave it where it is.

2. <u>Mode of Action Underlying O_3 Vegetation Effects.</u> Processes involved in ozone uptake and toxicity are better understood today than in 1996, based largely on advances gained through use of molecular techniques in following rapid O_3-induced changes within the leaf, as discussed in Chapter 9, Section 9.3. O_3 entrance into the leaf via stomata is a critical step in sensitivity. Initial O_3 reactions within the leaf remain unclear except for involvement of hydrogen peroxide. Also, reactions of ozone or its products with ascorbate and other antioxidants in the apoplastic space of mesophyll cells serve to lower the amount of O_3 or products available to alter plasma membranes of the cell. A primary trigger of O_3-induced cell responses appears to be changes in internal Ca levels; and the primary set of metabolic reactions triggered by O_3 comprise "wounding" responses like those generated by cutting the leaf or insect attack. Longer-term responses under low concentrations over long time periods, are linked to senescence or some physiological response very closely linked to senescence (*i.e.*, translocation, reallocation, reabsorption of nutrients and carbon).

Charge Questions D2.

Has any important new information been missed on mode-of-action for O_3-induced vegetation effects?

I am not aware of any important new information on mode of action for ozone induced vegetation effects that is not covered adequately in the 2005 CD on ozone.

Also, to what extent does the new information on the mode of action of ozone at the cellular, molecular or biochemical level significantly alter our understanding of plant effects?

Understandings deriving from molecular studies of the mode of action of ozone in plant cells are nice to know for their own sake. But I do not know how such understanding will help very much in learning better how to manage ozone effects on vegetation. Maybe this reaction on my part reflects my professional judgment that we should "get on with establishing a secondary standard for ozone" and not use our lack of understanding

of some fine molecular details in the cellular mode of action as an excuse to delay any further with the necessary process of decreasing emissions of ozone precursors in order to decrease ozone exposures and thus decrease ozone induced stresses on crops, forests and natural ecosystems.

3. Modification of Growth Response.
Chapter 9 notes that none of the few new studies since the 1996 review significantly alter our understanding of how other biotic and abiotic factors modify plant response to O_3. As for biotic interactions, new evidence on insect pests and diseases has not reduced uncertainties noted in the 1996 O_3 AQCD; we still cannot predict the nature of any particular O_3-plant-insect interaction, its likelihood or its severity or of O_3-disease interactions. Nor does new evidence improve our understanding of interactions between O_3 and root symbionts. The few new studies of O_3 effects of plant competition suggest that grasses frequently show greater resilience than other types of plants; but there are insufficient bases to predict specific plant competition situations, *e.g.*, successional plant communities or crop-weed interaction. Temperature is an important variable affecting plant response to O_3, but available data quantifying this interaction are limited and often contradictory. Evidence does suggest that O_3 exposure sensitizes plants to low temperatures by reducing important belowground carbohydrate reserves (which impairs grown in the following seasons). Both increased ambient air relative humidity and/or soil water availability appear to enhance plant sensitivity to O_3. Information on O_3 interactions with specific nutrients is still contradictory; but some experimental data suggests that low fertility increases O_3 sensitivity, while model simulations of tree growth suggest nutrient deficiency and O_3 interact less than additively. There is emerging information regarding potential interactions of O_3 exposure and global change factors, including concurrent elevated CO_2, elevated temperature, altered nutrient and water availability, as well as increased surface UV-B radiation. Studies using elevated O_3 in the presence of high CO_2 without elevated temperature are of limited value for assessing impacts of climate change on response to O_3.

Charge Question D3.
Was any important pertinent information missed in the Chapter 9 discussions of factors that modify plant growth response to O_3 exposure?

I do not know of any missing information on factors that modify plant growth response to ozone exposure.

Also, is there sufficient information in the literature and has it been discussed adequately [in the 2005 CD for ozone] to predict how elevated CO_2, temperature, drought and/or other climate change factors may modify plant response to ozone?

In my judgment, the wide range of possibilities for influences by these other physical factors on plant response to ozone has been discussed very adequately in the 2005 CD on ozone. As we move closer as a nation to serious concern about global warming and CO_2 fertilization effects, this is a very good topic to suggest for follow-up physiological studies after the 2005 ozone CD cycle is completed.

4. Exposure Indices.
One of the most important continuing challenges faced in the 1996 O_3 AQCD — and again addressed in Chapter 9 of the current draft Ozone AQCD — is how to incorporate plant biology

and interacting physical, site, and meteorological processes into air quality indices reflective of exposure- or dose-response relationships for O_3-induced vegetation effects. The few pertinent new studies since 1996 appear to substantiate earlier conclusions on the role of exposure components (*e.g.*, concentration, duration, and seasonal exposure patterns) in determining effects of O_3 on plant growth responses; and ambient exposure indices (*e.g.*, SUM06) continue to be seen by some as good surrogates for actual O_3 exposures affecting plant target tissues. New studies also demonstrate potential disconnects between peak O_3 events and maximal stomatal conductance periods, either due to site and meteorological factors or day/night differences in conductance. The lack of coincidence in temporal patterns of conductance and peak concentrations introduces uncertainty into regional and national scale assessments because of climate and site factors that modify response to O_3. A large amount of literature regarding a flux-based approach, in contrast to the ambient exposure approach for an index, is bolstered by much progress in developing and testing stomatal models that may be generally applicable across certain vegetation types and landscapes.

Charge Questions D4.

Are there ways that the Chapter 9 discussion of exposure indices can be improved? For example, are there any published data not appropriately considered in the Chapter 9 discussions?

I find Section 9.5 on "Effects-Based Air Quality Exposure- and Dose-Response Indices" to be one of the most well reasoned and instructive of all parts of the 2005 CD on ozone. The thoroughness with which this document lays out the advantages and limitations of the SUM06 is quite fine, and, quite to my surprise and delight, also the AOT 40 indices used widely within the European Union also have been dealt with very effectively. I have not followed all of the most recent publications from both North American and European studies on the comparative merits of these two particular indices but I have a general familiarity with the ozone management approaches used on both continents.

In September 1995, I attended the CASAC meeting called to review the second periodic review of the ozone criteria document on ozone, and discovered that a lack of consensus among the ecologists on CASAC about alternative forms of possible secondary standard for ozone was a principal reason for lack of closure on the criteria document at that time. Thus, together with Dr. Walter Heck, Chair of the Emissions and Effects Workgroup in the Southern Oxidants Study, and with encouragement from both George Wolfe in his role as Chair of CASAC and John Bachmann in his leadership role within EPA's Office of Air Quality Planning and Standards, Dr. Heck and I organized an SOS Secondary Ozone Standards Workshop. We invited 22 of the most skilled air-quality scientists in the US working on ozone effects on vegetation and requested that they join together in an attempt to develop a consensus statement on the adequacy of available information and a specific recommendation with regard to the four basic elements of a secondary standard: including the required indicator, averaging time, form, and level of a suitable standard. After two rigorous days of debate, the participants in this workshop came to a consensus that the "SUM06 was an acceptable secondary standard for ozone." The results of this workshop listing all participants and summarizing the principal points of argument and debate were published in Environmental Management Magazine in January 1997. This paper is cited appropriately – it is the as the fourth reference from the bottom on page 9-364 in the 2005 ozone Criteria Document.

The more recently published information summarized in Section 9.5 of the current Criteria Document only strengthen the consensus that was reached and published in the report from this SOS Workshop. Thus, I conclude that the time is ripe for EPA to proceed in its development of the 2005 Staff Paper on Ozone with confidence in the summary of science provided by this years' ozone Criteria Document.

To what extent are the conclusions from this section consistent with our current capabilities to address spatial and temporal factors in exposure and effects on plants?

My principal suggestion for revision of Section 9.5 is that a brief section be included showing more exactly how the SUM06 index is calculated from real-world data taken from several different parts of the US. A similar brief section on how the AOT40 index is calculated would also be instructive. Finally, the acronym AOT ought to be added to those listed on page III-xxi.

Are there new experimental data that would call into question the conclusions of 1996 that a best available exposure index is one that cumulates hourly concentrations over a three-month period and weights concentration and daylight hours?

I know of no information that would call this conclusion into question. In fact, I am confident that development of an exposure index that accumulates hourly concentrations over a growing-season long period of at least 3 months' duration and that weights concentration and daylight hours -- will prove to be a useful start in seeking to protect vegetation ecosystems from harm by ambient ozone in various parts of the US.

Are there sufficient data on the relationship between ozone flux and plant response to move away from an ambient exposure-based approach to developing an index at this time?

To the best of my knowledge, there is not sufficient information and data on the relationship between ozone flux and plant response to move away from an ambient exposure based approach at this time.

Also, are there adequate experimental exposure-response data for relevant crop species, annual and perennial plants species, and tree species as seedlings to support Chapter 9 conclusions regarding concentration levels of an exposure index that is protective of vegetation?

I believe that adequate experimental exposure-response data on relevant crop species, perennial plant species, and tree species are available to support the Chapter 9 conclusions regarding concentration levels of an exposure index that is protective of vegetation.

5. <u>Exposure-Response Relationships for Individual Plant species</u>.

Newly available information supports the 1996 O_3 AQCD conclusions that ambient O_3 concentrations are reducing the yield of major crops. New FACE studies support findings from earlier open-top chamber studies of deciduous tree species and crop species. New studies support earlier generalizations: woody plants (*i.e.*, seedling tree species) are less sensitive than are most annual plant species (including agronomic crops), with the exception of a few deciduous tree species. Current ambient O_3 concentrations in the U.S. are sufficient to reduce growth in seedlings of these sensitive species. Coniferous species are generally less sensitive

than most deciduous species in the U.S., and slow-growing species are less sensitive than fast-growing ones. Long-lived species present difficult problems in assessing O_3 impacts, because even multiple-year exposures do not expose trees to O_3 for more than a small fraction of their lives and because competition may exacerbate O_3 effects on individuals (thus making it difficult to determine effects on mature trees).

Charge Questions D5.
Does the discussion in Chapter 9 of exposure-response relationships for O_3 effects on individual types of plants accurately and adequately characterize the most pertinent available information on the subject?

Yes, I believe it does.

Was any important relevant information missed?

Not to the best of my knowledge.

How might the discussion be improved?

Perhaps by making some editorial effort to minimize some of the notable differences in perspective from sections that appear to have been written by different individual authors.

Are multiple species mixes and/or multiyear studies adequately covered?

Yes, I think so.

Also, are there adequate experimental exposure-response data for relevant crop species, annual and perennial plant species, and tree species as seedlings to support conclusions regarding concentration levels that might be judged to be protective of vegetation?

Yes, I believe so in this case as well.

6. Ecosystem Response.

Despite growing recognition of possible O_3 ecosystem effects, the database demonstrating and quantifying the degree to which O_3 is altering natural ecosystems is very limited, as discussed in Chapter 9. Much of the impact is speculative and based on several case studies of forest plot field-based data reporting on a number of different species. Little is known about O_3 effects on water, carbon and nutrient cycling, especially at the stand and community levels; and little is known about O_3 effects on structural or functional components of soil food webs or how these impacts may affect plant species diversity. Also, little is known about feedbacks between O_3 exposures and climate change effects on ecosystem productivity, given the lack of interaction studies with other components of climate change (*e.g.*, warming, water availability, N deposition). Most of the available data is from seedling studies and annual plants, thus limiting use of these data in developing an understanding of O_3 impacts on natural ecosystems and services derived from them. In general, methodologies to determine the important services and benefits derived from natural ecosystems are lacking, making it difficult to identify and quantify factors that could be used in quantitatively assessing O_3 –related ecosystem effects.

Charge Questions D6.

How can the Chapter 9 assessment of existing literature on ecosystem response to O_3 be improved?

My only suggestions for improvement are listed under "Charge Questions" D3 and D4 above.

Is the information discussed sufficient to evaluate whether current air quality is damaging natural or managed ecosystems?

Yes, in my view the discussion is adequate for the ecosystems with which I am familiar – mostly in the eastern US.

For example, does new information regarding the role of N in the San Bernardino forests alter our previous understanding of how O_3 affects the ponderosa pine ecosystem?

My experience is not adequate to provide a reliable answer to this question.

Was any new information missed by which to identify other useful endpoints or measures for assessing ecosystem response to O_3?

As indicated above, I believe that Chapter 9 has done a very commendable job of summarizing the endpoints and measures for assessing ecosystem responses to ozone exposures.

Also, are there appropriate measures of ecosystem services supported by published literature that would provide better linkages to economic or societal valuation of these services?

My knowledge and experience with the literature of ecosystem services is not adequate to offer a well-informed assessment of ozone effects on these vitally important societal-service functions.

Is the discussion of ecosystem services adequate for the available information at this time?

Here too my knowledge and experience with the literature of ecosystem services is not adequate to offer a well-informed assessment of ozone effects on these vitally important societal service functions.

Dr. James D. Crapo

Comments on First Draft Ozone AQCD
Chapter 8 (Integrative Synthesis)

James D. Crapo
Sverre Vedal

April 29, 2005

This chapter appropriately reviews and integrates the primary findings regarding health risks associated with human exposures to ozone in the United States. The fundamental conclusions of this chapter are that, while there has been a downward trend of ozone concentrations in the United States, the available health risk data coming from a wide variety of study designs demonstrate adverse health effects on human subjects, particularly sensitive populations at exposure levels that are below the air quality standards for ozone and within the common ambient exposures in outdoor environments. The scientific basis underlying this field is maturing, and there is substantial concordance of findings from both animal and human studies using a wide variety of different designs.

MAJOR ISSUES

1. While a large portion of this chapter is well written, the writing is not of consistent quality across the entire chapter and appears to have portions of it be a cut and paste from different authors.

Tables 8-2 and 8-3 should be deleted. They play no significant role in this chapter and are not used in the integrative synthesis. If a decision is made to keep this material, they should be combined into a single table. It makes no sense to have one set of criteria for assessing ozone responses in healthy individuals and another in individuals with an impaired respiratory system. When compared directly, the two tables only vary by the addition of a few additional indices of response in Table 8-3. There is no rationale for not applying the more comprehensive set of response factors to assess responses in all individuals.

2. Concluding synthesis.

The all-important concluding sections, sections 8.4.10-12, need to be rewritten in order to best integrate the experimental and observational findings into a meaningful synthesis. The writing here is imprecise and somewhat careless. It would be preferable to have this entire chapter written by either one person, or a small group working very closely together. Sections 8-1 to 8-3, while still requiring some work (detailed below), do not necessarily need to be rewritten.

The task in the concluding section, which is ably introduced (starting at section 8.4.10), is to assess the coherence of the scientific findings, specifically how the experimental human work and the toxicological work cohere, or fail to cohere, with observational findings. What we get instead are vague generalities mixed with reporting of specific findings that fail to make the intended points. We have a great deal of coherence in addressing ozone-induced acute lung function decrements. There is good coherence in addressing other respiratory outcomes such as hospitalizations and exacerbations, and arguably for asthma-related outcomes, specifically. There is less coherence in addressing cardiovascular outcomes, which is not addressed here. In short, we get little sense here as to where there is good coherence, where there is very little coherence, and where the data are inadequate for assessing coherence.

Specifically:

i. The discussion of AHR (8.40-41) loosely and repeatedly links AHR and decline in lung function. While there may in fact be such links, AHR and lung function declines are best treated as separate phenomena. How is AHR responsible for lung function declines seen in epidemiological studies (8.41[12])?

ii. There is repeated mention of "respiratory-related mortality" (8.44-46), whereas the epidemiological studies deal primarily with total mortality (hence, cardiovascular mortality), or the subset of cardio-respiratory deaths (dominated by cardiovascular deaths). Clearly there is some coherence when considering respiratory outcomes, but the evidence is pointing to more general mortality effects. Yet, there is no mention here as to whether this is plausible.

3. Adequacy of analysis of time-series studies.

The uncertainty that has recently been reintroduced into the PM time-series findings related to model specification of temporal trends and meteorology is likely as acute for ozone as for PM; there has just been less emphasis placed on it to this point. Therefore, statements such as "adequate control for seasonal patterns" (8.15[19]) are overstatements. The section that focuses on confounding by temporal trends and meteorology (p. 8.22) largely glosses over this, although the concluding paragraph here is appropriately cautious.

4. Cardiovascular mortality.

The recent multi-city time series all find associations between short-term changes in ozone concentrations and total mortality, indicating that the association is with cardiovascular mortality, since this cause-specific mortality typically "drives" associations with total mortality. When this is specifically addressed, this is in fact what is happening. There is a disappointing avoidance of the implications of this finding. Specifically, is it plausible given what is known about ozone toxicology, etc? Plausibility and coherence can be addressed within the epidemiological setting, or more typically, by integrating findings from human experimental, toxicological, and epidemiological studies. Limited to the epidemiological arena, the few studies in which associations with cardiovascular hospitalizations were assessed (p. 8.16) find none. Further, there are precious little toxicological or human experimental data that bear on this,

although there are some, and, given the significance of this finding, these should be summarized in this chapter.

5. Chronic effects of ozone (section 8.4.6).

The discussion of potential chronic effects of ozone is inadequate. The implication here is that we have very little data to address this question. This is not really the case. The highlights of work on this question include the infant non-human primate studies from Davis and the two university studies (the Tager and the Kinney studies), indicating effects on lung morphology and lung function, respectively, and the Southern California Children's Study and the ACS cohort study, indicating no effects on lung function and mortality, respectively.

6. Confounding of ozone exposure with PM, especially for mortality.

There is poor discussion of this issue and its implications. The strength of the data identifying an ozone related mortality effect independent of the PM effect needs to be more critically evaluated.

Dr. William (Jim) Gauderman

Chapter 6
Jim Gauderman

This is a well written and comprehensive chapter. I have the following comments:

6-4, line 17: This sentence is confusing, since the resting response to 0.3 ppm is not displayed on Figure 6-1. Such a curve should be added to the figure if possible.

6-6, line 11: add 'of' after 'function'

AX6-12, line 26: change 'realted' to 'related'

Figure AX6-2: The approach to estimating the SE should be clarified. From the legend, it sounds as if the variance in post exposure values was used as the variance of the differences. The formula for the variance of the difference Y2-Y1 is Var(Y1) + Var(Y2) – 2*Cov(Y1,Y2), where Y1 is the first measurement, Y2 the second, and the latter term is the covariance. It would be reasonable to assume that the post-exposure variance Var(Y2) is the same as Var(Y1) in this calculation, but it is not clear how the covariance term was estimated from the available data. Assuming this covariance is zero is not realistic and will result in artificially wide confidence bands on the plotted points.

6-7, line 30: Change 'During' to 'After' and change 'despite …' to 'as the concentration was decreased from 0.12 to 0.00 ppm (mean 0.06 ppm).'

6-16, line 7: Give some specific examples of the inflammatory response outcomes in these studies.

6-15, line 28: add a comma before 'develop'

Section 6.4: Much of the information presented in this section is also presented in greater detail in Section 6.5. The key point is that ozone responses vary across individuals. Section 6.5 summarizes the literature on specific modifying factors that have been identified that partly explain inter-individual variation. I suggest combining 6.4 and 6.5 into one section, with a brief introduction (such as the paragraph on 6-18, lines 17-28). This section should include a separate subsection for 'reproducibility' that summarizes findings on intra-subject variation. The section should end with a paragraph briefly summarizing the identified modifying factors but indicating that much inter-subject variation in ozone response is unexplained (similar to the paragraph beginning on 6-19, line 28 through 6-20, line 7).

6-19, lines 6-18: This text needs to be reorganized or dropped completely as per the suggestion above. The main results reported here deal with intra-subject variation, but the text is split between two paragraphs, both of which also make statements about inter-subject variation. There should be a separate paragraph (or sub-section) focused on intra-subject variation.

6-24, Section 6.5.7: Since genetic findings often vary substantially by ethnic group, the ethnic affiliations of the Bergamaschi et al. and Romieu et al. samples should be noted here. The Corradi et al., 2002 study should also be referenced here. Given the potential importance of genetic factors, I found this section a bit weak. Consider adding a table that documents the 'several recent studies', indicating the population and polymorphism(s) studied, and the resulting health finding.

Chapter 6, second set of comments
Jim Gauderman
5/4/05

Following are additional comments on Chapter 6, compiled during the May 4-5 public meeting. The italicized comments at the end of this document are those I provided in an earlier transmission to EPA prior to the public meeting.

6-2, line 11: This paragraph correctly points out the limitations of small-sized studies, particularly with respect to the power to detect effects. However, this theme was not woven throughout the subsequent summary of results with enough emphasis. Each result should also be accompanied by the corresponding sample size so that the reader can better judge the weight of the evidence. Sample sizes are provided for those studies tabulated in the annex, but not all studies discussed in the summary document are included in the annex. For example, the Linn et al. (1986) and McDonnell et al. (1983) studies do not report sample sizes, and thus it is not possible to fully compare them.

It is not clear why some pre-1996 studies were included in the annex tables while others were not.

Figures 6-1 and 6-3 are the same. One should be eliminated.

Section 6.9.3 is too long relative to the other sections. The information should be summarized more succinctly.

Overall: Each section mixes results from studies prior to 1996 with those post 1996, with appropriately more emphasis given to the latter. I'd suggest including two sub-sections within each section, entitled "Summary of pre-1996 studies" and "Studies from 1996-present". The former could be a brief summary of the most salient results as summarized in the 1996 criteria document. The latter could then focus on more recent results and include comparisons/contrasts with earlier findings. This would facilitate evaluation by the panel on what new evidence has emerged that might bear on evaluation of current ambient levels.

Overall: The overall organization of the sections might be improved to enhance the flow and readability. I suggest the following, which places the collection of different health outcomes in

the first parts (6.2 to 6.6) and then discusses effects of repeated exposures, modifying factors, and pollutant mixtures with respect to any of the aforementioned health outcomes.

6.1 Introduction
6.2 Pulmonary function effects in healthy subjects
6.3 Pulmonary function effects in subjects with pre-existing disease
6.4 Effects on airway responsiveness
6.5 Effects on exercise performance (current 6.7)
6.6 Extrapulmonary effects (current 6.13)
6.7 Inflammatory responses and host defense
6.8 Repeated Exposures (merge current 6.6, 6.9.4)
6.9 Modifying Factors (on any of the above health outcomes)
    6.9.1 Demographic factors (age, sex, race)
    6.9.2 Genetics
    6.9.3 Personal exposures (smoking, antioxidants, physical activity, anti-inflammatory agents(current 6.9.5))
    6.9.4 Temperature
6.10 Pollutant mixtures (merge 6.11 and 6.12)
6.11 Summary

In the above summary (proposed 6.10), I'd suggest including a one-page table that summarizes results organized by exposure level. For example, what are the important health effects (if any) observed at <0.08 ppm, 0.08–0.12 ppm, 0.12–0.20 ppm, etc.

Dr. Henry Gong

Individual Review Comments for Chapter 6, "Controlled Human Exposure Studies of Ozone and Related Photochemical Oxidants," U.S. EPA Ozone AQCD (first draft).
CASAC Ozone Review Panel.
Henry Gong, Jr., M.D., 4/29/05.

General Comments
The chapter appears comprehensive and logical in its progression of subtopics. Overall, the chapter represents a useful and accurate scientific update and summary. The use of an "executive summary" (pages 6-1 through 6-54) is interesting and effectively provides the "big concepts." However, the reader must still rely on Annex AX6 pages (AX6-1 through AX6-148) to best understand the subject matter. The numerous tables are very detailed. The two sets of References are complete, although somewhat redundant.

1. Page 6-2. The "important limitations" associated with ozone clinical studies are listed. I agree with this listing. Another set of limitations involves comparing study results that originated from different study designs and exposure conditions used by different investigators (e.g., see page 6-20). The difficulty with strictly comparing ozone doses (C x T x VE) (page AX6-14), the large intersubject variability of responses (page 6-18), and age-related lung function responses also complicate study comparisons.
2. Page 6-36. A newly published article "Validation of the Human Ozone Challenge Model as a Toll for Assessing Anti-inflammatory Drugs in Early Development" by Olaf Holz et al (J Clin Pharmacology 2005;45:498-503) presents interesting data about early airway inflammation and significant reduction (of sputum neutrophils) with corticosteroid pretreatment. This new data contradicts previous studies?
3. Page 6-20. Should there be a statement about the limited clinical study data for children, etc.? The discussion about age starts at 18 years and above.
4. Page AX6-4/line 18. What is "placebo control" for ozone exposures?
5. Page AX6-38. The cardiovascular study by Gong et al (1998) did find acute hypoxemia (compared to filtered air exposure) that was accurately determined by an increased alveolar-arterial gradient for PO2. This finding in "healthy" adults is clinically relevant and should be at least indicated in the pulmonary function section.
6. Page AX6-83/1. The type of nebulizer also matters in that different nebulizers can emit different concentrations and sizes of aerosol.
7. Page AX6-93/7. Dietary antioxidants. The referenced study (Trenga et al) is described in more "neutral terms" here, as compared to that on pages AX6-64 and –65. Needs more consistency of presentation?

Additional Individual Comments
Henry Gong, Jr., M.D., 5/5/05.

8. The major presentation of data in both the Chapter and Annex focuses on group means, with minimal consideration of the range of responses, confidence intervals, or variability. This

is surprising, especially in the section of intersubject variability of responses to ozone exposure. I recommend adding such information (some in Chapter and certainly in the Annex). One corollary to this is the example of an acute 5 or 10% decrease in FEV1 in an asthmatic or patient with COPD. Although quantitatively this amount may not be considered "significant." The clinical outcome and relevance also depend on baseline lung function, e.g., a patient with severe COPD may overtly realize the acute (albeit small) decrease in FEV1 due to a cold or acute ozone exposure. A clinical caveat is that real patients generally do not know their FEV1 but may be still very symptomatic with even unchanged FEV1, and the symptoms are what bring the patients to the doctor's attention.

9. The Chapter should be a succinct summary of key findings (including some key ones before 1996) and an interpretation of the studies' results and their overall relevance to science and standard setting. I like the current 1:3 proportionality of pages between the Chapter and Annex. However, the current Summary of the Chapter is just that, a summary, without an integrative interpretation of the chapter's reviewed findings and critical concepts. The current Summary also lacks some relevant findings/concepts discussed in the Chapter, e.g., triangular ozone exposures. I support: (1) using "bullet points" to truly emphasize important findings and/or concepts (interpretation); and (2) adding a succinct paragraph about research gaps or needs since these are the questions that logically follow the review of all the interval ozone health research.

10. Page 6-24/Section 6.5.6: Should you include the Medico City field studies and animal results using anti-oxidants here as well? The cross-disciplinary input here would be additively supportive since the few human studies appear less convincing.

11. Page 6-34/Section 6.9.3: Needs a concluding summary statement? Lots of data presented, but so what?? Any clinical significance of the results? Comparison with clean-air exposed results (i.e., the "normal range" of these biochemical mediators)?

12. Page 6-35/line30: Why is the Alexis study (2000) discussed here? His study was not a repeated daily exposure study. Is it the small airways that you are focusing on? How can you relate small airways and lung inflammation, etc.? (no data but you can carefully speculate about the link?)

13. Page 6-36: There is a weak transition to the section on mucociliary clearance. Its role in host defense is not indicated.

14. Page 6-38 and 6-39: The second paragraph is written like a conclusion or summary, but it does not follow from the previous paragraph?

15. Page 6-41/line 17: Does ozone responsiveness really begin to "decline" at 18-20 yrs of age? Isn't this the starting age at which the systematic measurements were made? Is the literature consensus that it is really more like 30-35 yrs?

16. Page 6-41/line12: the averaging time should be stated as well for the $\leq$08 ppm ozone.

17. Page 6-41/line 24-25: The correlation between baseline lung function and lung function response in asthmatics definitely needs a reference and discussion. I could not find such in either the Chapter or Annex. On the other hand, most asthmatic studies recruit and study mild asthmatics for safety and ethical reasons, so finding adequate numbers of moderate and severe asthmatics to study and compare results is most difficult, in my opinion.

18. Triangular ozone exposures: It is not clearly stated what the health significance of this profile is in both the Chapter and Annex. I suggest superimposing the time-lung function curves of both the Hazucha and Adams data into one figure. Triangular ozone exposure is not mentioned in the Chapter's Summary. Not relevant?

19. The development of airways inflammation in ozone-exposed healthy subjects and asthmatics represent a pathway for systemic inflammation and potential cardiovascular sequelae. It is still speculative but the PM-cardiovascular deaths present a precedent for this mechanism.
20. The standard-setting relevance of the numerous research studies summarized in the Chapter and Annex is lost in the "forest." Is there any simple and consistent way to emphasize or, at least, identify the relevant studies in the Chapter (without abridging or "threatening" what the eventual Staff Paper will do)? For example, what are the studies with 6-8 hr exposure to 0.08 ppm (or lower) ozone, whether or not they show symptoms and decreased FEV1?
21. Chapter 8: A statement that the cardiovascular results (Gong, 1998) were "negative" is too simplistic and not accurate. A better characterization is found in Chapter 6 on this topic. This is an example of the importance of cross-discussions and cross-checking of the same references in different chapters (by different authors) and disciplines so that incorrect concepts and misinterpretations can be avoided or minimized.

Responses to Charge Questions Posed by Lester D. Grant (letter dated 4/21/05) Pertaining to Chapter 6, "Controlled Human Exposure Studies of Ozone and Related Photochemical Oxidants," U.S. EPA Ozone AQCD (first draft).
CASAC Ozone Review Panel.
Henry Gong, Jr., M.D., 4/29/05.

A1. See my General Comments for the Chapter 6.

C3a(i). The current draft chapter covers the appropriate published ozone clinical studies, to my knowledge.

C3a(ii). The asthmatics' continued postexposure airway hyperresponsiveness is a plausible pathway for adverse health outcomes, or at least contributes to an increased susceptibility or tendency for asthmatic exacerbation. Ozone may effectively "prime" the epithelium in the nose and lower airways. The pre-existing immunologic airway substrate in asthma also promotes the inflammation and airway sensitivity. The increased airway "twitchiness" (sensitivity) enables even small amounts of allergen, particles, etc., to worsen the hyperresponsiveness and promote clinical attacks. The ozone-allergen studies generally support this concept.

C3b(i). The current information about lung defenses, inflammation, etc., appears to be adequately covered. How can EPA use this cellular and chemical information for setting standards (policy)?

C3c. Cardiovascular effects of ozone remain uncertain. Further research into the cardiovascular effects of potent oxidizing agents such as ozone should be encouraged and funded (much like for particulate matter). Animal models are very useful but do not always reflect human responses, e.g., the hypothermic responses to ozone exposure in animals are not observed in humans (Gong et al, 1998). In humans, blood chemistries (e.g. endothelin, inflammatory mediators) and relatively noninvasive procedures involving Holter monitoring (e.g., heart rate variability),

brachial artery reactivity, echocardiography, or specialized heart scans could be utilized to evaluate potential cardiovascular or endothelial effects.

C3d. The existing short discussion on systemic effects is inherently limited because few investigations have occurred or been published since 1996. I vote for keeping this section to remind everyone that such systemic effects may be present, we cannot totally exclude this possibility, and future research may find new systemic effects.

No revisions for this section, 5/5/05.

Dr. Paul J. Hanson

2005 First External Review Draft of the
Air Quality Criteria for Ozone and Related Photochemical Oxidants

Final Comments on Chapters 1 and 3
Submitted by Paul J. Hanson on 9 May 2005

Chapter 1 Comments

I found Chapter 1 to be a well-crafted introduction with appropriate background information leading to the other chapters of the document.

P1-8 Line 2

Should a distinction between tropospheric and stratospheric ozone be made on this line?

Chapter 3 Comments

Chapter 3 contains extensive information on the ozone environmental concentrations and exposure estimates, but I have the following questions and concerns that should improve the presentation when addressed.

P3-1 Line 12: The current EPA air database should be cited and a web address added:
http://www.epa.gov/air/data/

P3-2 Line 25: What kind of plant or plant group is the W126 index set up for? Crops? Trees? Both?

Table 3-1 on P3-4: To what extend did the development of the defined ozone-monitoring-seasons impact the evaluation of long-term trends?

P3-5 Lines 23 to 25: Isn't the real reason for difficulty in defining mean ozone distribution patterns a lack of measured data rather than point sources of pollutants?

Figure 3-1 would be much more useful if it was constructed as a contour plot. What period in time does this graph represent? Is it appropriate through 2003? This comment also applies to Figure 3-2.

Is Figure 3-2 intended to reflect the current NAAQS (Section 1.1)? If so, the figure legend should make this clear.

Figures 3-1 and 3-2 could be stacked together on the same page. They would also be more instructive if they were calculated for 1983, 1993, and 2003 and shown in a block of 6 graphs to allow the reader to see changes with time (if that is the case).

On P 3-3 'relatively clean remote sites' are introduced as a concept. How does this apply to the discussion on P3-6?

Figures from section AX3.2.3 could be brought forward into the main body of the report to provide the reader with a better understanding of ozone patterns across the country. I found Figures AX3-5 to AX3-10 to be especially useful.

P3-6 Lines 4 and 5: Relatively remote sites and non-urban locations are being discussed. Is the reader to assume that they are equal?

Tables 3-2 and 3-3 could be placed in the appendix.

Table 3-4 was useful, but I was looking for a graphical summary. Are any quantitative data from remote locations in Canada available for the assessment of background levels?

When I finished reading section 3.2 I asked myself where the comparison between the current NAAQS for ozone and the variety of exposure indicators was. How does the current NAAQS (based on health effects) stack up to the SUM00, SUM60, W126, etc.?

P3-27 Lines 4 to 11: Aren't the conclusions regarding minimum ozone concentrations biased by the concept of seasonal ozone measurements (Table 3-1)? If the mid-winter data were included wouldn't the lowest annual ozone concentrations occur during that period?

P3-27 Line 15: Sources of what?

The data included in the tables doesn't necessarily reflect all of the site data discussed in the text. For example, Lassen Volcanic National Park data do not appear to be included in Tables 3-4 or 3-5.

Section 3.2 needs a stronger conclusion. Tell the reader in a succinct manner what we can say about the status of clean-air or background sites. Have they changed over the past 20 years? If so, how would those rates-of-change agree with or conflict with the temporal patterns of change of the ozone concentrations discussed in Section 3.5?

P3-33 Lines 15 to 19: Given that the percentages pattern were not significant, I would start with the statement that no statistically significant change was apparent over the past 10 years, and then discuss the apparent decadal trends.

On P3-33 Lines 27 to 29 the authors list a variety of drivers responsible for inter-annual variation in ozone concentrations. How dominant are meteorological conditions with respect to the other drivers? To what extent are the high ozone levels of the 1980's attributed to meteorological vs. anthropogenic forcings?

P3-34 Figure 3-4: The dashed line in this figure is not the current NAAQS for ozone.

Page 3-35 is inadequately referenced. References to published literature are needed for the statements on lines 2, 3, 10, 13, and 14.

P3-35 Line 16: Which chapter?

P3-35 Line 22: The sentence suggests that individual monitoring sites showed upward [O3] trends for selected National Parks? What does the average data for each park suggest? Do the parks have adequate air monitoring to capture the mean and range of the exposures to the ecosystems in each park?

Section 3.5 should end with a stronger statement regarding the trends in ozone concentration. Don't make the reader tease this information from the Tables.

P3-51: I would add a clear statement at the end of Section 3.7 regarding the status of policy relevant background concentrations.

P3-67 Lines 5 and 6: If appropriate, I would reference Figures 3-4 and 3-5 at this point.

2005 First External Review Draft of the
Air Quality Criteria for Ozone and Related Photochemical Oxidants

Final Comments on Chapter 9
Submitted by Paul J. Hanson on 9 May 2005

****An addition or substantive change from my 28 April 2005 comments.**

Chapter 9 Comments

I found Chapter 9 on Environmental Effects to be a good first draft describing the 'state-of-science' since the 1996 Air Quality Criteria Document (AQCD) for ozone. However, in the following comments I raise a number of scientific and editorial issues for the authors to consider in the preparation of a second draft.

**Organization: I would place Section 9.3 covering mode of action before the section 9.2 on methods, but keep the methods section in the main chapter. It is important that the reader understand that different methods of studying plant exposure and response can lead to alternate conclusions, but have also shown similar relative responses in key studies. When previous AQCDs are cited it would be useful if specific page numbers were provided (these are really long documents).

P9-1: The introduction (9.1) is more than just an introduction to Chapter 9. It reads like the introduction to all of Volume III of the draft AQCD. I would limit the introduction for Chapter 9 to the content of Chapter 9.

P9-1 line 13: The word 'ecosystem' should be plural.

P9-2 line 20: Add the following to the sentence: "but are addressed in section 9.3."

P9-3 line 19: The Karnosky et al. (2001) reference should be 2001a, b or c.

P3-6 lines 10 to 12: The definable exposure provide by the OTC design could be considered an advantage given that alternative free-air systems have 'hot spots' with essentially undefined exposures.

P3-6 line 24: The word 'drops' should be 'crops'.

P9-9: This page includes good discussion of the nature of 'hot spots' expected for free-air exposures systems. Such variations in concentration have little impact on CO_2 studies, where the peaks and valleys are assumed to have no long-lasting impact on leaf function. However, for ozone exposures short duration spikes of high O_3 concentration probably shouldn't be considered balanced by short-duration low concentration periods.

A number of the exposure indices (e.g., AOT40) are described in the text before they are actually defined (Section 9.5). Brief descriptions might be provided at their first use to help readers that might choose to read only a portion of the final AQCD.

P9-13: Soil monoliths transported to various locations along natural ozone gradients might be an approach worth mentioning. Such an approach would eliminate some of the common confounding problems associated with the interpretation of gradient data.

Top of page9-15: To what extent have positive effects associated with EDU treatments been evaluated as an N addition effect?

P9-20 line 5: Something is wrong in this sentence. Can the words "the amount of injury" be replaced by 'ozone concentration'?

P9-20 line 8: This sentence illustrates just one of many examples where experimental data are discussed in the context of exposure indicators other than the current NAAQS for ozone. At some point in this chapter the adequacy of the current ozone NAAQS should be discussed and contrasted with the other exposure indicators that are obviously favored for plant responses. Does the current NAAQS for ozone based on human health adequately protect exposure and/or dose thresholds suggested by the other indicators?

P9-23 line 4: I would change µl L-1 to ppm to be consistent throughout the document.

P9-23 line 17: What is a 'firm' O3 effect?

Table 9-4 on P9-24: I would change the word 'related' in the 4th advantage bullet to 'correlation with'. The first disadvantage bullet is in agreement with this change.

P9-28 line 28: The word 'allocation' should be replaced with 'translocation' which is the process being discussed. Translocation is also used most commonly throughout the chapter. The authors should conduct a search for the use of the word allocation and make similar changes as appropriate.

P9-34 line 14: I would change 'poor' to 'inefficient'. Measuring ozone effects on mature trees has advantages.

P9-34 Lines 3 and 4: This statement seems a bit contradictory with respect to statements made on P9-17 lines 12 to 15.

P9-38 line 8: Taylor and Hanson 1992 is a good citation for this statement.

P9-42 line 21: Transport of what?

P9-63 Footnote #10: The number 500,00 is probably supposed to be 500,000.

P9-76 lines 1 and 2: This statement is not clear. What do the others mean?

P9-77 line 1: Change Allocation to Translocation.

P9-78 line 14: Please provide the Latin name for Pima cotton.

P9-79 line 25: The Sakaki and coworkers article needs a year (1983?, 1985?, or 1990?).

P9-79 lines 26 to 28: Does this statement contradict page 9-64 lines 19 and 20?

P9-82 Does the concept of a memory effect have equal application to conifers and deciduous trees?

P9-83 line 2: A primary reference is needed for the statement that carbohydrates are involved in carry-over effects.

P9-83 line 27: Translocation and allocation may be redundant.

P9-89 bottom of the page: Available data for *Populus* clones might also be mentioned.

P9-103 lines 22 to 25: Additional definition of the meaning of 'competitively disadvantaged or advantaged trees' would be helpful.

Page9-122 line 16: A primary reference for the ability of foliage to use N deposition directly should be supplied. For example:

> Garten CT, Hanson PJ (1990) Foliar retention of ^{15}N-nitrate and ^{15}N-ammonium by red maple (*Acer rubrum*) and white oak (*Quercus alba*) leaves from simulated acid rain. Environ Exp Bot 30:333-342.

Norby RJ, Weerasuriya Y, Hanson PJ (1989) Induction of nitrate reductase activity in red spruce needles by NO_2 and HNO_3 vapor. Can J For Res 19:889-896.

Hanson PJ, Garten CT Jr. (1992) Deposition of $H^{15}NO_3$ to white oak, red maple, and loblolly pine foliage: experimental observations and a generalized model. New Phytol 122:329-337.

P9-129 lines 17 to 20: This statement is incorrect. Recent data from the following papers clearly show a long term and sustained reduction in stomatal conductance under elevated CO2 for a number of species:

Ainsworth EA, Long SP (2005) What have we learned from 15 years of free-air CO2 enrichment (FACE)? ….New Phytologist 165:351-371.

Ellsworth DS, Reich PB, Naumburg ES, Koch GW, Kubiske ME, Smith SD (2004) Photosynthesis, carboxylation and leaf nitrogen response of 16…..Global Change Biology 10:2121-2138.

Gunderson CA, Norby RJ, Wullschleger SD (1993) Foliar gas exchange responses of two deciduous hardwood. Plant Cell Environ. 16:797-807.

Gunderson CA, Sholtis JD, Wullschleger SD, Tissue DT, Hanson PJ, Norby RJ (2002) Environmental and stomatal control of ……Plant Cell Environment 25:379-393.

The review material on CO2 effects on pages 9-143 through 9-146 is interesting, but it may not be essential to the AQCD for ozone.

P9-144 lines 30 and 31: This statement continuing on the top of the next page is incorrect. The articles just mentioned show sustained reductions in stomatal conductance from elevated CO2 for large deciduous trees over multi-year periods.

P9-145 line 5: Stomatal closure results in only a partial reduction in transpiration because leaf temperatures rise with stomatal closure increasing the VPD and sustaining much of the original transpiration rate.

P9-145 line 22: The word ‘ahowed’ should be ‘showed’.

P9-151 lines 18 to 24: Chapter 10 deals very little with the effect of UV-B on plants, but rather deals with the effect of Tropospheric ozone limiting surface UV-B exposures.

P9-157 line 18: Add the word ‘reduced’ as in ‘reduced growth’ within the parentheses.

P9-157 lines 26 to 28: Please repeat the primary reference for this statement.

P9-159 line 12: I would substitute ‘better correlation’ for ‘greater effect’ in this line.

P9-160 line 13: The word 'had' should be 'have'.

P9-164 line 7: I think the word 'both' should be 'all'.

P9-164 line 10: Two should be 'three'.

P9-174 lines 9 to 11: I found the meaning of this sentence to be unclear.

P9-177 line 23: Mikkelsen et al. needs a year (????).

P9-178: The concept of tissue repair in response to ozone damage is mentioned here. Can the authors provide a reference showing quantitative proof of this mechanism? It is a common concept also invoked at the following places in the document: P9-29 line 14; P9-35 line 7; P9-57 line 6; P9-73 line 6; P9-79 line 3; P9-184 line 16; and on pages 170 and 175 under the term detoxification. I believe that repair facilitated by enzyme, protein, and perhaps membrane turnover is a viable mechanism, but it deserves more discussion since it is critical to the identification of ozone response thresholds. It may be interesting to point out, however, that since ozone damage seems to be often associated with cumulative exposure or dose repair mechanisms are probably never completely successful.

Table 9-13 on page 9-185: Can this table be expanded to include data through 2003 and 2004?

P9-209: I believe Table 9-15 referred to on this page is actually Table 9-21.

P9-212: The material on this page is largely redundant with sections that came before. I recommend that the authors take a close look and combine concepts where possible. For example, the discussion of methods of exposure need not be rehashed at this point.

P9-220: The paragraphs within lines 6 to 23 are not necessary.

Pages 9-221 to 9-225: Move the content of section 9.6.4.5 and 9.6.4.6 to Sections 9.2 and 9.5 as appropriate. It does not need to be repeated here.

P9-235 bottom paragraph (line 26); It would be useful to provide the percent O3 response for all clones of *Populus* studies to show the full range of responses. Stating only that the mean response was an 18% reduction doesn't do justice to the extent of the field study. The authors might also comment on our knowledge of the representativeness of these clones to the natural populations of aspen across the US.

Is there any data from the SoyFACE project to be discussed in this document? Did I miss it?

P9-235 Laurence et al. 2000 cited reference is missing from list.

P9-245 lines 4 and 5: The Rhinelander FACE study shows that it is indeed feasible to expose long-lived plants in near natural settings. The scientific community has simply not called for

additional studies of this kind. However, pending reports of the ecosystem working group for the CCSP are calling for just such studies that would include O3 as a key variable.

P9-256 lines 3 and 4: The Johnson and Taylor 1998 reference is missing from the list.

P9-256 line 28: The '*P.*' should be spelled out. A number of options are possible at this point in the document.

P9-259 Table 9-22: Spell out the P for Populus on the 11th line down.

P9-261 Laurence et al. 2000 cited reference is missing from list.

P9-262 line 1: Spell out 'A.'

P9-270 line 11: Please provide a primary reference for the statement that drought can make trees susceptible to insect and pathogen attack.

P9-277 line 22: McAinsh et al. 2002 is missing from the reference list.

P9-277 line 26: McLaughlin et al. 2004 is missing from the reference list.

P9-297 Laurence et al. 2000 cited reference is missing from list.

P9-303 and 305: Laurence and Anderson 2003 reference cited but missing from list.
Laurence JA, Anderson CP (2003) Ozone and natural systems: understanding exposure, response, and risk. Environ Int. 29:155-160

P9-287 line 22: Delete 'and movement'.

P9-289 line 31: Samuelson and Kelly 2001 should be added to this list of references.

P9-289 line 31 and P9-290 line 1: This statement about the predisposition of seedling vs. tree response is species dependent. The current sentence is not true for northern red oak.

P9-290 line 15: Quercus 'robur' should be 'rubra', and add Hanson et al. 1994 to the list of references.

Section 9.7.9 doesn't reach a clear conclusion.

P9-303 Laurence et al. 2000 cited reference is missing from list.

P9-307 line 4: Kohut et al. 2000 is missing from the reference list.

P9-308 line 12: Should 'robur' be 'rubra'?

P9-308 Laurence et al. 2000 cited reference is missing from list.

P9-309 Laurence et al. 2003 cited reference is missing from list.

Laurence JA, Retzlaff WA, Kern JS, et al. (2003) Predicting the regional impact of ozone and precipitation on the growth of loblolly pine and yellow poplar using linked TREGRO and ZELIG models. For. Ecol. Manag. 174:607-607.

P9-314 and 315: Laurence and Anderson 2003 reference cited but missing from list.

P9-316 line 25: Daily 1997 is missing from the reference list.

**P9-331 line 1: Delete the word 'belowground'.

**Section 9.9

Although many of the paragraphs are excellent, the summary section is too long. Try to avoid just repeating material covered earlier and focus on the conclusions that the reader should remember as a new or key result from research conducted from 1997 through early 2005.

**P9-329 lines 29 to 31: The sentence starting on this page is an example of what I consider to be repeated discussion. The key conclusion was stated in the previous two sentences.

**P9-333 lines 36 to 43 continued on page 9-334: This material need not be in the conclusion section.

**P9-334 to 9-337: Section 9.9.4 wanders and doesn't reach succinct conclusions. Please consider reducing the text in this section.

**P9-338 lines 1 to 3: This statement should be placed right at the beginning of Section 9.9.5. In its present location its impact is lost.

**Section 9.9.5 could be streamlined by eliminating lines 4 to 29 on page 9-338 (i.e., it only needs to appear in the earlier discussion). Similarly, lines 6 to 21 on page 9-339 wanders without reaching a conclusion.

**To the extent that there is scientific agreement on the appropriateness of ozone exposure or dose indices they should come through strongly in Section 9.9.5. Something like the following statement might be considered: "Vegetation growth and yield responses to ozone are appropriately characterized by a cumulative exposure/dose index with crop species being generally more sensitive than deciduous trees, which tend to be more sensitive than coniferous trees." I know that some statements to this extent are already in the text, but they are hidden by extended extraneous discussion.

**If appropriate for inclusion in the AQCD, Section 9.9 also needs a strong statement about the appropriateness of the state-of-science for evaluating the current 8-h NAAQS for protection of vegetation of the United States.

**Section 9.9.6 also wanders without reaching clear conclusions. Try to keep material that is repeated discussion out of this section. For example, the text on lines 9 to 14 of P9-341 is out of place. Lines 21 to 31 on P9-342 and lines 1 to 3 on P9-343 also seem redundant.

P9-344: Laurence and Anderson 2003 reference cited but missing from list.

**P9-344 lines 29 and 30 continued on the next page: I believe current work from the *Populus* and Soybean FACE studies has shown that such a negating response will and does scale.

**Section 9.9.8 is not very useful as written. If it contained a specific set of action items for future research attention it would be useful.

References not cited that might be considered for the current document:

Andersen CP, Grulke NE (2001) Complexities in understanding ecosystem response to ozone. Human and Ecological Risk Assessment 7:1169-1182.

Berger S (2002) Jasmonate-related mutants of Arabidopsis as tools for studying stress signaling PLANTA 214:497-504.

Bielenberg DG, Lynch JP, Pell EJ (2002) Nitrogen dynamics during O-3-induced accelerated senescence in hybrid poplar Plant Cell and Environment 25:501-512.

Bjorn LO, Callaghan TV, Gehrke C, et al. (1999) Effects of ozone depletion and increased ultraviolet-B radiation on northern vegetation. Polar Research 18:331-337.

Bruno F, Cocchi D, Trivisano C (2004) Forecasting daily high ozone concentrations by classification trees Environmetrics 15:141-153.

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2005 First External Review Draft of the
Air Quality Criteria for Ozone and Related Photochemical Oxidants

Final Comments on Chapter 10
Submitted by Paul J. Hanson on 9 May 2005

Even though the available data are limited and preclude final conclusions, Chapter 10 provides a succinct and instructive summary of the influence of Tropospheric ozone on the penetration of UV-B flux to the earth surface, and the contribution of anthropogenic ozone as a greenhouse gas to issues of climate change. Unfortunately, the overall conclusions in section 10.3.6 are vague. What is the take-home message? Do we have sufficient information to judge the importance of ozone's role in UV penetration to the earth's surface and its role as a greenhouse gas?

The following comments point out errors or concerns that should be addressed by the authors:

P10-2 Line 2: WMO/UNEP 2002 is not in the reference list.

P10-9 Line 1: McKenzie et al. 2001 is not in the reference list.

P10-9 Line 11: The use of ppbv at this point (and in this section) is inconsistent with much of the document. I would convert the values to ppm.

Section 10.2.2

Although I recognize that it is important to provide quantitative and statistically robust information on the exposure of humans to ultraviolet radiation, some portions of this section come across as a discourse on the obvious. That is, the section essentially concludes that people that work outside or spend disproportionate amounts of recreation time in the sun are predisposed to UV exposure. Most people would find this to be an obvious conclusion. A brief explanation added early in Section 10.2.2 to explain why the quantitative evaluation of human exposure to UV-B is scientifically necessary would change the impression that I had while reading this section.

P10-19 Line 11: The van der Leun and de Gruijl 1993 reference is missing from the list.

P10-21 Line 19: Is 'Ruenger' spelled correctly? There is a similar reference (i.e., Runger) in the list on P10-55.

P10-22 Lines 10 to 18: Do we know if the increased rate of melanoma is the result of changing human activity patterns (i.e., more outside work/leisure time) or is this truly a change in the level of UV reaching the earths surface?

P10-27 Line 4: I had to look up the meaning of 'watermen'. Listing some examples (fisherman, boatman…) might help some readers of the AQCD.

P10-27 Line 16: The Longstreth et al. 1995 reference is missing from the list.

P10-30 Line 13: The US EPA 2002 reference is missing from the list.

P10-31 Line 29: The Arrhenius 1896 reference is missing from the list.

P10-32 Lines 10 to 11: The sentence could read as "This section summarizes…and describes…

P10-32 Line 14: The words 'will be' should be changed to 'are'.

P10-32 Lines 21 and 22: Can a reference for this statement be provided?

P10-32 Line 25: A reference should be provided for the IPCC 1990 and 1995 reports.

P10-33 Line 17: The reference for IPCC 1998 is missing from the list.

P10-33 Line 30: The meaning of 'ecological balances' is unclear. I would just delete the following words and punctuation 'in ecological balances;'

P10-35 Line 12: Bernard et al. 2001 is not in the reference list.

P10-35 Line 13: I would cite the 2001 IPCC report (Climate Change 2001: Impacts, Adaptation, and Vulnerability) in addition to the 1998 report. The 2001 report includes a region-by-region summary relevant to this statement.

P10-37 Line 15: The Ahrens 1994 citation is not in the reference list.

P10-39 Line 4: The Houghton et al. 1990 citation was not in the reference list.

P10-43 Line 2: You might change 'Many fewer' to just 'Fewer'.

P10-44 Lines 7 to 9: A reference for this statement is needed.

P10-45 Line 24: The IPCC 1996 reference is missing from the reference list.

In a number of Tables and text locations IPCC (2001) needs to be changed to either 2001a or 2001b. Do a search on the entire document to locate and adjust these citations.

P10-48 lines 20-22: Add a reference to IPCC 2001 Third Assessment Report.

I don't believe that the following listed references were used:

Evans et al. 2004
Fiore et al. 2002
Gauss et al. 2003
Liao et al. 2004
Mickley et al. 2004
Shindell et al. 2003
Wigley et al. 2002
Woodward and Boffetta 1997
Zeng and Pyle 2003.

Dr. Jack Harkema

Individual Comments on the First Draft AQCD Chapter 5 (Toxicological Effects of Ozone and Related Photochemical Oxidants in Laboratory Animals and In Vitro Test Systems)

Jack R. Harkema
May 3, 2005

General Comments:

Overall this chapter is well written and adequately covers the new scientific literature, since 1996 (last criteria document), related to the toxicological effects of ozone in laboratory animals and in vitro test systems. This is a thorough and comprehensive review of the recent literature in this field of study. The authors are to be commended on their thorough and comprehensive review and documentation of this body of literature. In general the authors have concisely and clearly stated the important findings of the individual studies and the major contributions each study has made to our knowledge of the toxic effects of ozone that are particularly relevant to human health. There are areas of this text, however, that could be improved. Some suggestions for improvement are listed below.

1) The overall framework of this chapter is well designed and appropriate for the material presented. The construction of each section with a brief introduction and historical background, followed by detailed descriptions of the new studies, and ending with a summary/conclusion of the major findings provides the reader with a format that is easy to follow. However, some sections contain introductions that are too brief with not enough background information to adequately set the stage for the detailed descriptions of the new work since the last criteria document. For example, there is inadequate description in the morphology section on the site-specific nature of ozone-induced injury. As the number of new studies on ozone toxicity diminish, it is important for the authors of the criteria document not to forget older, but key, toxicology studies that have provided insight into our understanding of ozone toxicology and into the potential risks of ozone exposure to human health.

2) Descriptions of the exposure regimen for the individual studies are inconsistently reported in this chapter. It is necessary at times to look up concentrations and durations of exposure in the annex to find this information. This disrupts the flow of the read and is not necessary. In addition, there are places in the text where it is not clear what animal species were used in the study. These problems may be the result of the new structure of the document with the addition of an "annex" to each chapter that covers in more detail the specifics of each reported study. Personally, I find this structure cumbersome and a duplication of effort. The main chapter becomes "watered down" and without the necessary specifics that are found in the annex. Furthermore, a large part of the material in the text of the annex (outside of the tables) becomes a reiteration of the text found in the main chapter. I suggest either 1) adding more detail to the main chapter along with

the tables and deleting the annex or 2) providing more detail in the main chapter and leaving only tables in the annex.

3) There is a lack of emphasis on the importance of both concentration and duration (time) of exposure (CxT) and its usefulness in understanding "dose/response" relationships. Too often the descriptions of the studies do not include the length of the exposure and the reader gets the impression that all that matters for a "response" is the ozone concentration. Though concentration may be the most important for some responses, the length of exposure is crucial for others.

4) Many of the section summaries are just a short list of the major results from some of the studies and contain little in the way of critique and meaningful conclusions.

5) There is little discussion anywhere in this chapter on the appropriateness of the exposure concentrations (or exposure durations) used in the animal or in vitro studies for predicting risk to human health in an environmental setting or for even determining a basic understanding of ozone toxicology. When is it appropriate to expose a mouse to 2 or 3 ppm ozone (or cultured cells to 1 ppm) and when is it not? This interpretation is crucial for determining risk. There should be some discussion (or interpretation) of this issue in the document. What studies were adequately designed and what studies were not?

6) An overall summary/conclusions section should conclude the chapter.

Some Specific Comments:

1) Some acronyms are not defined in the body of the text.
2) Why is section 5.2.1.5 (Protein Synthesis) limited to collagen.
3) It is surprising the limited amount of data in section 5.2.1.6 Gene Expression. May need to change the title to differential gene expression, since many other studies reported in this chapter looked at changes in the expression of only a few selected genes after ozone exposure.
4) Section 5.2.2.2 (Alveolar Macrophages) contains studies that used a tremendous range of concentrations and durations of exposure. The authors provide little insight in the investigators rationale for choosing these exposure parameters.
5) Introductory paragraph in section 5.2.2.4 (Interactions with Infectious Microorganisms) is an example of text that needs references to tie the past with the present.
6) Section 5.2.3.1 L16-17. The time of maximal increase in BALF protein, albumin and PMN is also dependent on the duration of the "acute" exposure. It would be better to state the time from the start of the exposure when these parameters peak rather than the time from the cessation of the exposure.
7) Section 5.2.3.2 (Concentration and Time of Exposure) is one of the few places in the chapter where CxT is discussed and here the discussion is too brief and too imprecise, and not referenced. The authors should have dug more into past studies to address this issue.

8) Section 5.2.3.6 (Summary and Conclusions – Inflammation and Permeability Changes) L11-21. This material was not covered in the previous sections, but yet was summarized in this section.

9) Section 5.2.4 (Morphological Effects) L8 "natural seasonal patterns" should be replaced with "episodic exposures."

10) Section 5.2.4.2 (Summary – Long Term Morphological Effects). There is no summary of the finding on the long term effects on the nasal mucosa that was discussed in detail in the previous sections.

11) Section 5.2.5.3 (Ozone Effects on Airway Responsiveness). Subsections on *Airway Responsiveness to Asthma and in Infants* could be shortened or deleted when not pertinent to the discussion on ozone.

12) Sections on *Pulmonary Function* and *Complex Mixtures* were well written and should be used as models for the rest of the chapter.

Dr. Philip K. Hopke

Comments on the Ozone Criteria Document
Philip K. Hopke
May 2005

Comments on Chapter 2

It is important to remember that the original NAAQS was for photochemical oxidants and it is the combination of ozone, PAN, peroxides, etc. can produce a variety of effects. A key aspect of the effectiveness of ozone as a NAAQS indicator is that it must be an effective surrogate for all of the collection of photochemical oxidants that could generate health and welfare effects. There is essentially no discussion of this key issue in the document. In this chapter, there needs to be a more extensive discussion of the oxidative reaction products. There is a good description of the initial steps in the ozone formation process and the oxidation of various classes of reactive hydrocarbons, but it needs to be extended to include the oxidative products.

Page 2-14 line 1. We are still measuring ozone and temperature. Why not prepare up-to-date plots rather than rely on plots from the 1980s and having to put caveats in the CD?

Comments on Chapter 3

To follow up on the oxidative species discussion above, this chapter needs to present what evidence is available with respect to correlations between the various oxidative products and ozone. Since changes in the concentrations, correlations and patterns of these other reaction products could produce significant changes in the resulting effects, there needs to be careful treatment of what is known and what is not so that a convincing argument can be made that ozone remains a reasonable surrogate species.

It is now recognized that ozone is a transported pollutant. How much is known (if anything) do we know about the transport of other oxidants? How stable are the oxidants likely to be? There needs to be an adequate discussion of the potential of transported co-pollutants.

There are particulate ROS species that derive from the photochemical reactions. There needs to be an adequate discussion of ROS species, gaseous and particulate.

The discussion in the chapter and the appendix are focused on other primary pollutants (NO_x, SO_2, etc) rather than the other oxidative products. Only NO_y is discussed. There needs to be an appropriate discussion of this key issue.

There have been major changes in the nature of anthropogenic VOC emissions given the change since the 1970s in the nature of gasoline (removal of lead, addition of oxygenates, change in engine technology). Has that resulted in changes in the mixture of reaction products? There needs to be a very clear and careful discussion of this issue in this chapter since it is the fundamental underpinning of having an “ozone” standard. Otherwise we are doing lamp post

science simply because ozone is easy to measure and are potentially making major errors with respect to protecting public health and welfare.

A General Question on Toxicology Results:

Are any of the O_3 only exposure toxicological studies really have any relevant to understanding the mixture of photochemical oxidants to which we are exposed in the ambient atmosphere? We use ozone as an easily measured surrogate for the panoply of oxidants that are present in the air with many of them having far more oxidative capacity than ozone. Thus, basing the level of the standard on responses of animals or humans to ozone alone could be highly misleading in terms of the effects of the other oxidants that correlate with ozone and for which we use ozone as a surrogate. Thus, only smog chamber studies in which the ozone is produced by appropriate atmospheric reaction sequences are likely to result in exposures that are analogous to those in the ambient air.

Question A1: To what extend is the document format restructuring useful and desirable? Can the restructuring be further improved? If so, how?

I think the general concept of shorter, integrated chapters with appendices is a major step forward. However, putting the annexes directly after the chapter still produces the negative impression of a massive document. It would work better to have volume 1 be all of the chapters and the annexes in volumes 2 and 3. This packaging would greatly improve the view of the document and really make it easier to use. It also appears that the welfare effects chapters have not been handled in the same manner as the other ones. It would really be useful to have all of the chapters done in the same manner.

Dr. Michael T. Kleinman

Individual Comments on Chapter 4 – Dosimetry
U.S. EPA Ozone AQCD (first draft).
CASAC Ozone Review Panel.
Michael Kleinman, Ph.D. 5/10/05

4-2 L 7 Insert a specific definition for DOSE. It should not be 'subjective'.

4-3 L 13 by 'discounted' is it meant "ignored"?

4-4 L 3-5 other factors should be noted. For example, O3 has limited solubility in aqueous fluids and saturation of the solution could also occur. In addition the O3 level (2ppm) is fairly high and these results might not be representative of what happens under more ambient-like conditions.

4-4 L 29 Is it speculation that the O3 was taken up in the lower airways or was it measured?

4-5 L 25 define how inhaled dose was calculated

4-8 L 2 "absorbed fraction (AF)" Earlier FA was used for fraction absorbed. Are these the same? If so the terminology should be constant throughout the text.

4-12 L21-31 The interpretation here is too general and unclear.

4-14 L 13-18 and subsequent The mechanisms of ozone effects at high concentrations are not always representative of those at more realistic levels. Drawing conclusions about the suitability of animal models based on exposures at 1 ppm and above is unwise.
4-15 L10 Change They to The
4-16 L16 at what level of exercise?

Individual Comments on Chapter 5 – Photochemical oxidants in laboratory animal and in vitro test systems. U.S. EPA Ozone AQCD (first draft).
CASAC Ozone Review Panel.
Michael Kleinman, Ph.D. 4/29/05

In general this Chapter is well written and comprehensively reviews the recent publications on ozone health effects in controlled exposures. The annex provides very useful information but there is considerable overlap with the main text.

I have some specific comments:

5-4 L 23 – The dissociation between airway function and inflammation could suggest that O_3 operates through multiple mechanistic pathways. For example there may be differential stimulation of T_H1 and T_H2 immune pathways that may be moderated by time and location in the airway.

5-12 L7 – All O_3 concentrations should be in the same units, most likely ppm.

5-17 L14-19 More detail should be provided on CxT relationships. This is critical to understanding some of the observed differences in responses and is also implicit in the setting of a standard.

5-22 L6-9 The effects on PAF imply changes in clotting and thrombolytic effects. This information should be included in the discussion of systemic effects and may be important in analyzing epidemiologic associations to heart attack and stroke.

5-21 L17 I presume the reference is to 'various' rather than varying levels of O_3.

Individual Comments on Chapter 6 – Photochemical oxidants in laboratory animal and in vitro test systems. U.S. EPA Ozone AQCD (first draft).
CASAC Ozone Review Panel.
Michael Kleinman, Ph.D. 5/9/05

This chapter could benefit from additional critical interpretation. For example, p 6-7 L 15-18 discusses the lower R for 0.08ppm exposures vs. that at 0.3 ppm. It might be more relevant to examine the slopes of the relationship and ask if they are different. The R values are strongly influenced by measurement variability (both of the O3 and the PF). The discussion of triangular exposures on pg 6-8 L 14-15 needs to be better discussed. The point is skirted that as the exposure concentration is reduced from the peak level, a point is reached at which the response begins to decrease. It is important to indicate whether the response returned to normal or not. A graph would be very helpful and would help put the recovery curve (Figure 6-2) into better context.

P 6-12 L 15 Change on to 'of''

P 6-23 L 16-17 It might be useful to indicate that SS smoke contains endotoxins which might contribute to the potentiation of O3 effects.

Responses to Charge Questions Posed by Lester D. Grant (letter dated 4/21/05) Pertaining to Chapter 5 – Photochemical oxidants in laboratory animal and in vitro test systems. U.S. EPA Ozone AQCD (first draft).
CASAC Ozone Review Panel.
Michael Kleinman, Ph.D. 4/29/05

Charge Question C3a(i) To my knowledge, no significant animal studies were missed in Chapter 5.

Charge Question C3a(ii) Animal studies support the contention that O3-induced inflammation facilitates development of allergies to antigenic proteins (e.g. house dust mite). In sensitized animals subsequent repeated exposures cause inflammatory responses and eosinophilia. Given that humans in epidemiological studies are subjected to antigens as well as O3, one should consider the possibility of a joint or exacerbating effect of the antigens during the period of O3-induced hyperreactivity.

Charge Question C3b(i) The new mechanistic data are adequately covered.

Charge Question C3b(ii) The gene-environment interaction for mice lends some biological plausibility to the discussion of differential sensitivities to ozone among humans. However sensitivity is much more complex and age, gender, nutrition, activity levels, among other factors should not be de-emphasized.

Charge Question C3b(iii) The OVA-mouse models are relatively widely used and characterized. However, there is a great deal of variability between different strains of OVA-sensitized mice with respect to the allergic manifestations evoked. To my knowledge, no single model adequately represents human asthma, but may represent specific facets of the airway disease state.

Charge Question C3c The section on cardiovascular effects was rather compressed. There are differences in rodent responses vs. human responses to O3. Humans in clinical studies and dogs exposed to O3 showed some tendency to increased heart and respiratory rates rather than the bradycardia demonstrated in rats. We therefore need to be cautious in evaluating this data.

Charge Question C3d The number of studies examining pollutant-related systemic effects is expanding. The current discussion adequately covers the available literature. This information could assume greater importance in future discussions and should be retained in the document.

Charge Question C4a The morphologic data suggests remodeling of the lung and potentially long term changes (e.g. bronchiolization of distal airways) that could provide reasonable plausibility for observed losses in PF.

Charge Question C4b There are very limited data regarding genotoxicity/carcinogencity effects of O3. It is not ruled out that O3 could be a co-carcinogen and act as a promoter by stimulating hyperplasia. Epidemiologic exposures are to O3 in combination with a complex particle-gas mixture that nearly always contains known carcinogenic components.

Dr. Allan Legge

May 17, 2005

REVIEW COMMENTS: Allan Legge

Air Quality Criteria for Ozone and Related Photochemical Oxidants
(First External Review Draft) January 2005 EPA/600/R-05/004cA

Chapter 9 - 'Environmental Effects: Ozone Effects on Vegetation and Ecosystems' and Chapter 3 - 'Environmental Concentrations, Patterns, and Exposure Estimates' where related to Chapter 9.

Overall Comments:
1. Chapter 9 is a comprehensive compilation of the scientific information published since the 1996 Air Quality Criteria Document (AQCD) entitled "Air Quality Criteria for Ozone and Related Photochemical Oxidants" (July 1996, EPA/600/P-93/004bF) with the inclusion of earlier published information to provide the needed context. The authors of the 'chapter' have made a good start. That being said, there is a need for the current text to be streamlined and reorganized to remove the frequent repetitions of almost the same information in different parts of the text. Further, this information needs to be consistent. One has the impression that the authors of the different sections in the text had differing views on the same information and that these differing views were never reconciled when the final draft text was compiled. Many of these inconsistencies are noted under 'Specific Comments'. From the standpoint of overall chapter format, it would be helpful to the reader for Chapter 9 to have the same format as the other chapters in the First Draft AQCD. The authors should also consider changing the title of this chapter to "Environmental Effects of Ozone and Related Photochemical Oxidants" to be consistent with the chapter titles for human health. While ozone concentrations can be measured in the field, 'related photochemical oxidants' may be playing a role as well.

2. Section 9.5 Effects-Based Air Quality Exposure- and Dose-Response Indices; and Section 9.6 Ozone Exposure-Plant Response Relationships.

These two sections need a considerable amount of work. The information presented in these two sections is contradictory as well as inconsistent with information and understanding found in other portions of the text. There is repeated confusion, for example, between ozone exposure-response and ozone dose-response. Reference is made to exposure indices in the text before the text explains what exposure indices are. The authors cannot assume that the reader will be familiar with the discussion in Chapter 3, pages AX3-2 to AX3-5 on this matter. The authors initially cannot seem to decide whether the experimental results from open-top chamber (OTC) experiments are environmentally relevant yet go on later in the text to assume that they are. One has the impression that the authors have drawn their conclusions before writing the current First Draft AQCD text by repeatedly indicating that the 1996 AQCD was correct after all.

There is a need for a broader and more balanced approach to the scientific information both here as well as in Chapter 3 in 'Characterizing Ambient Ozone Concentrations' on pages AX3-2 to AX3-5. Further, discussions of a potential secondary standard are inappropriate in a 'criteria document' which is intended to be a summary and synthesis of the 'state-of-the-science'.

3. There are discussions scattered through the text regarding the European approach to ozone management/control. This has merit but has been done in a very piecemeal and repetitive manner. It would be helpful to the reader for this material to be brought together earlier in the text. The history of this approach as well as the current status of the approach would be more useful. Further, there is confusion in the text regarding the European terminology when the terms 'critical levels' and 'critical loads' are treated as being the same when they are quite different.

4. The text is overly optimistic about the advancements in the state-of-the -science with respect to ozone/vegetation effects research results since the 1996 AQCD. Only a very limited amount of ozone/vegetation effects research has been carried out in the US due to the lack of funding. This can be clearly seen in the text with the heavy reliance on the results of European research efforts on 'critical levels' for ozone.

5. There are discussions scattered through the text regarding the use an application of EDU (ethylene diurea). It would be beneficial for the reader if all of this material were brought together and referenced in other sections as appropriate.

6. There is a problem with tense throughout the text particularly using the present tense when the past tense should be used. The past tense/present tense problem is most apparent in the text where the authors are relating pre- and post- 1996 AQCD information.

7. There are references missing from the reference list yet included in the text as well as the reverse. Further, there are references in the text which refer to a paper by a senior author that has more than one publication in a given calendar year in the reference list. Frequently, the reference list has these publications listed as (a) or (b) while the text does not make this distinction. The references in the text and the reference list need to be carefully cross checked for completeness and accuracy.

8. All abbreviations and acronyms need to be defined in the text when they are first used. Further, a more complete listing of the abbreviations and acronyms used in the text is required at the beginning. The current listing of 'Abbreviations and Acronyms' provided on pages III-xxi and III-xxii is very incomplete and has duplications.

9. A list of the important terms used in the text along with the definition of those terms would be very beneficial to the reader.

10. There are a number of places in the text where the authors refer to a 'recent' paper or a 'recent' review in which the paper or review is 10 years or more old. For

consistency, it is suggested that only a paper or review which is 5 years old or less be considered ‘recent’.

11. Many plant names are used in the text. For consistency, the common name should be followed by the Latin name in italics and in parentheses. In a given section once the common name and Latin name have been mentioned, one can use just the common name. The common name should not be in italics.

12. A summary of research needs regarding ecosystems is provided for the reader which is good. That being said, there needs to be an overall summary of the research needs as identified throughout the text. This would be extremely useful to the reader as it would provide clear directions where the science and understanding of ozone/vegetation effects research needs to go in the future.

Specific Comments:
1.Page 9-3, lines 3-5. ‘field observations’ should include biomonitoring.

2. Page 9-3, lines 6-10. The issue of ‘uncertainty’ needs to be incorporated.

3. Page 9-3, line 19. Is the “Karnosky et al. (2001)” reference (a) or (b)?

4. Page 9-4, line 9.
The “Heagle et al. (1994a)” reference is not listed as (a) or (b) in the list of references on page 9-364, lines 3-6.

5. Page 9-5, line 10.
The use of the word ‘recently’ when referring to papers published in 1995 and 1996 is questionable.

6. Page 9-6, line 24. The word ‘drops’ should read ‘crops’.

7. Page 9-6, lines 29-31 and page 9-7, lines 1-3.
Reference is made to the idea that ‘branch chambers’ are ‘essentially large cuvettes’. It would be more accurate to indicate that branch chambers are like large cuvettes without the precise temperature control characteristic of cuvettes.

8. Page 9-8, line 24.
The reference “Lee et al. 1975” is from a ‘Proceedings’ that is not readily available. The following reference is suggested as a replacement:

> Preston, E.M. and Lee, J. J. 1982.
> Design and performance of a field exposure system for evaluation of the ecological effects of SO_2 on a native grassland.
> Environmental Monitoring and Assessment 1: 213-238.

9. Page 9-10, line 4. Should read “… as well as the constant turbulence”

10. Page 9-11, lines 1-4.
This is a critique of ‘plume systems’ which makes some excellent points. That being said, it is noted that “they fail to achieve homogeneity of the air”. While this is true, the underlying problem is the lack of an adequate number of air quality measurements.

11. Page 9-11, line 16. N_2O_5 is the acid anhydride of nitric acid.

12. Page 9-11, lines 20 and 22. What is meant by ‘recent’?

13. Page 9-12, lines 18 and 22.
Reference is made to “The European standard” and “the seasonal exceedances of the standard” in the context of the AOT40 index. Two points: (1) the AOT40 index in not a standard in the US sense but rather a NOx/VOC management tool for the European Union; and (2) This is the first reference in Chapter 9 to an ‘index’ (refer to ‘Overall Comments’ 2 and 3).

14. Pages 9-14 to 9-16.
This is the first discussion of EDU. Refer to ‘Overall Comment’ 1 and 5. The discussion of EDU is scattered throughout the text.
15. Page 9-15, line 1,10, 15 and 17.
Reference is made to the AOT 40 index without any previous explanation of the term ‘index’.

16. Page 9-17.
i) line 1. An example of a ‘detector’ should be provided such as ‘milkweed’ (*Asclepias syriaca*) to be consistent with the example of the ‘sentinel’ provided earlier in the sentence.
ii) line 10. A more appropriate reference would be Krupa et al. (1998) which is the ‘Ozone’ chapter within the ‘Flagler, 1998' reference. The reference would read as follows:

Krupa, S.V., Tonneijck, A.E.G. and Manning, W.J. 1998.
Ozone: In Recognition of Air Pollution Injury to Vegetation - A Pictorial Atlas, Second Edition, R.B. Flagler (Editor), Air & Waste Management Association, Pittsburgh, Pennsylvania. pp 2-11 to 2-28.

17. Page 9-19, lines 4-24.
It should be noted somewhere in this short section that other air pollutants may be playing a role as well as ozone.

18. Page 9-20, lines 9 and 13.
This is the first reference to the SUM06 and W126 exposure indices. As noted earlier, there needs to be an explanation of the term ‘index’ and the various forms that are used before these indices are used in the text. One cannot assume that the reader will be aware of the discussion in Chapter 3 on pages AX3-2 to AX3-5.

19. Page 9-20, lines 22 and 27.
There are two Vollenweider et al. (2003) references on page 9-393 of the reference list which are indicated as (a) and (b) but are not indicated as (a) or (b) in the text. That being said, the (a) and (b) designations in the reference list are not correct. These should be reversed with the earliest publication in 2003 being given the (a) designation and the later publication in 2003 being given the (b) designation.

20.Page 9-22, line 16. Should read " (Pinus taeda)".

21. Page 9-23.
i) lines 17-18. What are " firm O_3 effects"?
ii) line 23. What does "O_3 concentrations were low" mean? This needs to be put into context.

22. Pages 9-24, lines 4-12 and page 9-25 lines 11-12.
This section on 'Calibrated Passive Monitors' needs work. On page 9-24, lines 7-9 it is indicated that ozone passive samplers provide a measure of total exposure for the period they are exposed which is "usually 7days". Ozone passives are exposed anywhere from 7 days to a month. The text then indicates that " - - they produce a measurement that resembles the instrumentally derived exposure SUM00 index." While it is true that one will get a measure of total ozone exposure for the period of time that the passive is exposed, it is common for this number to be divided by the number of hours of exposure to get an hourly average ozone concentration for the exposure period. Krupa et al. (2001) were able to mimic the underlying frequency distribution of hourly ozone concentrations from an ozone passive by comparison with a co-located continuous ozone monitor by using a Weibull probability model. This was taken further by Krupa et al. (2003) with the development of a multivariate, non-linear statistical model. The point here is that there is greater potential for passive ozone samplers than the text at this point would suggest. (Note: The two Krupa et al. (2001) and (2003) references are in the reference list, page 9-370, lines 40-44).

23. Page 9-27 and 9-28, Section 9.2.5 Improved Methods for Defining Exposure.
This Section is totally out of place. First, there has been no discussion in the text, up to this point, explaining how 'exposure' has been defined. Various exposure 'indices' have been mentioned but that is all.

24. Page 9-27, lines 2-3.
What is the "standard elevation above ground level"? This is important because the ozone concentration at some 'standard measurement height' may not be the same as the ozone concentration at plant height. This is especially true for most crop plants as well as natural grasslands. The net result is that ozone exposure of the crop plants will be overestimated as will the exposure index and the predicted crop loss derived from these ozone measurements [See Grünhage et al. (1999), complete reference found on page 9-363, lines 34-35].

25.Page 9-28, lines 11 and 13.

i) line 11. This should read “Efforts to develop regional scale models of O_3 “.

ii) line 13. Is the “Emberson et al. (2000)” reference (a) or (b)? See page 9-357, lines 31-34.

26. Page 9-29, lines 27-28.
It is noted that “Various forms of compensation, especially the stimulation of new leaf production and of higher photosynthetic performance of new leaves have been reported.” A reference is required to substantiate this statement.

27. Page 9-31, lines 24-25 and page 9-35, lines 6-7.
On page 9-31 it is noted that “Plant adaptations for surviving O_3 include exclusion or tolerance”. On page 9-35 it is noted that “Plants respond to O_3 similarly to other stressors on several levels: exclusion, tolerance and repair”. The same two references are used in both cases; Levitt, 1972 and Tingey and Taylor,1982. How is adaptation different from plant response?
28. Page 9-32, line 5. Suggest that ‘fumigation’ be replaced with ‘exposure’.

29. Page 9-34, lines 7- 10. These two sentences need to be rephrased. The word “unimportant” is inappropriate. It is important for the plant being studied to provide, at the very least, an adequate cross section of plant physiological processes.

30. Page 9-34, line 30.
What is meant by “- - to index injury”? Should this read ‘indicate injury’?

31. Page 9-35 line 14.
Should add ‘Mukammal (1965)’ as a reference.

32. Page 9-35, lines 22, 25, 27 an 28.
The term ‘dose’ is used rather narrowly here. This needs to be put into better context so as to avoid confusion when the term ‘dose’ is used in other sections of the text.

33. Page 9-38, Figure 9-5. What are the units in the upper right hand corner?

34. Page 9-45, Table 9-7.
Under ‘Double bond reactions’ ethylene appears to be missing.

35. Page 9-47, Figure 9-9.
The units are mixed between (b) and (c) above and the underlying legend for (b) and (c). The ozone concentration in (c) in the legend is missing. Keeping with ‘the mixed units’ it should read ‘0.5 ppm’. The authorship of the reference in (c) in the legend should read ‘Runeckles and Vaartnou, 1997'.

36. Page 9-74, line 18.
Should read “- - in which areas of ambient CO_2 (daytime 360 ppm)”.

37. Page 9-75,
The term ‘C_o’ needs to be defined somewhere in the text. It is not indicated in footnote 13.

38. Page 9-75, line 5. Should read “Farquhar et al. (1980) were”.

39. Page 9-86, lines 12-13.
It is stated that “- - - the purpose of this document is to support the review of the O_3 NAAQS, including standards to protect vegetation”. The authors must be very careful here. The purpose of the Ozone CD with respect to welfare is to provide a review and synthesis of the current state-of-the-science regarding the effects of ozone and other photochemical oxidants on vegetation and ecosystems. It is not the purpose of the Ozone CD to evaluate standards to protect vegetation. This is the role of the Staff Paper prepared by OAQPS after the Ozone CD has passed scientific review by CASAC.

40. Page 9-89, line 28. Delete the word ‘for’.

41. Page 102, lines 25-28. Suggest this be reworded for clarity. “Ozone had an indirect adverse effect on pine growth - - because the O_3 increased competitive pressure of the grass which resulted in a major reduction in pine growth.”

42. Pager 9-14, lines 10- 11. Should read “- - relative humidity (RH,”.

43. Page 9-116, lines 20-23.
The sentence as worded is awkward. Suggest that it read “ The 1996 ozone criteria document - - - and the wide range of species had limited the number of experimental investigations - - .”

44. Page 9-118, line 23. Suggest this read “The ambient air may have pollutant gases other than O_3 - - .”

45. Page 9-118, lines 28-31. Need to add ‘$(NH_4)_2SO_4$ ‘.

46. Page 9-120, line 27. There are two ‘Nussbaum et al. (2000) references in the reference list on page 9-380, lines 13-17. Neither are designated (a) or (b). Which reference is the correct one?

47. Page 9-121, lines 12-15.
The authors need to re-evaluate the Mills et al. (2000) paper. One must be very careful using the results of ANN (artificial neural network) models. Ambient concentrations of NO have never been found to be phytotoxic except at very high concentrations. It is not reasonable to suggest that “minimum daily NO concentrations was a significant contributor to adverse effects.”

48. Page 9-153, lines 26-31 and page 9-154, lines 1-8.
This introductory paragraph is very balanced and objective until the sentence on lines 5-

8 on page 9-154. This sentence is inappropriate and very misleading to the reader. It suggests that the needed research has not been done because the personal interests of individual groups of researchers have not been correctly focused and that the needed research can only be accomplished by coordinated systematic investigations. While there is merit in coordinated systematic investigations, there needs to be 'funding' for such undertakings. The 'funding' for such investigations has been lacking since the completion of the last Ozone AQCD in 1996. It is inappropriate to blame the scientific community for this lack of funding and to criticize those scientists in the ozone/vegetation effects community that have kept this type of research going despite the lack of financial support.

49. Pages 9-157 to 9-181, Section 9.5 Effects-Based Air Quality Exposure-and Dose-Response Indices.
This section is problematic and not very well done for several reasons. First, there are statements relating to the setting of an air quality standard. This is inappropriate in the Ozone CD. This relates to the setting of policy and not science. Second, the authors of this section have not made a balanced presentation but rather have concluded that the conclusions of the 1996 Ozone CD were correct by indicating that the exposure indices SUM06, W126 and AOT40 are the best the current science has to offer and that peak ozone concentrations are important.

No one is suggesting that the science behind the SUM06, W126 and AOT40 indices is not good science. One must ask, however, the extent to which these exposures indices realistically reflect how plants respond to ambient ozone concentrations under field conditions. The uncertainties of the results of open-top chamber (OTC) experiments are ignored despite being noted in earlier sections of the text. There are numerous places in this section where references are cited which do not appear in the reference list. This is especially true in Section 9.5.5.1 Models of Stomatal Conductance on pages 9-175 to 9-178. Further, ozone exposure and ozone dose are repeatedly confused. An example is the following statement on page 9-180, lines 21-22: "The cumulative concentration-weighted exposure indices are acknowledged surrogates for effective dose that are simple conceptually and easy to measure."

50. Page 9-181, line 16. Should read " - - for a give species is". The word 'species' is both singular and plural. A 'specie' is coin as distinguished from paper money.

51. Pages 9-181 to 9-254, Section 9.6 Ozone Exposure-Plant Response Relationships.
This section lacks balance, objectivity and is not very well done. It has problems very similar to Section 9.5 discussed under 'Specific Comment' 49, above. The authors have taken the position that the conclusions of the 1996 Ozone CD were correct. The information in the different sections of the text appears to almost have been shuffled like a deck of cards. The information does not logically flow and there is significant repetition.

i) Page 9-221, line 14. Should read. "… This issue was addressed in Section"

ii) Page 9-221, lines 17-31.
This paragraph is very misleading to the reader. The authors are basically saying that the experimental results from OTCs can be used and extrapolated to ambient field conditions. This is in strong contrast to earlier sections in the text where it is clearly shown that you cannot readily extrapolate the results of OTCs to ambient field conditions.

iii) Pages 9-224 to 9-227.
Reference has been made many times in the text regarding the European approach to ozone management. This is the first time in the text where 'critical levels' for ozone are discussed. This should have been presented much earlier in the text. Further, it should be presented in a more historical context showing how the Level I 'critical levels' were derived and how this has evolved into the Level II 'critical levels'.

iv) Page 9-227, line 14. Should read "results summarized in the 1996 AQCD - -"

v) Page 9-228, Table 9-21. The 'S' is missing from the 'header for the second column.

vi) Page 9-230, lines 28-29.
How is it possible for ambient ozone to have mean values of # 4 ppb?

vii) Page 9-235, line 14.
Table 9-20 refers to EDU Effects On vegetation Responses to Ozone. Is this the correct Table?

viii) Page 9-240, line 23.
This is the first mention of the Level II approach and it is not explained what it is.

ix) Page 9-244, line 23.
Should read "- - . Based on studies with evergreen seedlings in OTCs, major evergreen species"

52. Page 9-269, lines 4,5,11 and 23.
There is a need for consistency in the text. When a plant species is first cited, the common name is followed by the Latin name in italics. The common name is them used. Here we have an incomplete mixture.

53. Page 9-273, line 15.
Should read "…, birch (*Betula papyrifera*), - - "

54. Page 9-274, Table 9-26.
This table is incomplete. The letters in the columns need to be defined in a footnote.

55. Page 9-275, lines 18-28.
The authors need to clarify what is meant by 'critical loads' in line 18 because the remainder of the discussion relates to 'critical level', 'critical exposure level' and

unacceptable level'. Critical loads and critical levels are quite different and the terms cannot be used interchangeably.

56. Page 9-279, lines 14 and 23.
For consistency the common name of the plant species should precede the Latin name.
57. Page 9-283, lines 15 and 16.
The common plant species name should not be in italics.

58. Page 9-283, line 31, page 2-284, lines 1, 26 and 29, page 9-285 lines 2, 12, 13, 14, 15, 19, 20, 21 and 22.
The common name of the plant species is missing.

59. Page 9-286, lines 1, 7, 27 and 29.
The 'describer' of the Latin name has been included. This should be removed for the sake of consistency in the text.

60. Page 9-296, lines 13 and 14 and page 9-297, line 6.
The common names of the plant species are missing.

61. Page 9-302, lines 3,5,7,11,19, 22 and 23.
The common names of the plant species are missing.

62. Pages 9-314 and 9-315.
A summary listing of research needs on natural ecosystems is provided. This is very good. It would very beneficial for there to be a summary listing of all of the research needs which have been identified in the First Draft Ozone CD.

63. Page 9-328, line 29.
Should read "NAAQS" and not "SNAAQS".

64. Page 9-337, lines 27-29.
The text has repeatedly indicted that 'exposure indices' are "a biologically relevant surrogate for uptake". This is not a true statement.

Dr. Morton Lippmann

REVIEW COMMENTS ON VOLUME II OF FIRST DRAFT OF O3 CD BY M. LIPPMANN

Chapter 4 - Dosimetry

General Comment:

This chapter is a good initial draft that lays out a logical format and covers the relevant literature quite well. It needs a careful editing that responds to the critiques of the Panel members and the public. My own specific suggestions for changes follow below:

Specific Comments:

page	line(s)	Comment
4-2	21	delete "all"
4-3	7	delete "In comparing" and "they"
4-4	30	What does "This" refer to?
4-6	30	Insert "By contrast" before "when"
4-9	1-3	This statement is inconsistent with the one on page 4-11, line 10.
4-12	30-31	While the animal work is certainly interesting and worth discussing here, the statement that they "appear consistent with the modicum of studies focusing on long-term effects in human populations" is a considerable stretch. What constitutes a "modicum"? The ACS cohort analysis (Pope et al, 2002) shows no association of O3 with annual mortality, and the Gauderman et al (2000, 2002, 2004) papers show no significant effects of O3 with lung function growth in children. The laboratory animal studies used relatively high O3 levels, while the epidemiological studies involved co-exposures to PM2.5. PM2.5, but not O3, was associated with the excess mortality in the ACS cohort and with reduced lung growth in the CHS cohorts of children.

Chapter 5 - Toxicology

General Comments:

Chapter 5 is also a good initial draft that lays out a logical format, but covers the relevant literature in excessive detail. Much of the extensive discussion is inconclusive or of marginal, at best, relevance to the setting of O3 NAAQS. Serious consideration should be given to transferring much of the detailed descriptions of specific studies to the Chapter 5 Annex. In my view, the distribution of main text and Annex text in Chapter 6 provides a suitable model. In any case, the text needs a careful editing that responds to the critiques of the Panel members and the public. I have only a few specific suggestions for changes, which follow below:

Specific Comments:

5-12 13 Delete "recently"

5-16 17 Delete "recent"

5-17 28 Delete "new"

5-18 15 Delete "Recent"

5-29 1 Delete "new"

5-35 13 Delete "New"

5-41 16 Delete "Recently"

5-42 19 Delete "new"

5-48 13 Clarify what is meant by "may suggest"

5-51 10 Delete "New"

5-52 15 Insert "More" before "Recent"

5-52 23 Delete "Recent"

5-57 30 Change "New" to "Newer"

Chapter 6 - Controlled Human Exposure Studies:

General Comments:

This chapter is a good initial draft that lays out a logical format and covers the relevant literature quite well. It needs a careful editing that responds to the critiques of the Panel members and the public. My own specific suggestions for changes follow below:

6-1 26 Insert "permeability" after "hyperresponsiveness,"

6-2 26 Change "filter" to "filtered"

6-35 6 What was "not necessarily recognized"?

6-37 19 A citation to Foster's paper on the effect of smoking cessation on responsiveness to ozone should also be cited here.

Chapter 7 - Epidemiology

General Comments:

This chapter is very well written, and provides a comprehensive review on a vast literature. It addresses all of the many technical issues in a direct and straightforward way, summarizing what is known, as well as what the unresolved issues are on each topic in ways that should prove useful to OAQPS when they draft the ozone Staff Paper.

I have enumerated many specific comments and suggestions for changes below. The only sections that I found seriously deficient were those dealing with the issue of thresholds for effects. There I found tortured efforts to justify the creation, later in the NAAQS process, of risk assessments based on assumed thresholds.

Specific Comments:
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page line comment
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7-3 7 Change "eloquently" to "clearly"

7-6 20 Change "often" to "generally"

7-6 22 Change "often are" to "are generally"

7-6 29 Change "concentrations" to "outdoor concentrations at central monitoring sites"

7-7 2 Insert "outdoor" after "ambient"

7-7 3 Change "ambient levels" to "personal exposures"

7-7 11 Insert "infiltration and" before "ventilation"

7-7 22 Insert "and not in close proximity to sources of NO" after "time"

7-13 1 Change "NOx" to "NO"

7-18 27 Insert "eliminate interindividual variations in baseline function" before "exposure"

7-19 18 Insert "other spirometric indices" before "those", and "only" before "measure"

7-19 20-22 This sentence implies that FEV1 and PEF are interchangeable measures, when they actually measure different things. For ozone, there are generally greater changes in PEF than for FEV1. A paper showing that PEF as measured with a small field device was equivalent to PEF as measured with a spirometer should be cited here. [Lippmann and Spektor,J. Expos. Anal. Envirn. Epid. 8:101-107, 1988]

7-24 18-22 This sentence implies an inconsistency, when in fact the results are more likely to be what would be expected. The earlier studies were for brief exposures to outdoor air and there was no evidence of a threshold. It is well established, based on the 6.6hr Chapel Hill chamber studies, that the magnitude of the function decrements grow with increasing hours of exposure. Thus 11 hour work shifts could easily be expected to produce large functional deficits.

7-27 9-10 The absence of effects in "seniors" could have been due to their lower ventilation rates. More likely is that responsiveness drops with age, as discussed in Chapter 6.

7-34 17 Inner-city children with moderate to severe asthma in seven US communities were studied to determine the effects of ambient air pollution on lung function, respiratory symptoms, and school absences. The results are described in a paper prepared for the New England Journal of Medicine [O'Connor, Neas, Vaughn, et al]. If in press in time for the 2nd draft of the O3 CD, this paper will need to be cited.

7-75 22 Doesn't the sentence need to include "the continuously exposed monkeys," before "suggestive"?

7-78 1 Insert "the seasonal" after "that"

7-78 2 Insert "at least partially" after "be"

7-78 27 A paper by Avol et al describing the effects of relocating to areas of either higher or lower air pollution on lung function growth in S. CA children should also be cited here. It provides significant support for the Gauderman papers that are cited. [Avol et al., Am J Respir Crit Care Med, 164:2067-2072, 2001].

7-87 2 In the last line under this bullet, change "not as conclusive" to "inconclusive"

7-87 3 In the last line under this bullet, insert "annual" before "mortality"

7-87 10 Add "and hospital admissions" after "studies"

7-87 15 Change "suggested" to "indicated"

7-88 23 Delete "may"

7-94 31 Change "immediate" to "short-term"

7-96, 7-97, 7-98 Figures 7-15, 7-16, and 7-17 are excellent in terms of presentations of findings with regard to the significance of lagged effects.

7-107 3 Insert "indoors" after "concentrations"

7-107 21 Add "and the subjects are outdoors and physically active" at the end

7-110 10 Change "is" to "are"

7-117 31 Change "probably" to "probable"

7-122 6 I find it hard to believe that the discussion of possible thresholds failed to discuss the papers of Brauer et al (1996) and Korrick et al (1998). Even allowing that these studies did not explicitly address evidence for a threshold, they did report robust findings and quite high coefficients of response at very low levels of ozone, demonstrating that any threshold would have to be at current remote site background levels or below them.

7-130 11 Insert "Thurston et al, 1997" within the parentheses

7-130 12 Change "heath" to "health"

7-132 2 In the last line, change "investigated" to "considered in the risk assessment"

7-133 1 I find this paragraph to be inconsistent with the weight of the evidence presented in this chapter. I do not believe that there is any persuasive evidence presented for an effect threshold at any level above the current world wide background level of 40 ppb. A threshold below this concentration would be of academic interest, at best.

7-133 4 This paragraph is quite misleading without reference to the well established evidence that respiratory function responses decline substantially with age after young adulthood.

Chapter 8 - Integrative Synthesis

This chapter is a good initial draft that lays out a logical format and covers the relevant literature concisely and quite well. It needs a careful editing that responds to the critiques of the Panel members and the public. My own specific suggestions for changes follow below:

8-1 19 Change "atmosphere" to "troposphere"

8-1 25, 26 Delete , even in the absence of photochemical reactions in the troposphere"

8-6 1 Change "monitors located outside MSA's" to "those areas located outside MSA's having monitors"

8-7 2 Add ", consistent with maximal stratospheric/tropospheric air exchange in the Spring in the northern hemisphere" after "May"

8-7 12 Insert "maximal daily" before "O3"

8-8 15 Add ", in large populations" after "exposure"

8-8 19 Delete "Children and"

8-9 5,6 Delete "and nitrogen dioxide (NO2)"

8-20 24 Expand this discussion to include the Childrens Health Study results indicating lung function deficits associated with long-term exposure to PM2.5, NO2, and acid vapors, but not with O3.

8-23 3 It should be noted here that O3 concentrations are not generally highly correlated with those of the other criteria pollutants.

8-24 24,25 It should be noted here that O3 is also significantly associated with school absences.

8-32 26 Change "these" to "animal"

8-33 5 Insert "partially" before "transient"

8-33 9 Change "an" to "human"

8-33 21 Add "both" at end of line

8-33 22 Insert "and human" before "lung"

8-33 23 Delete "including humans,"

8-35 2 Change "decreasing" to "altering"

8-44 17 Also cite here the findings on O3 and school absences.

8-46 1 Add "short-term" at end of line

Overall, I commend Dr. Grant and his staff for producing health-related chapters in this first draft of the O3 CD that are well written and edited and provide an excellent database resource for the O3 Staff Paper.

Dr. Frederick J. Miller

Chapter 4 – Final Comments

General Comments

Chapter 4 is well written and covers the new information published since the 1996 CD. More information is available on species homology that involves the nonhuman primate relative to lung architecture, enzymes, and repair mechanisms that should be included in this chapter. The authors could use a table that compares the rat, monkey, and human for various aspects of lung geometry or a series of figures providing similar information. For example, Table 1 on p. 518 of Miller (1999) could be modified to include similar information on the monkey (Miller, F.J., "Dosimetry of Particles in Laboratory Animals and Humans" in Toxicology of the Lung, ed. Gardner, D.E., Crapo. J.D., and McClellan, R.O., Taylor & Francis, Philadelphia, PA, pp.667). There would also be useful information that could be obtained from Parent's 1192 book on Comparative Biology of the Lung.

Although ozone dosimetry is just now being conducted in monkeys, the homology information would strengthen the statement made in the chapter that there is significant homology between animals and humans, serving as a basis for interspecies extrapolation. The authors of this Chapter have captured the salient points concerning factors that influence ozone dosimetry and have done so in a way that the reader can follow. The quality of the chapter would be strengthened if some of the points made were illustrated with figures from the referenced papers (e.g., the data that show differences in V_D account for intersubject variability differences in ozone dose). There are a number of specific comments listed below that need to be addressed. Also, there is a need for a careful read to correct numerous grammatical and punctuation errors.

Specific Comments

p. II-vii	AX4 and AX5 should be labeled similarly, probably with both using Annex
p. 4-1, l. 13	Add an "s" to animal and to human
p. 4-2, l. 2	The definition of dosimetry is incomplete. Dosimetry also covers the subsequent disposition of the gas once it has been absorbed.
p. 4-2, l. 28	It should be noted here that prior to the 1996 CD, animal modeling studies and uptake experiments for a number of compounds by Morris clearly show that total respiratory tract uptake increases with increased flow while nasopharyngeal uptake (measured by FA) decreases with increasing flow and that localized flux increases. One can also refer to Aharonson et al (Effect of respiratory airflow rate on removal of soluble vapors by the nose. J. Appl. Physiol. 37: 654-657, 1974).
p. 4-3, l. 11	This sentence should be restated. What was meant was that the main focus was on what got to the tissue as ozone and that reaction products formed in the ELF were not tracked to determine absorption by them into the tissue.

p. 4-3, l. 28	Insert the word "in" after "continued".
p. 4-4, l. 3	The explanation provided by Rigas et al. for their bolus 2 ppm study with continuous exposure is suspect. Calculations (by John Overton of EPA) for the amount of material available to react with ozone would say this is not the case. A more plausible explanation is that the bolus penetrated to a depth of the conducting airways where the mucous layer may not be continuous.
p. 4-4, l. 13	Reference could be made to the modeling paper of Overton et al. (1996) that shows the conducting airway volume, which is part of V_D, to be the driver of intersubject variability in ozone uptake.
p. 4-4, l. 21	Remove the space between "in" and "to".
p. 4-5, l. 24	One could also point out that this is the reason the early attempts using the product of tidal volume and breathing frequency seemed to be a good predictor of responses to ozone exposure.
p. 4-5, l. 29	Add "As would be expected," to the start of the sentence "The FA …..".
p. 4-7, l. 29	Which authors are being referred to in this sentence?
p. 4-8, l. 26	This reviewer disagrees with the explanation given implying the oral vs. nasal difference are due to antioxidant capacity. This reason does not seem biologically plausible. A more reasonable explanation involves the transit time and V_D being less for oral breathing than for nasal breathing.
p. 4-8, l. 31	Insert "a" after "using".
p. 4-9, l. 8	It would be worth noting the modeling results of Miller et al. (Inhalation Toxicology: The Design and Interpretation of Inhalation Studies and Their Use in Risk Assessment, eds. D. Dungworth, G. Kimmerele, J. Lewkoswski, R. McClellan, and W. Stöber, Springer-Verlag, New York, pp. 139-155, 1988) also shows a linear relationship across species for protein leakage in the BALF.
p. 4-9, l. 18	Clarify that the sentence "About 0.07 of the …" is referring to humans.
p. 4-9, l. 20	Clarification is needed as to uptake in which major RT region was there no agreement. There is also a difference mixing the words uptake, FA, and absorption efficiency.
p. 4-10, l. 3	Either strike the "s" from distributions or change "is " to are.
p. 4-11, l. 30	Should be "significance" and not "significant".
p. 4-12, l. 21	While this sentence is correct, it should be given greater visibility. One way is to make it a stand alone sentence with "However," as the lead in.
p. 4-12, l. 28	This reviewer does not agree with this statement. The urban-profile chronic study conducted by EPA clearly showed pulmonary functions decrements indicative of structural lung changes observed by Crapo and colleagues. There are also other studies in rats and primates that reinforce this finding.

p. 4-15, l. 26	Rather than "confound extrapolation", a better choice of wording would be "complicate extrapolation".
p. 4-16, ¶ 1	The discussion about the previous extrapolation in the 1996 CD should be expanded to cite (and refer to where discussed in this CD) the work of Calderon in Mexico City children.
p. 4-16, l. 16	In this paragraph, the authors go against all the similarities between andimals and humans cited earlier before coming full circle at the end of the paragraph to state likely comparable animal to human exposure scenarios. The paragraph could use some rewording.
p. 4-17, l. 7	There is no mention in the summary of the structural changes in animals with chronic exposure, which given the species similarities would raise concern for such effects in humans.
p. AX4-1, l. 11	Same comment as before.
p. AX4-3, l. 3	Even the earliest ozone dosimetry models by Miller and colleagues tracked the amount of ozone in the mucuous layer. The point is that a dose metric based on ozone in the ELF was not felt to relate to the major biological changes seen in the lungs of animals.
p. AX4-9, l. 8	The SD indicates a value of 0.56 is more than 4 SD from the mean and probably represents either a technical error or a true outlier. Given the small sample size, how does the FA compare to that from other studies is a reasonable question, the answer to which should be included in the description of this paper.
p. AX4-10, l. 12	This reviewer considers the statement about uptake efficiency decreasing over an hour to reflect a statistically significant change that is most lilely not a biologically significant one.
p. AX4-11, l. 15	This reference should be Overton and Graham (1995).

Chapter 5 – Final Comments

General Comments

Consistency is needed in presenting the exposure concentration and duration whenever studies are discussed as this information is needed by the reader in order to place the results into perspective relative to potential usefulness in judging the likelihood of similar results being seen in humans. This reviewer agrees with comments made at the May 4-5, 2005 review meeting that the sections in the chapter should not be descriptive of results but rather describe what we think the data are telling us and then provide examples of data that support the story. Studies above 1 ppm should be deleted from the main body of the chapter as they contribute little, and in fact may mislead the reader, to our understanding of effects of ozone at near ambient concentrations.

Specific Comments

P5-2, l. 10	Missing from this section are statements that relate to the bioavailability of the molecules ozone reacts with that takes into account their abundance as well as their structural configuration. For example, some of the antioxidants may not be structurally available to react as easily as say amino acids.
p. 5-4, l. 29	Do the authors contend uric acid is reacting with ozone in the lumen of the airways? The wording implies that but the nature of the experimental set up doesn't support this.
p. 5-5, l. 12	Delete "is"
p. 5-5, l. 26	The study by Long et al. does not warrant inclusion in the CD given the levels and length of exposure. Massive edema at the two highest concentrations, which were the only ones to show effects, precludes any environmentally relevant conclusions or extrapolations.
p. 4-3, l. 11	This sentence should be restated. What was meant was that the main focus was on what got to the tissue as ozone and that reaction products formed in the ELF were not tracked to determine absorption by them into the tissue.
p. 5-19, l. 1	Acute mortality from such high ozone exposures is not relevant. Delete the Prows et al. (1997, 1999) studies. The Savov et al. (2004) study that follows is far more useful.
p. 5-27, l. 8	The point brought up here indicating in multiple species that structural changes are greater for intermittent compared to continuous exposure support the notion that a seasonal or some kind of moving average standard may be more appropriate for ozone than an 8-hour annual average daily standard.
p. 5-29, l. 1	Without incorporating dosimetry, statements such as the one made here are suspect and should be avoided, and, if made, should have the appropriate caveats.
p. 5-29, l. 12	The study by Plopper et al. (1998) and other studies by Plopper and colleagues are exemplary of the type of studies needed to be able to comment on the relative contributions of dosimetry and tissue sensitivity to the effects arising from exposure to ozone.
p. 5-30, l. 24	The title of this section is a misnomer if it is to include exposures > 1 week. What happened to the toxicological convention of acute ($\leq$ 1 week), subchronic (> 1 week and up to 13 weeks), and chronic (> 13 weeks) as nomenclature related to exposure duration?
p. 5-35, l. 19	Studies of 2 ppm ozone exposure effects on lung function are too high to be relevant to ambient considerations and should be deleted.
p. 5-35, l. 28	Same comment as for l. 19 of this page and from line 28 to the end of this section. Delete the material.

p. 5-39, l. 26	Clarify the dose is that of the challenge material and not that of ozone.
p. 5-40, l. 21	This reviewer does not agree that the high exposure studies necessarily shed light on mechanisms associated with airway responsiveness at environmentally relevant ozone levels. High-dose and low-dose mechanisms are often different for a chemical entity, and ozone is unlikely to be an exception.
p. 5-52, l. 23	Strike "Recent". 1994 to 1999 is certainly not recent.
p. 5-54, l. 5	This reviewer advocates eliminating this section. None of the studies are relevant to standard setting and even the 0.5 ppm concentration in the Valacchi et el. (2000) study is a stretch.
p. 5-57, l. 1	Here again, 1997 is not recent. The authors should check the entire chapter for such statements.
p. 5-57, l. 28	This section should be deleted. The formaldehyde levels used are totally non-relevant to investigation on non-carcinogenic effects.
p. 5-58, l. 26	Again, 1997 is not recent.
p. 5-60, l. 30	Where are the data supporting that ozone can absorb on particles? Also, what about absorb and stay as fee ozone?
p. 5-61, l. 8	Remove "the".
p. 5-62, l. 13	The concentrations used in the Kleinman et al. (2000) study should be provided.
p. 5-62, l. 22	What was the ozone concentration used in this study?

Chapter 6 – Final Comments

General Comments

Overall, this chapter is well written and adequately documents what is known about the effects of ozone from controlled human studies. There is a consistent balance among the sections in how the information from the 1966 CD is discussed and summarized. There are some sections for which the definitive studies were conducted by the time of the 1996 CD. However, that does not mean they should not be mentioned in the current CD (e.g., the McDonnell and colleague studies for prolonged exposure on a given day and for repeated exposures, the EPA study of ozone in combination with other primary pollutants present in the urban mixture). The summary section on page 6-41 starts out with the first few paragraphs providing an excellent summation of current knowledge about ozone effects in controlled human exposure studies. However, the last couple of paragraphs of the summary do not inclusively reflect the information contained in the chapter on inflammation, and a summation of Sections 6.10 to 6.12 is not included. The chapter would benefit from a reading by a technical editor, as there are numerous grammatical and editorial changes that should be made, only a few of which are listed below.

Specific Comments

p. 6-2, l. 4	Should be “repeatedly”
p. 6-6, l. 4	Insert “a” after “also”
p. 6-7, l. 14-15	The exponent “2” has been left off the “R” in these lines.
p. 6-27, l. 25	Delete “that”
p. 6-35, l. 5	This sentence needs rewording
p. 6-35, l. 29	Delete the first “and”
p. 6-39, l. 3	This sentence is incorrect. Ozone penetrates further into the lower respiratory tract than either SO2 or NO2. In fact, SO2 is almost completely removed in the head.
p. 6-41, l. 21	Insert “of” after “distribution”

Chapter 7 – Final Comments

General Comments

Compared to the first couple of iterations of the epidemiology chapter of the PM Criteria Document, this ozone epidemiology chapter is much further along. While not ready for “prime time”, the Agency is off to a good start. Some sections are in much better shape than others (e.g., the section on spatial heterogeneity begs the question for 8 pages while the section on hospital admissions for respiratory diseases provides a relatively concise discussion of ozone effects in a few pages).

The pulmonary function results from field studies emphasize statistical significance of most typically 40 to 90 ml changes in FEV1, but do not put these changes that are on the order of 1-2% into a biological significance context. Indeed, such changes in individuals are far from the kind of changes a pulmonary medicine doctor would consider as being clinically significant. This lack of attention to the context of disease leaves the reader wondering what all these studies really mean. The same kind of criticism can be raised when 30-day lag effects are discussed fro a study on school absences when no justification is provided as to why ozone exposure up to 30 days earlier should reasonably be expected to lead to illness.

There is no consistency in the presentation of effect estimates. Besides the point estimate, the standard deviation and sample size are needed, not just a statement as to the estimate being statistically significant or not. This is particularly true for when the effect estimates are small because without this information one can not tell if there are some “responders or sensitive individuals” that one should be concerned about.

Specific Comments

p. 7-5, l. 10	Assessing that the "transfer during analyses" is correct is not possible unless EPA reanalyzed all of the studies. What are the CD authors really trying to say here?
p. 7-6, l. 7	The comma should be a semicolon. Then insert a comma after "however" and also after "section".
p. 7-8, l. 17	Except for mortality, the reasonableness of the choice of lag period should be guided by the results from controlled human exposure studies. These studies would indicate a 0-1 day lag for functional changes and up t a 2-day lag for inflammatory endpoints.
p. 7-9, l. 13	The comma should be a semicolon.
p. 7-13, l. 19	The comma should be a semicolon.
p. 7-16, l. 9	What do the authors mean by focus on studies "most directly applicable for development of criteria"?
p. 7-21	For the entries in this table, this reviewer would like to have listed the % change in FEV1 from baseline so a comparison could be made to the ATS values for when a change in FEV1 would be considered to be clinically significant. The sample size and an error estimate are also needed for all table entries.
p. 7-24, l. 14	The estimate of 30 L/min being maintained for 11 hours is highly suspect. This level of exertion is near the oronasal switching point associated with moderately heavy exertion/exercise.
p. 7-26	Dose is a gross misrepresentation in Table 7-2. The dose shown is the total mg of ozone inhaled but calculations show that the numbers are the total µg of ozone inhaled. We know that FEV1 changes are associated with small airways. One would not expect the total mass inhaled to correlate with FEV1 changes, particularly since there is a nonlinear increase in mass with increasing flow rate.
p. 7-25, l. 21	The upper bound of the first confidence interval should be 2.8 not 28. These changes are nowhere near being biologically significant nor do they account for the exercise-induced effect that would be factored in from FA exercise, as can be done in controlled human exposure studies.
p. 7-43, l. 29	What is the logic behind a 30-day lag for ozone effects? This doesn't fit with the controlled human study effects for ozone on pulmonary function or inflammation. This study appears as a prime candidate for a multipollutant model – in fact, if PM 2.5 was not present in the model, the results should probably be discounted.

p. 7-44, l. 13	This section does not put heart rate variability into perspective of what it means for human health, as was done in the PM CD. The last sentence of this section represents an overstatement of what this endpoint can legitimately be expected to reflect.
p. 7-47, l. 2	What are the daily total hospital admissions for respiratory causes and what fraction of this does the 1-3 ozone-related admissions represent? (i.e., is the statement here warranted?)
p. 7-50, l. 13	Data "were" not Data "was"
p. 7-52	Figure 7-7 is hard to follow because of the study citation being reported for every age group. Why not only list the citation the first time the study appears?
p. 7-65, l. 11	In the summary paragraph, the authors should make clear that these are single pollutant model studies.
p. 7-76, l. 3	This reviewer strongly disagrees with the state made here. The plausibility of the occurrence of human health effects with chronic exposures has been more than amply demonstrated from chronic animal studies at ambient or near ambient exposure levels. The only question is that of the exposure scenario leading to comparable effects in humans. Enter dosimetry modeling to link concentrations from animal studies to equivalent human exposures yielding the same dose at the target site, such as the proximal alveolar region.
p. 7-82, l. 6	What is the relevant time interval for DNA repair of these cells? If it is a relatively short time period (i.e., < 60 days), then the observation of increasing DNA damage with increasing age is more likely due to increased ozone dose or other pollutants rather than accumulation of damage due to ozone exposure.
p. 7-85, l. 11	The conclusion paragraph overstates the case for chronic ozone exposure "likely contributing" to the adverse respiratory health responses in susceptible populations.
p. 7-95, l. 23	For the results presented here, was PM2.5 included in the model? If so, how did it change the effect estimate for ozone?
p. 7-103, l. 10	One gets the feeling that the authors have a pre-set conclusion for this section, as evidenced by the nature of the wording and the rambling writing to "explain away" the lack or lesser effect of ozone on mortality during the winter. Eight pages are over kill before getting to the last paragraph of the section, which comes across correctly as "we just don't know".
p. 7-112, l. 1	Data "were" not data "was".
p. 7-112, l. 21	Data "were" not data "was".
p. 7-117, l. 15	Change "were" to "was".

p. 7-121, l. 10	Data "were" not data "was".
p. 7-124, l. 15	The data in this section do not support characterizing the spatial variability in ozone effects as "slight". For example, the Canadian 16 Cities study saw hospitalization rates more than double among cities (3.1% to 7.7%), COPD in 5 European cities saw 9.8% in Paris to less than 3% in two Dutch cities, and 80% of mortality estimates around the globe vary from 0 to 7% excess risk. The authors would be better off acknowledging these ranges and then return to the fact that within the U.S. there is considerably less variability for a number of health endpoints.

Chapter 8 – Final Comments

General Comments

The chapter needs to do a better job of integrating effects from ozone exposure along a disease perspective. What is the evidence that the reversible small changes in FEV1 are not telling the whole story compared to the inflammatory changes? What about episodic exposures in light of the primate studies showing intermittent exposure leading to greater changes than continuous exposure? How strong is the evidence for an "effective biological threshold" or a "nonlinear concentration-response curve"? These are the kinds of questions the reader should find answers to in this chapter.

Specific Comments

p. 8-8, l. 5	The route of breathing is also important for the uptake of ozone.
p. 8-9, l. 1	Reference should be provided to a section in the CD that discusses what compounds could be produced with greater toxicity than ozone.
p. 8-9, l. 14	"extend" should be "extent"
p. 8-11, l. 13	This is too all-inclusive and grand a statement concerning effects associated with ambient ozone concentrations encountered in the U.S.
p. 8-12, l. 3	Ch. 7 acknowledges confounding potential with PM such that this sentence should incorporate this uncertainty.
p. 8-13, l. 8	With the slope given, an 80 ppb exposure would be associated with a 40 ml decline in FEV1, which is an extremely small decrement that is nowhere near biologically significant. The real issue concerns repeated or chronic exposure if such decrements persist.
p. 8-14, l. 5	Here again, the -1.18% change is overstated as to its significance. Statistical but not biological significance is present.
p. 8-14, l. 14	Are the odds ratios cited here statistically significant ones?

p. 8-20, l. 4	The wording here for robustness is certainly different from the conclusion stated on page 7-67, lines 25-30.
p. 8-20, l. 9	This range of 0 to 7% is not what one would consider as being narrow.
p. 8-25, l. 24	The sentence is written apologetically. Why not state "In this section, the epidemiological evidence discussed above is integrated with results …"?
p. 8-28, l. 10	There are many animal studies that used ambient or near ambient ozone concentrations.
p. 8-28, l. 14	Inhalability is not an issue for any gas. In addition,"deposition, clearance and retention profiles" should be changed to "absorption and distribution profiles" since we are dealing with a gas and not a particle.
p. 8-28, l. 26	The statement made in this sentence is contradicted in the next paragraph.
p. 8-29, l. 9	The statement about an inverse relationship only holds for uptake in the head due to the decreased transit time. Once the ozone reaches the lungs, there is more than ample time even at large ventilation rates for the gas to be absorbed.
p. 8-29, l. 22	Change PBPK to dosimetry. Why introduce different nomenclature at this point?
p. 8-31, l. 18	Change "contract" to "contrast"
p. 8-35, l. 9	The statement about the exposure level not being relevant to ambient exposures could change if this is similar to the rat to human difference that was seen in exposure levels for effects on alveolar macrophages in studies conducted by EPA.

Dr. Maria Morandi

Maria T. Morandi.

Chapter 5 – Toxicological Effects of Ozone and Related Photochemical Oxidants in Laboratory Animals and *in-vitro* Tests

General Comments

As in previous Ozone CDs, the current draft provides a comprehensive summary of studies done since the 1996 CD, through roughly 2004. The introduction to Chapter does a good job at explaining how the information for Chapter 5 in the draft CD is presented, i.e. brief summary of the pertinent findings present in the 1996 CD, new studies not included in the 1996 CD, comparison of new data with the prior CD, and the conclusions drawn from the integration of the new information with the older data, with the more detailed presentation of study methods and results presented in Appendix AX5.

The current draft document format departs from prior CDs in the presentation of the information, and the authors should be commended for improving the understanding and usefulness of the CD. Traditionally, the documentation supporting the Agency's NAAQS has been largely descriptive and, as such, has provided a useful compilation of knowledge on a particular criteria pollutant. However, the integration of the knowledge in terms of understanding the chain of events underlying the exposure-to-effects continuum has been less than optimal. The current format of the CD lends itself to having the integrating of study results in a manner that represents current understanding of ozone effects from a mechanistically standpoint, with the detailed, supporting information presented in the Appendix. This approach would provided a more useful tool for supporting the Agency's regulatory efforts by increasing clarity and, importantly, it could lead both the Agency and the scientific community to identify gaps of knowledge in cause-effect mechanisms so that Agency's scientists and other researchers can formulate research questions that may, or not, support proposed mechanisms .

However, while there is evidence of some motion towards integrating rather than purely describing findings, the draft CD, it does not quite achieve the promise. There is still the tendency towards describing results in the main Chapter in language that is completely duplicative of the corresponding text in the Appendix). Section 5.1 indicates that "Longer discussions of new studies are included where warranted." However, the text in the Chapter presents results in a duplicative, although somewhat reduced manner (frequently verbatim) compared to the Annex. Thus, the reader is not infrequently left with the impression of reading the same information twice and wanders why two separate sections (the chapter and the Appendix) are needed. Instead, if the discussion in the Chapter were focused on the integration of results for supporting current understanding of cellular and intracellular effects as supported by past and new findings, so that the CD clearly presents:

a) what specific mechanism had been postulated at the time of publication of the 1996 CD,
b) the consistencies or inconsistencies of new study results with prior understanding as presented in the 1996 CD,
c) how and which specific new findings advance or change prior hypothesized mechanisms, and
d) additional knowledge that could contribute to such understanding.

Likewise, some of the material in the Annex, if expanded, would be more useful in the main chapter. An example is Figure 5-1 (see page 5-2), that could be complemented with known and hypothetical pathways following the post-inhalation generation of ozonides, aldehydes, and peroxy radicals. Such diagrams could be used as a framework for integrating the prior relevant results from the 1996 CD with the new findings in each of the subsections of the Chapter.

As in previous (an in other) CD's, although study shortcomings are mentioned occasionally, there is little critical evaluation of the strength of results presented in the Chapter. This is not an argument for excluding studies, but certainly not all studies can be given equal weight in terms of providing supporting evidence for an effect. A careful consideration of design, method, and interpretation of results is especially important (even necessary) when studies appear to have contradictory findings (for example the role of inducible NO in inflammation, in the case of Chapter 5). This comment also applies to Chapters 4, 5, 6 and, especially Chapter 7.

Specifically in Chapter 5, the limited critical evaluation in the presentation of new findings is reflected in the scarce presentation of limitations in methods and interpretation, as well as in the lack of incorporation of relevant knowledge from Section 3.1 of Chapter 3, and Chapters 4, 6, and 7. For example, the upper range of exposures in the new in-vitro studies is quite high compared to current ambient concentrations and exposures. The use of high exposure concentrations in animal toxicology studies is a traditional approach that has some utility, but it also poses questions of relevance to humans because exposures are quite lower, and it is known that the events observed at very high concentrations may differ significantly from those observed at lower concentrations. For example, are the Gehil et al. (2003) results on gene expression consistent with findings from in-vitro and in-vivo studies presented elsewhere in the Chapter that looked at the products of some of some of these genes as end points (for example some of those presented in 5.2.2)? How do these results at ppm levels of ozone compare with those observed in hyperoxia experiments and, if the observation at high oxygen concentrations are consistent with those at high concentrations of ozone, is the exposure protocol used in the gene expression studies appropriate and compelling for raising concerns about gene expression changes at current ozone concentrations and patterns of exposure? Are the results observed with different animal models equally persuasive considering the appropriateness of anatomy and function in the specific animal specie as a model for humans? For which specific effects do the toxicology in-vivo and in-vitro experimental results support the controlled human exposure and epidemiology observations? And if they do not support those observations, can the disparate results be explained by considerations of dosimetry, appropriateness of animal model (anatomical and physiological), and exposure protocol?

In connection with the above, another issue that is not presented consistently across sections is the comparatibility of responses across different animal models, species within the same animal model, and if the animal or cell is considered a good model for human response. If there are no

data available to do such comparisons, perhaps a brief sentence to this effect would help put the results in the larger context. Chapter 4 presents a lot of this information as it relates to dosimetry.

To the extent that the major considerations that might explain each type of effect are frequently common, the subsections should be organized using similar subsection titles. For example, one of the sections (5.2.3.2) briefly considers the relative importance of concentration and duration of exposure (and to which intermittent patterns of CxT should be added). Since CxT considerations are important and applicable to the whole range of animal and in-vitro exposures (as well as to controlled human exposures), each section should include, when possible, some evaluation of the relevance of the exposure protocol with respect to CxT, especially for studies targeting the same or similar endpoints. Similarly, susceptibility factors (age, gender, sex, etc) are only presented in some sections (for example 5.2.3), but briefly or not mentioned at all in others. Again, if data on these factors are lacking, and they could be important, a statement to the effect should be added.

Similarly, comparisons of results for animal studies exposed to ambient air pollution in different cities need to be couched because there are differences in atmospheric pollutant composition across cities, beyond ozone.

The subsections discussing results from exposure to ozone in binary mixtures and multiple co-pollutants needs to be strengthen by expanding the discussion of secondary products resulting from reactions between ozone and other chemicals, about which little is known. The Chapter seems to be somewhat dismissive of the potential for other ambient oxidants to play a role in the effects attributed to ozone alone. In ambient air, the same photochemical mechanisms leading to ozone formation also result in the production short-lived radicals and secondary particles that contain highly polar compounds. The fraction of secondarily produced particles varies across cities and, one would suspect that this is also true of the proportion of more reactive polar organic compounds. At least some of these reactions also occur indoors via catalytic mechanisms. Little is known about the specific composition of the secondary aerosol, in particular the more polar components because at least some of these compounds are fairly reactive and they do not survive through the typical extraction and analysis methods unless they are derivatized. Thus, one might wonder if, in part, outdoor ozone not only has direct effects but is also acting as a surrogate for other secondary, polar compounds that are formed concurrently in ambient area during the photochemical cycles, as well as indoors as a result of catalytic processes via reaction between infiltrated ozone and indoor organic compounds.

Having diagrams that present the current understanding of what the mechanisms are that might explain observed results shown early in the narrative of a section, and then linking the subsections using the diagram as a template and weaving the new information with some of the synthesis in the summary paragraphs, followed by a separate conclusion paragraph, could promoted better integration of the information.

The Chapter will benefit from adding sections and page numbers when cross-referencing information to the Annex (and to other chapters.) It also requires careful editorial review and checking of correspondence between citations and references.

Specific comments by section

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5.2.1. This section, as others present relevant information but not necessarily in a clearly and consistent manner. The lipid-ozone secondary product formation needs to be separated into a section that describes interactions with extra cellular lipids separate from membrane lipids (again, a guiding diagram (s) that would integrate the summary information for the section would be useful)

5.2.2.4. The conclusion statement in section 5.2.1.4 needs to be rephrased (or the meaning is not clear. Certainly, if secondary lipid oxidation products mediate downstream toxic effects, uncertainty about their specific effects on the surface tension of the lung cannot be interpreted as not being "biologically relevant and affect(ing) human health" since other endpoints are involved.

5.2.3 Inflammation and Lung Permeability Changes

This section, most than others needs to have an overall framework for presenting the information in a manner that clarifies how the various study results may fit into a framework of explaining inflammatory responses. The lack of a formulation of this framework even reflects on the summary section that reverts back to presenting individual study results rather than integrating the data already presented earlier.

5.2.4 and 5.3 tend to integrate animal study results with those form human and epidemiology studies. For consistency, and clarity, the discussion should be limited to the animal studies, and the comparison with human studies moves to Chapter 6 and 7, as required.

Responses to charge questions relevant to Chapter 5 and others where I have comments.

Charge Question A1.

To what extent is the document format restructuring *(i.e.*, main chapters of the draft Ozone AQCD focused on evaluative/interpretive aspects, with descriptive materials presented in annexes) useful and desirable?

Answer: As stated above, the new format is a significant improvement over past CDs.

Can the restructuring be further improved? If so, how?

Answer: As stated above, it would be helpful to have a framework (aided visually, if possible) for the information. In the case of Chapter five, it could be a diagram summarizing the conceptual mechanisms believed to be responsible for the reported effects. Other comments on structuring can be found under the general discussion above.

Charge Question B4. Have the techniques for measuring O_3 and its precursor molecules been adequately described? To what extent do monitoring-related uncertainties raise issues with regard to utilization of the ozone monitoring data, *e.g.*, in estimating potential health risks in epidemiologic analyses?

Answer: There were comments by API on the potential for interferences in current ozone monitoring methods. The data presented during the public section meeting of the panel were compelling enough that an effort is needed to resolve the potential bias question. In my opinion, an effort to perform collection studies at appropriate locations that have on-going FRM monitoring for the NAAQS, and with a range of concentration for potential interfering compounds should be done to address this question.

Charge Question B5. Do the discussions in Section 2.2 discussions on ozone photochemistry and Sections 3.6 and AX3.7 on relationships between ozone and other species reflect well the current state of the science? Do they provide useful background information on "related" oxidants that may be toxic? Does the information given in Sections3.6 and in AX3.8 on the co-occurrence of ozone with other criteria pollutants usefully inform judgments related to later discussions of epidemiologic analyses? Is the use of threshold values for calculating co-occurrences appropriate?

Answer: The Chapter can be enhanced by having a distinct subsection on indoor chemistry describing the reactions between infiltrated ozone and indoor-generated VOCs, especially as they may generate radicals and highly polar derivatives.

Charge Question C3a(i). Have any important new human or laboratory animal controlled exposure studies been missed in Chapter 5 or 6 discussions of short-term O_3 exposure effects on pulmonary function and/or respiratory symptoms?

Answer: Yes.

Are the discussions on mouse strains with genetically determined differential susceptibility to O_3 sufficiently clear and useful?

Answer: Yes, but with the caveats indicated earlier about meaningful exposure levels.

Do the chapters adequately discuss newly available controlled exposure studies of airway responsiveness in humans and/or laboratory animal models, and what are CASAC panel views on the discussion of new insights into the mechanisms related to airway hyperreactivity?

Answer: Yes

Are the discussions in both Chapters 5 and 6 (as well as in Chapter 8, Integrative Synthesis) adequate to help 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 or respiratory disease status)?

Answer: Yes

Charge Question C3a(ii). Controlled human and animal exposure studies show that O_3-induced deficits in pulmonary function typically resolve quickly (within a few hours) to baseline when exposure ceases in normal individuals. However, asthmatics can have an extended period (up to 24h) of recovery from lung function decline and airway hyperresponsiveness. To what extent do such findings help to explain the increase in emergency room visits, hospital admissions, and use of asthma medication in asthmatics observed in new epidemiology studies?

Answer: It is difficult to provide a quantitative estimate, because there are multiple factors that could contribute to the observed increases.

Charge Question C3b(i). Do these discussions, including possible exacerbation of listed effects by preexisting respiratory disease, adequately cover new research in this area?

Answer: yes

Charge Question C3b(ii). A large component of Chapter 5 is presentation of data from studies of mice strains with differing genetically-determined sensitivities to O_3. These mouse strains differ in O_3-induced inflammatory responses, lung permeability, and pulmonary responses. NCEA staff consider these studies important as a possible explanation for differing human sensitivities to O_3, though the links between the mouse and human have not yet been established. Does the Panel agree with the inclusion and emphasis placed on this area of research? Do these discussions adequately cover the important new research in this area or were any important studies missed? How might the discussion be improved?

Answer: NCEA staff incorporated these studies correctly, since it would be reasonable to assume that there is at leas some portion of human response variability that might be genetically explained. These studies are useful for understanding the underlying mechanisms leading from exposure to effect. The chapter has the appropriate emphasis, but should strengthen the discussion by emphasizing that corresponding human polymorphisms are not known.

Charge Question C3b(iii). Some preliminary data from acute O_3 exposure animal toxicology and some controlled human exposure studies support epidemiological studies suggesting that asthmatics are a potentially sensitive sub-population. To what extent are the animals models of asthma using rodents sensitized to ovalbumin useful in modeling human asthma? Do these animal models provide useful information in modeling human asthma? To what extent do they provide credible support for the plausibility of the epidemiologic findings?

Answer: there is a debate in the scientific community about the appropriateness of the rodent ovalbumin model for asthma in humans. The problem is that there are no alternative models. At this time, the only approach that the CD can take is to clearly state the limitations of the model in the Annex, with a brief reference in the main Chapter.

Charge Question C3c. Can the panel suggest further inputs that may allow a more complete evaluation of potential cardiovascular effects of O_3?

Answer: The evidence for cardiovascular effects (as well as other systemic effects) of ozone alone is weak. The narrative should address them, but not couch the findings because of the weakness of the evidence and the fact that is it difficult to provide a mechanistic explanation.

Charge Question C3d. Is the existing discussion of such systemic effects adequate? Should it be expanded to take into account any pertinent studies that may have been missed that show such effects at more relevant O_3 exposure levels? Or, alternatively, should this section be dropped entirely as irrelevant for current purposes?

Answer: see answer to prior question.

Charge Question C4a. The issue of differing health risks of continuous versus intermittent daily exposure is discussed in the Ozone AQCD. A series of studies evaluating the longterm morphological effects of simulated, seasonal O_3 in rhesus monkeys is given considerable emphasis. Does the Panel consider these studies to be important in lending biologic plausibility to the causal relationship observed in epidemiology studies between seasonal O_3 exposure and adverse health effects such as lung function decline? Is the discussion of season-specific O_3 health effect estimates adequate?

Answer: primate studies are highly relevant to humans, although the exposure protocols may not mimic the patterns of those of humans. The results, consequently, would tend to provide a biological support for the epidemiology studies.

Charge Question C4b. The weight of evidence from toxicology studies does not support ambient O_3 as a carcinogen in animal models, but a few epidemiologic studies from Mexico City suggest a link between ambient O_3 exposure and genotoxic effects. The Ozone AQCD attributes this inconsistency to possible interspecies differences in this health point and inadequate exposure characterization. Do the present O_3 AQCD discussions adequately cover the state of knowledge regarding the possible genotoxicity/carcinogenicity of O_3?

Answer: the epidemiological evidence for the genotoxicity/carcinogenicity of ozone is very weak because of the limitations of the studies, including the lack of appropriate exposure measurements, and the presence of co-pollutants (airborne particles).

Charge Question C5a. The Ozone AQCD discussions of observational and field studies mainly focus on studies of potential O_3 effects among the general population, school-aged children, the elderly, asthmatics, and outdoor workers. Do the studies and the document discussions adequately cover the key populations that should be considered? Are discussions of differences in individual vulnerability and susceptibility adequate?

Answer: The susceptible populations are appropriately identified, with the probable exception of the elderly with not preexisting condition (the CD discusses this issue appropriately). They are susceptible either because of increased exposure (outdoor workers, and school age children), preexisting disease (asthmatics), and age-dependent developmental factors.

Charge Question C5b. Chapter 7 highlights the evaluation of two large multi-city studies that examined ambient O_3 effects on mortality, *i.e.*, the study of 95 U.S. communities and the study of 23 European cities. These studies show positive and significant O_3 effect estimates for all cause (non-accidental) mortality. Does the discussion of those studies adequately address questions regarding possible confounding by co-occurring PM, *i.e.*, indicating that the O_3 effect on mortality is independent of PM? Also, is the issue of the seasonality of O_3- mortality effects adequately addressed?

Answer: in my opinion, the evidence for an ozone-specific effect on mortality is not compelling. The studies should be reported but the text needs to emphasize that the variability in findings across cities (including apparent protective effects) and the confounding with PM makes this association suspect.

Charge Question C5c. The temporal relationship between O_3 exposure and the occurrence of health effects is important in animal toxicology studies, controlled human studies, and epidemiology studies. Most epidemiology studies find an immediate O_3 effect, with health effects having the strongest associations with acute exposure on the same day and/or previous day. What are the views of the Panel on the adequacy of the discussion on choice of lag period between ozone exposure and the observed health effect? Are sensitivity analyses appropriately considered to address model specification for adjustment of potential confounding by temporal trends in epidemiologic studies?

Answer: In my opinion, a lag effects identified in models need to be supported by some biological explanation.

Charge Question C5e. The O_3 AQCD evaluates the appropriateness of O_3 exposure assessments used in the epidemiological studies. Does the panel consider the discussion of ambient versus personal monitoring and choice of exposure indices to be adequate? How might it be further strengthened?

Answer: The discussion of personal exposure vs. ambient concentrations is discussed appropriately. As stated above, perhaps and additional statement on the possibility that ambient ozone may in part act as a surrogate for other oxidants in outdoor air (photochemically-produced) as well as oxidants produced indoors (catalytically) via oxidation of VOCs with infiltrated ozone may be useful.

Charge Question C6b. Myriad health effects described in both epidemiology and controlled exposure human and animal studies (including decreased pulmonary function and various respiratory symptoms) are highlighted as being of possible health significance in chapter 8 and elsewhere. Are the earlier discussions in Chapters 5 and 6 adequate to help 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)? How much short-term or reversible impairment is necessary to be considered a "biologically significant adverse effect?" for adults, children or adults with varying severity of asthma, etc.)? Does Table 8-2, brought forward largely intact from the 1996 O_3 AQCD, still accurately characterize mild through severe functional and symptomatic

responses? Also, is Table 8-3 still relevant for characterizing gradations of individual responses to short-term O_3 exposure in individuals with impaired respiratory systems?

Answer: Chapter 5 and 6 support the effects highlighted in Chapter 8. The question of how much reversible, repeated impairment of function can occur before it becomes an adverse effect in a sensitive population cannot be answered at this time.

Mr. Rich Poirot

Comments on 1/05 Ozone CD, Chapter 10. Tropospheric Ozone Effects on UV-B Flux and Climate Change Processes

Since the topics of UV-B flux and climate change could each easily fill a criteria-document-length volume of its own, and since the associations with tropospheric ozone (especially considering the relatively minor changes in US-only ozone levels that might result from the current criteria review & standards cycle) remain highly uncertain, the rather brief summary here seems adequate. In some cases it's a challenge to know even the directional influence that modifications in ground level ozone might have on health & environmental effects from UV radiation and climate change, and any quantitative assessment of such effects is not currently feasible.

Since these topics are taken on, however, it might be useful to modify the chapter title & content slightly to address "tropospheric ozone effects on <u>and from</u> UV-B & climate change processes." Surely an increase in mid-latitude surface temperatures or an increase in UV radiation could also be expected to exert positive "forcing functions" on precursor emissions and/or concentrations of tropospheric ozone. Recent reports (last month's European AGU meetings in Vienna) indicate that this past winter's arctic & northern latitude stratospheric ozone levels were among the lowest ever recorded – reversing a recent improving trend – and that the cause was not increasing concentrations of ozone-depleting chemicals, but rather an increased presence of stratospheric clouds, which, may in turn be associated with tropospheric warming, to which tropospheric ozone is a significant contributor… (see: http://www.physorg.com/news3902.html).

The first few introductory sections for both UV and climate change are especially well written. But some of the later sections on effects are less well organized and don't provide a lot of useful information – other to emphasize the uncertainties.

Quite a few of the references cited in the text are missing from the "References" section, and several of the listed references are not cited in the text. In the sections on climate change, it seems notable that most of the recent references cited are from international efforts (IPCC, WMO, UNEP, etc.), and that there are no cited US government publications after 2000, nor any EPA publications more recent than 1997. If the absence of such references reflects the absence of an active EPA climate change research and assessment program, it becomes increasingly difficult for EPA to conduct credible assessments of criteria pollutants, or to otherwise develop any effective strategies to assure national environmental quality.

Specific Comments

10-3, Figure 10-1 caption. Insert "of" or "at" between "absorption" & "specific".

10-7, lines 29-31. "complicated interactions" doesn't provide much useful information. For example,…?

10-9, lines 2-4. While the cited Barnard et al. (2003) paper does include a speculative mention of "Possible increases in combustion engine exhaust, which contains black carbon, over the past 20–30 years", it does not specifically examine national trends in black carbon or other combustion-associated PM over the past several decades, but is focused instead on detailed analysis of a 4 to 5 month period in 1997 at a site in Riverside/Rubidoux, CA (one of our most heavily polluted urban areas), with (remarkably successful) testing of the resultant regression equation at a remote eastern site in NC. Thirty years before present would bring us to the mid-1970's period when US emission trends in most primary PM and secondary precursors were peaking. Trends in PM2.5 mass and EC have not been increasing at most IMPROVE sites over the past 15+ years of record, and are both clearly decreasing at many of these sites. As indicated in the Barnard paper, ambient concentrations of BC and other PM can and do efficiently adsorb UV radiation, and so may mask ability to detect UV trends, but there is no real indication of offsetting trends. One important and much more relevant observation from this (regression) analysis that could be mentioned is that, while there were highly significant (inverse) associations between measured UV-B and PM-10, BC, and total column (primarily stratospheric) ozone, "One pollutant that was not included in eq 1 is the ground-level ozone. Long thought to be one of the significant absorbers of UV-B radiation, it statistically did not meet the 0.05 significance level in this model."

10-9, lines 19-22. A recent study by Koloutsou-Vakakis et al. showed what? At the end of this paragraph might be a good place to mention the regression results from Barnard et al., 2003 emphasized in the preceding comment, as these do provide quantitative estimates of UV absorption by tropospheric ozone and PM.

10-12, lines 12-14. Some introduction to this apparently very sparse EPA-UV monitoring network might be appropriate here. What about other networks like USDA (http://uvb.nrel.colostate.edu/UVB/home_page.html)?

10-12 through 10-16. This detailed summarization of various human activity factors affecting UV exposures doesn't really add much useful information, and includes some apparent contradictions. I wonder if there might be a typo somewhere, as p. 10-12 lines 27-28 indicate that teenagers see higher doses than children or adults, but p.10-13 lines 29-30 indicate adults and children see higher doses than teenagers, while p.10-14 lines 1-2 indicate children see the highest doses…

10-18, lines 18-19. Is this correctly stated – that repeated exposures lowered the minimal erythemal dose in darker-skinned subjects?

10-29, line 26. It's not clear here what "deaths attributable to reduced UV-B exposure" refers to. Reduced from or compared to what?

10-43, lines 1-2. I don't think the ozone sonde data plotted in Figure 10-6 (between 630 & 400 hPa – or roughly 4 to 7 km altitude) "are surface concentrations only". In addition to this indirect (IPCC, 2001) citation to Logan et al., 1999, another good reference – which more directly addresses the regional trend topic might be:

Randel, W. J., R. S. Stolarski, D. M. Cunnold, J. A. Logan, M. J. Newchurch, J. M. Zawodny (1999) Trends in the Vertical Distribution of Ozone. Science 285: 1689-1692

10-45, line 24: add “been” between “have” and “reduced”.

Dr. Armistead (Ted) Russell

Review of Air Quality Criteria for Ozone and Related Photochemical Oxidants (First External Review Draft)

Preface, second line: I hope that the NAAQS are promulgated to protect public health and welfare, as mandated by Sections 108 and 109.

Chapter 1. Table 1-1: There are too many significant figures in the concentrations given in ug/m^3 units.

Chapter 2. Physics and Chemistry of Ozone in the Atmosphere

Overall: This Chapter summarizes what is known about the physics and chemistry of ozone in the atmosphere, with particular emphasis on tropospheric ozone and literature published since the last criteria document. Overall, the chapter, along with the annex, provides a comprehensive picture of what we know about how ozone is formed, transported and removed from the troposphere, and thus provides the necessary foundation for the rest of the document in terms of providing a basic amount of information to a reader with relatively little knowledge of atmospheric ozone dynamics. As noted below, the chapter I think suffers from the charge to review the most recent science (i.e., since the last Ozone Criteria Document, or OCD), and that our understanding of ozone chemistry and physics was already pretty mature at the last writing. Thus, concentrating on what is new since then sort of skews the presentation.

I am, however, concerned about a few things. First, it is not well laid out in that it seems to skip around and have strange transitions. That can be fixed (comments are made on the hard copy to be returned). A deeper concern is that I believe it over emphasis uncertainties, and could be construed as to suggest that there is a lot of uncertainty as to how ozone might respond to controls. Yes, there are uncertainties, but our understanding of ozone dynamics is relatively mature, and we generally understand how ozone will respond to controls. Also, it seems to spend more time discussing stratospheric intrusions than is called for given the relatively minor effect that has on exposure of the general population to elevated ozone. This, too, might detract from conveying an accurate reflection of our state of knowledge on ozone control.

If one looks at our advances in the study of tropospheric ozone since the last criteria document, I would emphasize four things: 1) Intercontinental transport, 2) Advances in modeling tools (e.g., CMAQ/MM5/SMOKE and specific source apportionment approaches), 3) Improvements, but continued uncertainties in emissions estimates, and 4) linkages to particulate matter. While mentioned, these are not at all stressed in this chapter in proportion to their importance. I would also note that we are just now developing a modest level of understanding of how climate change might impact future ozone levels and management. Associated with this, but not discussed in this chapter is how recent weather patterns have impacted ozone levels. There should also be more of a discussion about what was found as the reason for the periodic very high levels of ozone in Houston.

Thus, I would suggest that a revised chapter consider providing greater emphasis on the four topics listed above, providing a more balanced assessment of our state of the knowledge, focus on what one needs to know to address human (and ecosystem) exposure to elevated levels of ozone, and what changes in ozone dynamics might occur due to climate change (though, the latter should be couched as being highly uncertain). I would also not constrain the chapter to primarily highlighting more recent studies. Again, our knowledge of ozone dynamics is relatively mature, and was so at the time of the last criteria document. Highlighting the most recent literature skews the discussion to topics that are of less central concern as those were addressed earlier on.

Specific Comments:

2-1-7 (i.e., Chapter 2, Page 1, line 7). It concerns me that they do not, up front, include CO as a precursor to ozone given its impact in urban areas. Later on, this is discussed, to a limited extent. However, it is appropriate to include it here.

2-1-10: the phrase: "atmospheric mixing and processing on cloud and aerosol particles" is too limiting. There is much more happening in clouds. I might rephrase as atmophseric mixing, cloud processing, reaction with aerosol particles. Also, deposition, emissions and surface characteristics should be added to the list.

2-2-2: Note that HNO3 and sulfuric acid form PM and HCHO is a toxic.

2-4-6: Reaction with Cl is brought up here, but not for alkanes. However, if Cl is to have a main impact, it is the reaction with alkanes. I think the whole discussion of Cl chemistry is a bit overblown given its importance (as discussed somewhat in the Annex). NO3 also reacts with alkanes (though this is more minor). The discussion of alkane and alkene chemistry should be made more parallel. The major difference is reaction with ozone, and that alkene oxidation proceeds by addition at the double bond.

2-5-13: This sentence is contradicted by the Annex. The mechanism for the reaction between OH and an aromatic is reasonably well understood… it is the further steps that are uncertain.

2-5-18. What are you trying to say about particle formation: The particles might reduce ozone, or just the loss of carbon from the system reduces the potential to form ozone?

2-6-12: HONO formation could increase ozone.

2-6-23: This section overemphasizes tropospheric folding, and underemphasizes the real causes. As noted in Chapter 3, this is not a major process contributing to elevated exposures.

2-11-2: Repetitive.

2-12-1-2-12-7. Not sure the point, and lacks quantitative information. Does this really impact exposure to high levels of ozone? How often is this important (if ever)?

2-12-26… While there is not as strong of a trend in the Phoenix data, it appears as though there is some trend. The discussion of why ozone goes up with T in New York is too brief to be useful, and as it currently exists, is misleading. Ozone goes up with temperature more in New York than Phoenix because of other factors that correlate with T: wind speeds, mixing heights and emissions.

2-14-9: There is a net destruction of ozone in the plume very near to a power pant. Further downwind, there is ozone production.

2-14-17: Oxidation of VOCs can consume free radicals at low NOx (RO2-RO2; RO2-HO2 reactions). This sentence should be rethought.

2-14-24: Use "involving," not "invoking.". Also, Jaegle et al is not in the ref. list.

2-15-18: Your discussion about Houston suggests that OPE is highly impacted by VOC levels as well.

2-17-17: rearrange: "…numerical algorithms describing the processes shown in Fig. 2-9…"

2-18-1: Not sure of the basis of the statement that existing mechanisms neglect many important processes. If this were the case, the mechanisms would not work so well. This sentence brings a cloud over the current state of practice that, I think, is not true.

2-19-7: Add "Nationally" before "About"

2-19-30: remove "vehicles" before the "."

2-22-29. This last sentence, while true and I believe more correct than one might garner from the bulk of the text, is not really in the prior parts of the chapter. The prior part of the chapter should provide a foundation for this statement.

Section 2.5 in general: Should be more concrete about the current performance of CTMs. Is there significant doubt as to their ability to be used to help assess controls and to be used for scientific investigation? (no).

2-27: Zhang et al (1997) reference is incomplete.

Annex: Specific comments on the Annex are contained on the hard copy. Generally, the Annex is a relatively complete assessment of our knowledge, but suffers from many of the same problems as the chapter: emphasizing less important issues and being couched more as "what we do not know" than "what we know".

Chapter 3: Environmental Concentrations, Patterns and Exposure Estimates

Overall: While I think Chapter 3 provides an adequate foundation for supporting standard setting, like Chapter 2, I found this chapter a bit scattered, and when I got done wondered what was meant to be conveyed. On the other hand, there has been a substantial increase in our knowledge in terms of ozone trends, background levels, intercontinental transport and exposures since the last OCD. In this chapter, they recapped much of the new information, though rather selectively, and this led to an imbalance in the presentation.

In terms of the sections on Ambient Air Quality Data for Ozone, I think they would have been better off to present various ozone maps that are common to EPA, except showing the metrics of interest, and the diurnal variations of ozone at representative stations. This is done in the Annex on a region-by-region basis, which sort of chops things up (and the graphics leave a bit to be desired). Many of the tables they have are usually too long to make a point, and can be put in the Annex (e.g., Table 3-2, 3-3 and3-5). In discussing trends, at the end of the section I was left wondering what point they were trying to make: is ozone going down or not, where is it going down, etc. Again, EPA has some nice figures showing trends in various locations, and those might help (e.g., the Figs. AX3-49 and 50 do this better than their current discussion). The discussion of "co-occurrence" with other pollutants, as discussed below, did not contribute much.

One section that I liked was the discussion of policy-relevant background ozone. This was relatively short, to the point, and had a good foundation. I have some issues with a bit of the interpretation, as discussed below.

The discussion of indoor sources of ozone did a good job of presenting the state of knowledge, though it would have helped if they had made a better linkage between the rate of ozone emissions of some indoor sources, AERs and resulting concentrations, even if just approximate.

The human exposure section did give a reasonable view of that part of the exposure assessment issue, though I would have liked to see more hard results, though this was covered in relatively good detail in the Annex. I did like where in the subsection on Personal Exposure and Ambient Concentrations they gave a nice, solid, bottom line, i.e., the last sentence beginning with "Results from these…". More of the chapter would benefit from having similar bottom lines at the ends of the subsections and are as motivated by the preceding discussion and extended discussion from the Annex.

Detailed Comments:

3-1-21-23: There are a lot of special study data that can provide additional information on the relationship between ozone and other oxidants, and one can also use the results of various models.

3-3-1 to 3-3-7: This should not be couched in urban vs. rural. Many power plants and other facilities with large emissions are not in urban areas. Likewise, major highways can have marked local impacts in non-urban areas.

3-3-6 (and other areas): NO emissions depress ozone both by direct titration as well as radical destruction. As noted in the prior chapter, this NOx-saturation (often called radical-limited) region of the ozone formation regimes can be very important in lowering ozone locally.

3-3-12: Again, why just urban?

3-3-17: What do you mean "allowable" ozone season?

3-5-11: Not sure what the point is: They start out saying that "Ozone concentrations measured at the center city sites are often lower" Then give some statistic about the frequency of levels which is a nonsequiter from the prior sentence. Then they talk about where the highest values are found (Texas and So.Cal) at a very different scale. They end up talking about more exceedences of the one hour than eight hour standard.

3-5-30: Variation in what? Years, sites, regions? The way this sentence is worded, it seems as though they are using it as causal in reference to Table 3-4. The concluding sentence (3-6-1) is rather vague: what else is there to significant importance?

Tables 3-3, 3-4: So long as to make them contribute little. Relegate to the Annex.

3-27-29 and on to 3-28-10: This paragraph really does not provide much support to using the Mt. Lassen data for estimating background trends. In fact, it provides significant evidence (particularly along with the later analysis from Fiore et al.) that it is impacted, and should not be used.

3-28-25: This is not primarily a high vs. low elevation issue. It is primarily urban vs. rural issue (or near sources of NOx vs. more removed).

3-31-5: Should be "as"

3-31-21: This paragraph seems to start out with a (rather weak) conclusion, then provide some support. Suggest revising it, and strengthening the foundation.

Table 3-6: Define CoD

3-35-7 though 10: Be specific as to where it would take 70-90% reduction. Tha is not universal.

3-35-13: Not appropriate use of process analysis unless integrated over the whole domain (vertically and horizontally). They should note, in this case, that process analysis does not distinguish if the CO is emitted or produced in the atmosphere.

3-35-13: The impact of the Asian emissions increase on surface ozone is still very uncertain, and the Fiore et al. results suggest it is not big.

3-36-3: Note the type of test used.

Section 3.6: Relationships Between Ozone and Other Species: This section is rather weak, and often arbitrary in the approach taken. While the data shown in Figure 3-6 mean something, the data presentation approach used to develop Figs. 3-7 to 3-9 relies on an arbitrary value for high ozone and the other pollutant. What if they chose 0.02 ppm: then they might get a high frequency of co-occurrence. I would shorten this whole section, and present the data as in Fig. 3-6 or something similar. Also, I don't see a big need for this section.

Section 3-7: As noted above, nice piece.

3-45-13: Strange citation format.

3-46-19 (and other places) Do not need the "a" in 2002 and 2003 Fiore et al. references.

3-47-5: From what is shown, the cutoff should be 1.5 km. Also, When I look at 3-11, Apr-May low lying sites, the background is NOT consistently lower.

3-49-1: This statement, which is true, should be reflected in the discussions in Chapter 2.

Fig. 3-12: Context?

3-51-14: Remove "and".

Table 3-9: Define the regions used.

3-57-4: How important are the OH reactions? This is a bit weak.

3-59-5: The co-occurrence with fine particles does not make it difficult to assess ozone dynamics and exposure patterns. It may make it difficult to assess the impacts of exposure.

3-59-11: Should also reference Chapter 2 which has a more complete discussion.

3-60-9: Need to define breathing zone to make this paragraph meaningful. How big is this breathing zone?

Other corrections contained on the hard copies.

Annex: Comments on the hard copies, though is a rather massive amount of information, presented in a somewhat scattered fashion. However, some approaches to data presentation are better than the Chapter.

Additional comments from Ted Russell.

Chapter 10. I thought the discussion of the impact on global climate change was well done, except that given the potential magnitude of the problem, and certainly the debate over the potential contributors, more is called for. First, the presentation was almost solely in terms of radiative forcing, not potential health and welfare effects. While this may be one of the more uncertain aspects of climate change, the real concerns are these downstream effects. Note that there are uncertainties, but provide descriptives of the potential effects. A second comment is that this section should be tied to Chapter 3's work on PRB, and hence, the increased ozone due to North American emissions. I would also note that the discussion of local enhancements in ozone should be reduced as it probably plays a very minor role in climate. Global climate change may have the greatest environmental and health effects (need to consider people outside the US) of any of the endpoints expressed here: to what extent does the ozone problem contribute? Start laying the foundation here.

CH.3. There was some discussion and debate about policy relevant background (PRB). The Mt. Lassen discussion should probably be removed from the chapter totally as it adds nothing: that site is impacted by regional influences, and thus the data are not useful for assessing the PRB. The Trinidad Head data are more useful. One asks how different they are than the modeled PRB. It does not look big, and one must remember that those data are also impacted by the hemispherical increase in ozone due to North American (NA) emissions. Thus, they likely represent an upper bound at that location, but relevant for discussion here. The approach taken using GEOS-Chem is appropriate and probably the only way to get region specific PRB. The document should probably note that models end to have a flatter range than individual monitors, as seen here, but the evaluation for this application is solid. I would format this section as laying out the approach you plan to take using GEOS-Chem, then end with an evaluation between the PRB from GEOS-Chem and the Trinidad head observations, noting the difference in period and that Trinidad head is going to be influenced by the increase in hemispherical background from NA emissions. I would also consider assessing the Mozart and GEOS-Chem data to get the differences between the two models of PRB, as well as the combined mean and range. (It should be noted that the +/- given is variability, not uncertainty).

Dr. Elizabeth A. (Lianne) Sheppard

Chapter 7. Epidemiological studies of human health effects associated with ambient ozone exposure

General comments

Organization: Overall I think the organization of the chapter into prose discussion followed by tabular summaries of the studies is a good approach. I have several suggestions on ways to improve the tables (noted below).

Tone of the discussion:

Statistical significance focus. The majority of the discussion focused on statistical significance as though this made a study and its results important. Often the information needed to interpret results was omitted (one key component is effect estimates; these often were omitted or reported without confidence intervals). The entire tone of the discussion needs to be changed to reflect a deeper understanding of the theory of hypothesis testing. The definition of statistical significance reflects the allowable rate of error in the decision problem constructed from assuming a simple null hypothesis is true. It is a conditional probability; the probability that the value of a statistic is less than 0.05 (typically) given the null hypothesis (typically of no effect) is true. Focusing only on statistical significance summarizes key study information (about effect size, sample size, and variability of the effect) as a single binary indicator variable. Statistical significance can be dominated by any one of these and knowing a result is significant doesn't indicate which one is driving the result. Worse yet, statistical significance does not reflect biases due to study design or inadequate analysis. These require scientific judgment.

Multiple testing. Hypothesis testing provides evidence about a prior hypothesis. With multiple testing, the actual Type I error rate (significance level) is actually higher than the nominal level (typically chosen to be 0.05), thus clouding interpretation and weakening the evidence against a null hypothesis. The document shows appreciation for the importance of controlling the overall Type I error. This can be done by limiting the number of hypothesis tests done or considered, adjusting for multiple testing, or explicitly addressing model uncertainty by Bayesian model averaging. Since review of published papers is the focus of the CD, I recommend limiting the number of hypothesis tests considered as primary a priori hypotheses in each published paper. I recognize clearly identifying prior hypotheses can be difficult to discern. Ideally papers discussed in the CD will have clearly prioritized their prior hypotheses. If not I suggest reviewers choose the most likely prior hypothesis based on the justification given in the paper and the reviewers' understanding of the state of the literature at the time the paper was written. Any further analyses discussed from the paper beyond those defined by the prior hypotheses should be reported as sensitivity analyses. The sensitivity analyses provide greater insight into the study data and they can reveal insights into relationships, but they shouldn't be given the same inferential strength as the original hypothesis-driven analyses. Thus sensitivity analyses can add to a study without clouding the inference based on the a priori hypotheses.

Study quality weighting. All papers appear to be given equal weight, even though some are evidently of poorer quality than others. I think there should be a screen for study quality (perhaps a rating system?), so lower quality papers aren't given the same weight as higher quality ones. Papers that pass the peer review screen are not necessarily good papers.

Definition of terms: I recommend including a glossary to clarify definition of terms that are often used as technical terms, but that aren't precisely defined. Uses of technical terms in this document don't always appear to reflect the technical definitions. Among these I suggest defining: robust [e.g. p. 7-58 l. 4], significant [throughout], efficient [e.g. p. 7-117; 2], "understandable power" [p. 7-127; 29], "non-GAM studies" [p. 7-14; 27], suboptimal [p. 7-14; 15], power [p 7-28; 14, 15].

Reporting: An effort has been made to rescale results to consistent units of O_3 change, and for the most part this has been successful. There are a few additional places where this rescaling should be done. In exposure studies, focus on reporting slopes in addition to correlations. Don't ever quote an effect estimate without also including its standard error or CI. Don't rely too heavily on statistical significance. Statistical significance does not imply scientific importance. For instance, FEV_1 decreases in two studies of 60.8 and 56.0 are remarkably similar in magnitude, irregardless of the fact that one is not statistically significant [7-25].

Appendix tables: I think enhancements to the tables will impact the conceptual discussion of results. While the general framework is good and a great deal of summary information is already included, there are important features that I recommend be added to the tables. Along with mean O_3, I think there needs to be a standard deviation or interquartile range, indicating how variable this concentration is in the particular study. For multi-city studies, it is good to see the range of means across cities. Along with that, please include an average within-city measure of variability, or some other summary of within-city variation (at least where available, e.g. for studies analyzed over time). Note the study design in broad terms (e.g. time series, case-crossover, panel) either separately for each study, or if appropriate, as part of the section numbering scheme. Specify the mean model and link function. Note the dependence model. Make sure analyses that are discussed in the text have details provided in the table. Specifically if there is a summer only and an all-season analysis, make sure summary information pertains to each of these. Key study issues need to be highlighted; these may be study- or design-specific. For instance, are there systematic chunks of missing data? Do panel study subjects come and go over the study period? (What is the actual duration of data collection? Can the percent of subjects reporting by study day, averaged over study days be calculated?) What is the referent scheme in a case-crossover study? Clarify key analysis details. Make it easier to find the results of any given study by providing a new index of studies in the appendix or including the page number of the appendix as part of the bibliography. Consider incorporating some kind of evaluation of study quality into the appendix, e.g. by adding comments about limitations.

Added information to include: Possibly as an appendix, please include details on:

Creation of density plots (e.g. Figure 7-2): These plots are not common in the literature and readers may not fully understand what they are presenting, particularly when results from a study are summarized to create a plot. Simple transcriptions of effect estimates and standard

errors from the more common percent change estimate and 95% CI to density plots will require relatively little explanation, but should be included for clarity and completeness. (And consideration should be given to the "value added" from this form of presentation.) More complex density estimates that are based on information summarized from the source papers require more detailed explanation. Readers will need to find the explanation for why in some cases the resulting distribution is not normal.

Calculation of cumulative lags: Papers report cumulative distributed lag models from a variety of constrained or unconstrained distributed lag models. The distributed lag effect estimate is the sum of effect estimates from all included lag days.* Thus, when the effect can be both immediate and persist over several days, the cumulative distributed lag will be larger than a single day lag estimate because it is incorporating the effect over multiple days. It is important that readers of the CD understand the difficulty behind comparing and contrasting multi-day vs. single-day lag studies since the parameters estimated from these studies are not the same.

Conversion of concentration and ventilation to dose (Table 7-2): Details of this calculation are needed, along with the simplifying assumptions.

Comments by section

7.1.3:. Study designs and analysis methods:

- Exposure assessment: The importance of using concentration vs. exposure or dose in an analysis shouldn't be lost on the conclusions. Separation of ozone sources into ambient-generated and non-ambient-generated allows better understanding of the strengths and weakness of epidemiological studies that use ambient concentration as a substitute for personal exposure (see e.g. Sheppard et al, in press; Sheppard in press). Use this conceptualization to help readers understand statements about misalignment of personal exposure and ambient concentration [e.g. p. 7-16]. The key issues accompanying the use of concentration instead of exposure in epidemiological analyses will vary by study design.
- [p. 7-16 and 3-60] Zeger et al (2000) describe three important sources of measurement error that are now repeated as dogma in description of measurement error. While this conceptual framework has merit in analyzing a time series study design, the study design that was being considered in that paper, the concepts do not generalize without modification to all air pollution epidemiology studies. (For further elaboration, see Sheppard et al, in press; Sheppard in press).
- [e.g. p. 7-8, l 28-30] Clarify the important time period for risk calculation. Specify whether overall risk should be presented as the sum (or integral) of risk over time, or as an average of daily risks. There appears to be some confusion about magnitude of risk estimates on single versus cumulative day lags.
- [p. 7-10; 17-20] The appropriate amount of smoothing in a time series study analysis is not identifiable from the data. (See the May 2003 HEI Special Report on revised time series analyses, page 66.)
- The discussion of model uncertainty and multiple testing is inadequate and shows lack of appreciation for the underlying statistical theory. (See also section 7.6.7) AIC and BIC model selection criteria don't incorporate model uncertainty into the conclusions [e.g. 7-13; 21-22]. As discussed above, the heavy reliance on significance tests, particularly within any single study, is problematic because the resulting Type I error rate will be

much higher than the reported value. By focusing on "possibly not identifying the best model" this literature neglects the bias and over-interpretation that results from model selection. Models are not a representation of reality but rather a useful (and often highly simplified) description of some aspect of reality.

- Data availability: There can be hidden effects on study results due to missing data, particularly when these data have strong structure. For O_3 an important consideration is for studies that rely on temporal variation -- are all seasons represented similarly in all areas. If not, this should be reported as it could affect the conclusions.

7.2 Field studies (panel studies)

- Panel studies that are conducted over a long time period, or have subjects who are not observed over the entire time period, may be subject to bias in the acute effect estimate if proper control of confounding is not included. One approach to the analysis is to separately estimate and not interpret the effect of average individual exposure over the time period of their data. I can't tell from the document if this was needed or done in any of the studies.
- There is insufficient information in this section to determine the quality of the analyses and judge the studies.
- [7-27; 24] Lack of statistical significance does not imply existence of a practical threshold.

7.3 (time series studies)

- Analysis approach is not study design [7.51; 4]
- It was difficult for me to determine whether the cool season analyses were more confounded than the warm season analyses. It is clear from the data presented in this chapter than population average ambient source exposure, due to time spent outdoors and infiltration, is typically higher in the warm season. I don't think the differences in results are driven by residual confounding alone, but likely also by differences in measurement error and concentration-exposure relationships by season. I suggest focusing on season-stratified analyses whenever possible.
- Specifically summarize how much of the year is represented in each of the cities in the 95-city analysis (Bell et al 2004). (For instance, what percent of the cities have data all year and what percent for various time periods.)
- Make sure the differences in cumulative lag effects versus single lag effects are not just a feature of the estimates. Quite likely these are estimating scientifically different parameters and should be treated as such.

7.6.2 (Exposure assessment)

- Discuss exposure assessment results in terms relevant to epidemiological studies. (See Sheppard et al, in press for ideas on how to do this.)
- Different measurement issues and exposure properties will dominate for different study designs. In particular, separate consideration of acute vs. chronic effect studies and individual-level vs. aggregate-level analyses.

Charge comments:

In responding to the charge questions, I focus my responses to my particular expertise, specifically issues pertaining to study design, analysis, and interpretation.

Charge Question C5b. *Chapter 7 highlights the evaluation of two large multi-city studies that examined ambient O_3 effects on mortality, i.e., the study of 95 U.S. communities and the study of 23 European cities. These studies show positive and significant O_3 effect estimates for all cause (non-accidental) mortality. Does the discussion of those studies adequately address questions regarding possible confounding by co-occurring PM, i.e., indicating that the O_3 effect on mortality is independent of PM? Also, is the issue of the seasonality of O_3-mortality effects adequately addressed?*

I'm concerned that data availability could be affecting conclusions in these large studies. For instance, many cities in the US only measure ozone for five to seven months of the year. Analyses that are supposedly year-long could be only incorporating information from some seasons. Clarify what information year-long analyses incorporate.

I'm not convinced that the seasonality issue can be sorted out without also addressing time-varying data availability and personal exposure vs. ambient concentration relationships.

Charge Question C5c. *The temporal relationship between O_3 exposure and the occurrence of health effects is important in animal toxicology studies, controlled human studies, and epidemiology studies. Most epidemiology studies find an immediate O_3 effect, with health effects having the strongest associations with acute exposure on the same day and/or previous day. What are the views of the Panel on the adequacy of the discussion on choice of lag period between ozone exposure and the observed health effect? Are sensitivity analyses appropriately considered to address model specification for adjustment of potential confounding by temporal trends in epidemiologic studies?*

Discuss the definition of cumulative lag mathematically, and justify its use scientifically. Strive to ensure there is some scientific justification for any lag period that is discussed. Otherwise the possibility that any one study is reporting the results of the most significant lag can become magnified in the synthesizing discussion.

Charge Question C5d. *Given our experience during the past several years in dealing with GAM-related statistical issues in the recently issued PM AQCD (October 2005), NCEA staff has generally excluded epidemiology studies using GAM with default convergence criteria from consideration in the current draft O_3 AQCD. Is the CASAC Panel in agreement with this choice?*

Based on my own reanalysis experience and my reading of the literature, I don't think GAM analysis with default convergence criteria is any worse than the effect of any one of a whole host of other issues that affect time series studies, and most likely smaller than many of these issues. For instance, Sheppard (2003) found the effect of single imputation (e.g. substituting in a predicted value for a missing pollutant observation) induced positive bias that was approximately equal in magnitude to the bias due to default convergence criteria in GAM. I favor including

important studies analyzed using GAM with default convergence criteria while noting this limitation in the analysis.

Charge Question C5e. *The O_3 AQCD evaluates the appropriateness of O_3 exposure assessments used in the epidemiological studies. Does the panel consider the discussion of ambient versus personal monitoring and choice of exposure indices to be adequate? How might it be further strengthened?*

With a limited few exceptions, epidemiological studies use ambient O_3 concentrations as the exposure variable. We know O_3 is highly reactive and very little O_3 penetrates indoors, particularly in closed buildings. Exposure is affected by personal behavior and this behavior has a population average seasonally varying component. Thus it is clearly important to consider the concentration – exposure relationship when discussing epidemiological study results for O_3. I think conceptualizing personal exposure into ambient and non-ambient source exposure is a valuable framework for epidemiological studies (see discussion above and Sheppard et al, in press). It is useful to estimate the concentration – response relationship, because this is the estimable quantity in an epidemiological study. However, it is important to also convey that the parameter being estimated is not toxicity, but rather (in time series studies) the product between toxicity and population average attenuation. The apparent community by season interaction in infiltration and the effect of smog alerts on high exposure [discussed e.g. 7-91] have important implications for analysis and interpretation of epidemiological studies.

Page-specific comments:

[7-6;23-25] Justify or reference statement.

[7-6; 25-31] This paper refers to measurement error in a specific study design.

[7-8; 28-30] Reference or justify statement.

[7-10;27-30] Unclear.

[7-14; 1-2] Allusion to Lumley and Sheppard is unclear to me.

[7-14; 4] Discuss how cross-validation helps or drop the reference.

[7-14; 6-7] I disagree.

[7-16; 20] I suggest replacing “more weight” for “emphasis”.

[7-16; 17-20] The sentence is stating that sample size and variance (both of which make up the estimate of variance of the effect estimate) are important components of the precision of a study. Sentence needs to be reworded.

[7-17; 1] I think the word is approach (i.e. analysis approach), not study design.

[7-18; 10] The use of "aggregate results" is unclear here.

[7-18; 20] Other acute study designs are presumably time series studies? Be precise when possible. The distinction being made is the individual-level vs. aggregate-level data and analysis

[7-18; 25] No question the limited number of observations over days and subjects limits power relative to time series studies. The loss in power is not offset by the increase in power possible from individual exposure assessment, but it is correct that the individual-level information is scientifically more valuable, at least when there is sufficient power.

[7-19; 21-22] Doesn't more variable imply less reliable?

[7-20 8] First occurrence of a statement that suggests that statistical significance is an indication of scientific importance.

[7-20] Table 7-1a: In order to compare, contrast, and interpret the analyses summarized in this table, it would be really helpful to know the mean models.

[7-25; 9] Example where inclusion of the CI would suggest the two studies being discussed have fairly comparable results, even though one is statistically significant and the other isn't. Of course additional information (about e.g. ventilation rate in the forestry workers, or other reason) might suggest otherwise.

[7-25; 20-21] Result was regardless of hike duration?

[7-27; 22-24] I don't understand the concept of a practical threshold used here.

[7-27; 28] I would want to know more about the details of the analysis before I would be completely comfortable with this statement.

[7-28; 13-16] While I agree cross-sectional studies can't distinguish between- and within-person variability (they only incorporate between-person variability), the issue is not specifically a power issue (although a longitudinal study with the same number of subjects and repeat measures on each subject will have more power, although, not to estimate the cross-sectional effects). Rather it is an interpretation issue.

[7-29; Figure 7-1a] It would be best to show only a single estimate for a specific group from each study. Ideally all would be single day lags (or the same distributed lag). For codes 3 and 4, why does the apparent cumulative lag effect have a wider confidence interval?

[7-32;13-15 and Figure 7-2] Here is an example where the derived density curve for the combined city-stratified analysis should be documented in an appendix. I don't understand why the combined city-stratified analysis was based on more subjects – both appear to be derived from the same dataset, just from analyses that use the data in different ways. Is the city-stratified analysis an average within-city estimate? Please clarify.

[7-34; 6-8] Please develop the personal vs. fixed-site comparison discussion more, either here or elsewhere in the document.

[7-35; 3-5] Here's an example where model selection could be the reason why it is the 10-day cumulative lag that is significant. Focus on the prior hypothesis, if identifiable, in reporting the results of this study.

[7-36; figure] It is difficult to tell if the included studies are comparable in terms of study populations, outcomes, lag days (both number and actual value), etc.

[7-38; 14] Also there was no significant interaction between cities found in the paper, suggesting no heterogeneity between city-specific estimates.

[7-40] Please rework the discussion of results using personal exposure.

[7-44; 8] Replace "lagged" with "accumulated"

[7-51; 3] Presumably the word "analysis" was meant rather than "study design"

[7-61] Why are there more apparent seasonal differences in the Samet et al study than the Bell et al study? The data represent longer time series and a few more cities in Bell et al, but really aren't that different. Is it fair to call the "all data" analyses of Samet et al and Bell et al "all year" analyses? I think seasonally-defined missing data leads to inherent difficulty in interpreting the results as all-year results.

[7-76; bottom] I didn't follow the results discussion for the Frischer et al study.

[7-77;30 – 7-78;2] Confusing.

[7-79;7] Insert "per day"

[7-80;12-16] Unclear

[7-82;1-8] Is there evidence these Mexico City results aren't driven or magnified by other pollutants?

[7-84;10-11] Good

[7-85;20-22] Unclear

[(7-88 to) 7-89; 1-2] While I agree with this statement in principle, I'm not convinced it is helpful. When ambient concentration is used in a health analysis, the effect estimate is a product of the pollutant toxicity and the attenuation of concentration to ambient source exposure. However, it is the concentration-response relationship that can be estimated directly from the data. Effects of changes in concentrations can still be estimated from concentration-response models, even if they need conversion to quantify effects of changes in ambient-source exposure.

[7-89; 8-16] The key consideration here is the estimate of β and what it says about exposure (which is addressed by discussing the percent of time spent outdoors) and not the statistical significance or lack thereof.

[7-89; 22-27] Reporting of slopes would be much better than correlations here (although reporting both is most informative).

[7-90;1-3] These results suggest the variability of non-ambient source exposures is similar in the two groups.

[7-90; section 7.6.2.2] It depends upon study design which exposure assessment improvement is the most important.

[7-91; 2-3] This gives clear evidence of a community by season interaction in infiltration due to major differences in population behavior in the different communities.

[7-91; 26-28] Population-average change in behavior as a function of high concentration makes it much more difficult to estimate health effects from population-based studies. This suggests sensitivity analyses should be done to eliminate high concentration days, particularly in areas where avoidance behavior is common.

[7-94; 12-13] Unclear

[7-94; 7-10] I agree that there is an important role for exploratory analyses in understanding relationships. The problem comes when these are reported as hypothesis testing results.

[7-95; 25-26] Isn't this just because the parameters being estimated are different?

[7-99; 7.6.5] Please expand the title to indicate this pertains to the time series study design.

[7-101; 14] The word is "temporal".

[7-102; 1-14] Another consideration is that due to seasonally-varying population behavior and ventilation, the estimated exposure effect isn't constant by season. The two approaches to analysis are reassuringly similar when the seasonal variation in the exposure effect is removed by stratification.

[7-103; section 7.6.5.2] I think this section needs to also address data availability, time-varying infiltration, and time-varying time spent outdoors. Thorough revision of the section is probably necessary.

[7-107; 22-31] Clearer description of summary density curves is needed; please provide a reference and/or details in the appendix. Is a "pooled normal distribution function" still normal as is implied by the wording? (Or is this actually a mixture distribution?) If so, why is its

derivative "distribution-free"? Perhaps "non-standard" is a better word than "distribution-free" since a distribution can't be distribution free.

[7-110; 3-4] I don't understand and probably don't agree. The estimates from concentration – response models are a product of toxicity (which may not vary across season) and attenuation (which almost certainly varies across season).

[7-116; section 7.6.7] Thorough revision of this section is needed.

[7-117; 20] I don't think the Koop and Toole paper is of sufficiently high quality to merit discussion in this document.

[7-119] The threshold discussion needs revision.

[7-122; 10-11] While the statement is most likely true, the key question is how. The answer to this question will vary by study design since study design is a lens through which different aspects of exposure are magnified or blurred.

[7-127; 14] Doesn't change in ventilation affect dose rather than exposure?

Chapter 3 Comments

[3-37] Please report the estimated trends and standard errors (or CIs). It would be preferable to fit the models to all the data rather than the annual maxima. I wouldn't be surprised if the results for all the data vs. the maxima were different.

[3-60] Same comment as above for the Zeger et al (2000) paper implications.

*__More comments on distributed lags__ (Summarized from Schildcrout and Heagerty, under review; see also Diggle et al (2002), section 12.4.2)

Assume a disease model of the form

$$g(E(Y_{it} \mid \mathbf{X}_i)) = \alpha + X_{it}\omega_0 + X_{i(t-1)}\omega_1 + X_{i(t-2)}\omega_2 + X_{i(t-3)}\omega_3 + X_{i(t-4)}\omega_4$$

where the outcome Y_{it} is conditional on the entire history $\boldsymbol{X}_i$ of exposure on that subject. This model represents a 5th order distributed lag model. The coefficient $\omega^* = \omega_0 + \omega_1 + \omega_2 + \omega_3 + \omega_4$ is a summary measure, the cumulative distributed lag coefficient. Fitting a model with exposures X_{it} on days t through t-4 will give coefficient estimates $\hat{\omega}_0, \hat{\omega}_1, \hat{\omega}_2, \hat{\omega}_3, \hat{\omega}_4$ and an unconstrained distributed lag estimate $\hat{\omega} = \hat{\omega}_0 + \hat{\omega}_1 + \hat{\omega}_2 + \hat{\omega}_3 + \hat{\omega}_4$. Note that the cumulative lag estimate assumes an equal one-unit increase in exposure over all five exposure days. Alternatively, we can assume a cross-sectional model with only exposure on the current day included:

$$g(E(Y_{it} \mid X_{it})) = \alpha + X_{it}\beta_0$$

While the outcome is still dependent upon the entire covariate history (i.e. the underlying model is the full history model given above), the cross-sectional model assumes dependence only on the previous day. The parameter β_0 is approximately a sum of ω values, but this sum has weights that depend upon the day-to-day correlation in the exposure series. For an underlying linear distributed lag model (i.e., $g(\cdot)$ is the identity function), a stationary and mean zero exposure series with autoregressive dependence structure (AR-1 with parameter ρ), the cross-sectional model will have parameters α and β_0 where $\beta_0=\omega_0+ \rho\omega_1+ \rho^2\omega_2+ \rho^3\omega_3+ \rho^4\omega_4$. This relationship holds approximately for other link functions. Note that when the health effect is distributed across multiple days, both the cumulative distributed lag and the single day lag (cross-sectional) model parameters are distributed lag parameters, just with different weights applied to the different lag days. The single-lag model gives weights induced by the structure of the exposure series.

References

Schildcrout JS, Heagerty PJ. Regression analysis of longitudinal binary data with time-dependent environmental covariates: Bias and efficiency. Conditionally accepted to Biostatistics

Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. Analysis of longitudinal data, 2nd edition. Oxford, Oxford University Press, 2002.

Sheppard L. Acute air pollution effects: Consequences of exposure distribution and measurements. *Journal of Toxicology and Environmental Health*. In press (July 2005)

Sheppard L, Slaughter C, Schildcrout J, Liu L-JS, Lumley T. Exposure and measurement contributions to estimates of acute air pollution effects. *Journal of Exposure Analysis and Environmental Epidemiology*. In press (online version available as of Dec 15, 2004).

Zeger et al (2000) [reference listed on page 7-147, lines 44-46]

Dr. Frank Speizer

Review of Chapter 7, Ozone CD, Draft 1.

Submitted by Frank Speizer

General Comments:

Although the Chapter follows a logical outline of moving through acute and chronic effects of Ozone from morbidity studies to mortality studies and from acute effects to chronic effects, and thoroughly covers the topics, I found the presentation ponderous and repetitive. In addition, I am concerned (although the effect was to shorten the document somewhat) that by cross referencing to the PM document as a source for some of the details (which may not be needed anyway), that the Ozone CD may suffer or be criticized as not being able to stand alone. I am not sure to what degree that is important.

As I have criticized previous recent CDs this one also is too long and repeats material that in 2005 does not have to be in a CD. For example, I do not think that quoting Hill's postulates is necessary any longer. And going to the extreme of specifically quoting from his paper of 40 years ago seems over the top. Another example is the paragraph on top of page 7-9 (7.1.3.4 Model Specification Issues).

The section 7.1.3 that provides details of study design and is indicated as a preamble seems to be written by a frustrated author who would like to publish a general textbook on air pollution epidemiology. This is compounded further by section 7.6 that considers all the elements of confounding, measurement error, and bias again.

The other concern is that there are sections that again would be better left out since they are covered in the previous chapters and although stated here to put into context, do not add significantly to the understanding of the points being made and could just as easily had the reader refer to the previous chapter (which is at least on the same computer disc, rather than in a different CD)

Finally, data **are** always plural and a general search for the verb after the use of data as noun needs to be done.

Specific Comments:

Page 7-20, line 6 and subsequent table: Unless there are more serious concerns about Scarlett et al, 1966, I do not understand the justification of leaving out FEV.75. It could be converted easily to an estimate of FEV1.

Page 7-21, Table 7-1b: By not taking level of FEV1 into account and using absolute change in FEV1 the data in the table cannot be compared across different studies. A 50cc drop in FEV1

for a child is much larger that a similar drop in an adult. It is precisely for this reason that some of the studies used % change.
Page 7-26, table 7-2 and line 6 at bottom. Statement says 'confirm and extend clinical observations…" But table shows no dose response relations between dose and change in FEV. In fact lowest dose has greatest change and highest dose least change.

Page 7-30, Fig 7-1a and 7-1b: The logic of showing the data by difference in effect size seems inappropriate. The presentation is misleading and suggests a lot more data than actually exists. For example studies 3, 5, 12 are the same children with 1,0, 2-day lags.

Page 7-31, line 16, change: …subpopulation of asthmatic children with a history of low birth weight or prematurely had significant …

Page 7-31, lines 19-though end of next page: Explanation of summary density far too wordy and could be simplified and much shorter.

Page 7-33, line 12: Don't the declines have to be associated with a change in level of O3? If so, what level?

Page 7-33, line 14-16: What are authors trying to say. Is there a threshold at 80?

Page 7-40, line 26: Add: "However, there are a number of well conducted, albeit relatively smaller studies, that have not found these effects".

Page 7-40, lines 30-31, move: "in school children" to …reported in school children evening …

Page 7-43, Para 7.2.6 first and then line 21: Why does 1933 subjects get counted as especially valuable and 27,793 not? Yes, there may be more comprehensive characterization of health outcome but is not size.

Page 7-44, end of line 11: It is not necessarily the case. Time outdoors, crowding, lack of potential interaction with other pollutants, all potentially different, and besides do not need to justify that might be generally applicable.

Page 7-51, sentence ending line 8. I think the evidence is weak at best and this conclusion ought to indicate that.

Page 7-51, lines 20-25. These factors related to all time series studies, particularly with O3 and not just hospital admission.

Page 7-52, figure 7.7 European data seems plotted wrong. Not clear how all ages can have higher effect levels than the various sub groups for the same lags. In addition I found the table fairly useless since different age groups and different lags are similarly presented.

Page 7-53, figure 7-8, Suggest taking out all ages since it simply falls between the subgroups and clutters the figure.

Page 7-62, figure 7-10: Presenting different lags for different studies makes for confusion in this figure. May need to separate into separate figures with consistent lags.

Page 7-65, line 14: The 7% figure seems a little high. It seems to come from one Australian and one Canadian study, and none of the US or European studies are that high. Suggest use a lower figure, and indicate the potential higher figure for outliers.

7-72, line 18-21. May want to break this into two sentences as effects on respiratory mortality seem stronger, albeit, less impressive in terms of numbers, than cardiovascular.

Page 7-74, line 9-10 and summary 16. May be putting too much weight on Sunyer et al. The number of cases with severe asthma aged 2-45 with mortality is quite small. Need to soften conclusion.

Page 7-84, line13-14: This sentence could be eliminated.

Page 7-85, line 21. Need to define better where the 556 hours comes from.

Page 7-87, Section 7.6: The key word here is "Interpretative Assessment"

I do not find this section doing what it is supposed to do. It simply repeats much of what has already been said. In fact sections 7.6.2-7.6.3 reports what is in earlier chapters. There is also a long discussion of what is in the preamble to this chapter.

Figures 7-15-7-17: These probably belong closer to the text that describes the data with lags. It would better serve those sections and reduced the confusion in the previous text that mixes all the lags together. Put here they are wasted as the section ends on page 7-99, line 16.

Sections 7.6.5 up to page 7-130 is really a repeat with further details of what is in the introduction. Each section of it is even more frustrating as it ends with more research is needed. I do not see this as interpretive.

Section 7.6.11, Summary: This is simply a restatement of the conclusions in every other section with added words that really are not helpful. If one were interested in not having a standard that one could quote back to EPA the statements such as "confounding may be of concern"….."morbidity and mortality outcomes is still inconclusive" …."bias effects estimates toward the null" …."multiday lags should be investigated" …"uncertainty regarding extent of confounding" …."seasonal variability may be considerable" …"Bayesian models…may be useful but limited" …."conflicting evidence regarding thresholds" I am sure some reviewers will. All these things may be true and have been discussed in the text. What is needed here is a summary that will get us closer to providing staff with number they can use to promulgate a standard rather than reject one!

Dr. James Ultman

Ultman's Comment on Chapter 4: Dosimetry, Species Homology, Sensitivity, and Animal-to-Human Extrapolation

GENERAL COMMENTS

I) The EPA Reference Concentration Method (not referenced in the AQCD) provides a framework for determining equivalent exposure concentrations between rats and humans. This method is based on providing an equal O_3 flux to target tissue. The method becomes more reliable, the more we know about lung geometries, regional distribution of mass transfer coefficients, and the location of the most critical damage sites. Since the last AQCD, progress in the geometric construction of airways by MRI and other imaging modalities has improved our definition of lung geometries in rats and in man. Three-dimensional mathematical modeling methods have also improved out knowledge of mass transfer coefficients, particularly in the nasal passages.

I suggest that some reference be made to the Reference Concentration Method (RCM) in the revised document. As suggested by Fred Miller, chapter 4 currently lacks a discussion of the basic principles on which dosimetry modeling rests. Materials from the RCM including figures may provide useful in that regard. A summary of the chapter could then be framed by the question: "how far have we come in providing the information required by the RCM in order to make a reliable extrapolation from animals to man?"

II) Whereas previous dogma was that O_3 damage was focused in the proximal alveolar region, recent data in young nonhuman primates has indicated that far more attention should be paid to the conducting airways, particularly in the developing lung. Evidence is also accumulating that some products of biochemical ozonolysis may be toxic. This has not been adequately or realistically included in most mathematical models to date.

SPECIFIC CHANGES

4-2-27 Delete "the"
4-3-26 Add "distribution" after "absorption."
4-4-20 to 4-5-4 These few sentences are difficult to follow. The material should be rewritten so that there is a more logical flow.
4-5-20 This sentence is not correct as written. It should state that "Fractional absorption ranged from 0.56 to 0.98 and had a statistically significant but weak dependent on concentration, minute volume and exposure time.
4-6-3 "Intersubject differences.."
4-6-13 …"At a fixed minute volume, they found an inverse correlation…"
4-6-16 and 17. "…a general decrease in uptake efficiency as breathing frequency increased and tidal volume decreased.
4-6-17 and 18 "Ozone uptake rate correlated with percent changes in individual bronchial cross-section…"

4-22-22 and 23 "…the hypothesis that changes in cross-sectional area available for gas diffusion are related to overall O_3 retention.
4-7-7 Can a reference by cited for the statement that "shorter paths showing greater damage."
4-8-17 and 18. This sentence is incorrect. See Eq. 9 in the Bush(2001) paper.
4-9-17 Delete "of"
4-9-23 and 24 " …O_3 is removed equally by mouth and nose" is not consistent with the bolus data of Kabel, J.R. et al. (J. Appl. Physiol. 77:2584-2592, 1994) or with the bolus data of Nodelman et al. (J. Appl. Physiol. 87:2073-2080, 1999).
AX4-14-9 What are the two situations that "1 to 25%" and "1 to 40%" refer to?
AX4-16-21 "…ppm O_3 for 3…"

Ultman's Comment on Chapter 11: Effects of Ozone on Man-Made Materials

Chapter is well-organized and effectively presents the limited data available in the peer-reviewed literature. I would guess that a far greater amount of data is available in internal manufacturer's reports.

Chapter begins with a section on mechanisms of ozone damage (as of yet incomplete?) that only discusses elastomers. This is followed by sections on; Textiles & Fibers; Dyes, Pigments & Inks; Artist's Pigments; and Surface Coatings (paints, varnishes and lacquers).

What is missing from this chapter is the relevance and the relative economic importance of these data in practical situations (e.g., art galleries, painted buildings, tires). A major problem in this regard may be that the data is, by in large, on "pure" materials whereas actual materials contain mixtures or even layers of mixtures.

Dr. Sverre Vedal

May 2005
Critique of Ozone Criteria Document draft
Sverre Vedal

Chapter 8 (Integrative synthesis)

Overriding issues:
1. Concluding synthesis.

The all-important concluding sections, sections 8.4.10-12, need to be rewritten in order to best integrate the experimental and observational findings into a meaningful synthesis. The writing here is imprecise and somewhat careless. It would be preferable to have this entire chapter written by either one person, or a small group working very closely together. Preceding sections, while still requiring some work (detailed below), do not require this degree of revision.

The task in these concluding sections, which is ably introduced (starting section 8.4.10), is to assess the coherence of the scientific findings, specifically how the experimental human work and the toxicological work cohere, or fail to cohere, with observational findings. What we get instead are vague generalities mixed with reporting of specific findings that fail to make the intended points. We have a great deal of coherence in addressing ozone-induced acute lung function decrements. There is good coherence in addressing other respiratory outcomes such as hospitalizations and exacerbations, and arguably for asthma-related outcomes, specifically. There is less coherence in addressing cardiovascular outcomes, which is not addressed here. In short, we get little sense here as to where there is good coherence, where there is very little coherence, and where the data are inadequate for assessing coherence.

Some specific points:

i. The discussion of AHR (8.40-41) loosely and repeatedly links AHR and decline in lung function. While there may in fact be such links, AHR and lung function declines are best treated as separate phenomena. How is AHR responsible for lung function declines seen in epidemiological studies (8.41[12])?

ii. There is repeated mention of "respiratory-related mortality" (8.44-46), whereas the epidemiological studies deal primarily with total mortality (hence, cardiovascular mortality), or the subset of cardio-respiratory deaths (dominated by cardiovascular deaths). Clearly there is some coherence when considering respiratory outcomes, but the evidence is pointing to more general mortality effects. Yet, there is no mention here as to whether this is plausible.

2. Adequacy of analysis of time-series studies.

The uncertainty that has recently been reintroduced into the PM time-series findings related to model specification of temporal trends and meteorology is likely as acute for ozone as for PM; there has just been less emphasis placed on it to this point. Therefore, statements such as "adequate control for seasonal patterns" (8.15[19]) are overstatements. The section that focuses on confounding by temporal trends and meteorology (p. 8.22) largely glosses over this, although the concluding paragraph here is appropriately cautious.

3. Cardiovascular mortality.

The recent multi-city time series all find associations between short-term changes in ozone concentrations and total mortality, indicating that the association is with cardiovascular mortality, since this cause-specific mortality typically "drives" associations with total mortality. When this is specifically addressed, that is, when cardiovascular mortality is specifically examined, this is in fact what is happening. There is a disappointing avoidance of the implications of this finding. Specifically, is it plausible given what is known about ozone toxicology, etc? Plausibility and coherence can be addressed within the epidemiological setting, or more typically, by integrating findings from human experimental, toxicological, and epidemiological studies. Limited to the epidemiological arena, the few studies in which associations with cardiovascular hospitalizations were assessed (p. 8.16) find none. Further, there are precious little toxicological or human experimental data that bear on this, although there are some, and, given the significance of this finding, these should be summarized in this chapter.

4. Chronic effects of ozone (section 8.4.6).

The discussion of potential chronic effects of ozone is inadequate. There is an implication here that we have very little data to address this question. This is not really the case. The highlights of work on this question include the infant non-human primate studies from Davis and the two university studies (the Tager and the Kinney studies), indicating effects on lung morphology and lung function, respectively, and the Southern California Children's Study (8.20) and the ACS cohort study, indicating no effects on lung function and mortality, respectively

5. Ozone exposure and its effect on interpretation of epidemiological findings.

Exposure is more problematic for ozone than for PM, for example, especially for mortality outcomes where those at risk of death likely have the least exposure to ozone, and are least likely to be exercising. The attempt to discuss the implications of this is not adequate (pp. 8.20-21). While it may well be true that there is good correlation between ambient and personal ozone concentrations over time, thereby motivating use of central monitoring in time series studies, a measure of correlation does not provide the complete picture, since even though correlations may be good, the absolute concentrations of personal exposures are considerably lower. This implies that if the time series associations are valid, the estimates of effect based on ambient monitors must be biased upwards.

This raises a further issue of plausibility. Effects are being estimated at relatively low ambient concentrations. True population exposures are, however, substantially lower than these already low concentrations, implying that if these effects are real, they are occurring at very low concentrations indeed. The implications of this for the interpretation of the epidemiological findings need to be included in this chapter.

Measurement error also has implications for being able to detect a threshold (8-24) at the population level in epidemiological studies (Brauer, Risk Anal 2002). However, while the measurement error is likely nondifferential in the case of PM, in the case of ozone there is both a bias upward in the estimated population exposure, as well as scatter around this estimate (Berkson error). The impact of these measurement errors on threshold detection has not been studied for the case of ozone.

6. Where is a discussion of ozone-allergen interactions?

Some years ago there was great interest in the potential effect of ozone exposure on enhancing airways responsiveness to allergen challenge. I find no mention of this potentially important effect in this integrative chapter.

Specific points:

I would prefer changing all mention of adaptation or tolerance of ozone effects, which are loaded terms, to attenuation, for example, a term that has less of a mechanistic connotation.

p. 8.4-5. Tables 2 and 3 summarizing criteria for determining ozone responses from the 1996 document are out of place here. If these are felt to be important, which is doubtful, placement in the discussion of the toxicological and experimental findings (8.27) is preferred.

p. 8.11. I don't believe that the statement that the role of GAMs was to make quantitative mortality estimates more *meaningful* is using quite the correct descriptor. Perhaps *valid* might be better, although even that is arguable.

p. 8.24. While it is true that ozone mortality effects are correctly described as "small," this does not distinguish them from PM effects.

p. 8.29. Mention is made that cells in the conducting airways are the primary targets for ozone, but later it is stated that cells in the CAR (8.33) are the primary targets. I presume the latter is the case.

p. 8.33. One should be careful in taking the findings from the Sherwin study (line 9) at face value, given concerns about the reliability and meaningfulness of the histological findings in that study.

p. 8-36. It is claimed that there is no experimental evidence of adverse human cardiac effects, but this is not strictly true (see Gong, Am J RespCrit Care Med, 1998).

p. 8.42-43. The points in this discussion are important enough to require much clearer exposition. Also, the infant rhesus monkey findings indicate more than "possible injury-repair processes."

p. 8.44. The focus here is on respiratory mortality, for which there is reasonable coherence. But, the findings also implicate cardiovascular mortality (see discussion above in point 3. Also, these effects can in no way be described as *strong* effects. Based on the size of the effect estimates, these are weak effects.

Editorial:

p. 13 (9) "field"

p. 16 (15) "APHEA"

p. 8.38. "pathological symptoms" in animals?

Chapter 7 (Epidemiology)

Overriding issues:

1. Tone.

The preamble section (7.1) does a good job of identifying important issues in interpreting the findings of the epidemiological findings on ozone effects. I find the presentation and interpretation of findings in this chapter refreshingly fair. There is also appropriate caution regarding the complexities involved in modeling seasonal effects of ozone (section 7.6.5).

2. Cardiovascular effects.

Because the findings with respect to mortality indicate, as was the case for PM, that not only are the associations present for respiratory mortality, as expected, but also for cardiovascular mortality. See my comments on chapter 8 cardiovascular mortality effects.

3. Exposure and plausibility.

One is left with the impression that because there is good correlation in some studies between ambient and personal ozone concentrations over time, that exposure issues in the epidemiological studies are not so critical. On the contrary, exposure issues are more acute in the case of ozone than they were in the case of PM. Not only is there misclassification in individual exposures when a single ambient measure is used, or when any single population measure is used (Berkson error), but this ambient measure seriously overestimates mean population exposure to ozone, which is dramatically different from the case of PM. This overestimation results in bias, in this case a bias to the null.

This raises a further issue of plausibility. Effects are being estimated at relatively low ambient concentrations. True population exposures are, however, substantially lower than these already low concentrations, implying that if these effects are real, they are occurring at very low concentrations indeed.

4. Chronic ozone effects.

In line with my comments on this topic for chapter 8, it is recommended that p.7-87 (line 2) change wording from "not as conclusive" to "inconclusive." Further, my take on the finding from the ACS study on long-term ozone exposure and mortality, the most important in this regard, suggests that this merits more than "The current evidence is conclusive…" (line 3); I suggest "There is currently little evidence…".

Specific points:

p. 7.3. Panel studies do not seem to fit into this classification of designs.

p. 7.7. The second type of error has little to do with indoor sources in the ozone context. This error is simply one of overestimating exposure when using ambient monitors.

p. 7.8. When choosing a largest single day lag, there is an upward bias away from null, not toward it. This choice, however, does likely underestimate any cumulative lag effect of ozone, but this is not a form of bias, just a function of what one wants to estimate. That is, single day effects are not attempting to estimate the overall impact of ozone. A better exposition of these issues is presented elsewhere in this chapter (pp. 7.51 and 7.61).

p. 7.18. To be clear, rarely are individual level data on exposure available in field studies.

p. 7.35[10]. The interpretation of the seasonal drop in lung function in berry pickers (Brauer 1996) as being due to ozone is an overinterpretation. The design of the study did not allow an effect of ozone to be distinguished from that of any other cause of such a seasonal drop in these workers.

p. 7.43. The findings purporting to show an effect of long distributed lags on school absenteeism (Gilliland 2001) are accepted at face value. However, it is almost impossible to tease out ozone effects from other temporal effects over this length of time span.

p. 7.44. The study by Gong (Am J Respir Crit Care Med 1998) is described as finding no evidence of an effect of ozone on cardiovascular outcomes, but that is not strictly true.

p. 7.51. Given the many studies in which no association between ozone concentrations and respiratory ER visits is found, this conclusion is perhaps too strong.

p. 7.76. There are many references in this chapter to growth in lung function. No one knows whether the observed effects have anything to do with lung growth, or whether, for example, these are effects that are reversible over the short term, implying perhaps airway inflammatory effects rather than effects of lung growth. Even though investigators commonly refer to lung growth, this chapter should be more careful.

p. 7.80. The authors put the Sherwin study in the proper perspective by pointing out concerns about the histological findings in that study.

p. 7.83. Mention should be made that the findings on new onset asthma in the McConnell study were based on a very small number of subjects and should therefore be interpreted very cautiously. This findings needs to be balanced against the large number of findings, albeit largely cross-sectional, that have found no association between asthma prevalence and ozone concentrations.

p. 7.86. The effect in the Pope ACS study cannot be described as a strong effect.

p. 7.89. There was no reference to the initial Brauer study (J Air Waste Manage Assoc 1995), which is perhaps more informative than the one actually referenced.

p. 7.90. Again, while it may well be true that there is good correlation between ambient and personal ozone concentrations over time, thereby motivating use of central monitoring in time series studies, a measure of correlation does not provide the complete picture, since even though correlations may be good, the absolute concentrations of personal exposures are considerably lower.

p. 7.112. Note that the issue of interest here is not the correlation between personal exposure to ozone and personal PM, but rather to the ambient component of personal PM, which might be indirectly reflected in personal sulfate measurements. The findings on personal ozone and personal sulfate should therefore be discussed here.

p. 7.118 (section 7.6.8). This discussion of thresholds could add some discussion of the impact of measurement error on the ability to detect a threshold in population studies.

p. 7.122. Note that the individual city effect estimates in this study were the Bayesian estimates of city specific effects, not the unadjusted individual city effects as presented in the NMMAPS findings on PM. These are therefore "shrunk" to a common mean, making them more similar and less likely to give an impression of heterogeneity than the unadjusted estimates. While either approach may have some merit, and there is clearly justification for taking a Bayesian approach, the fact that this was done should be clarified.

Dr. James (Jim) Zidek

Comments of the Draft Ozone AQCD, 2005
General & Chapter 3

1. Document as a whole

1.1. Major accomplishment. The authors have done an extraordinary job of synthesizing a huge literature on large number of topics and they are to be commended. The **Draft,** as it will be referred to hereafter in these comments, is written with clarity and balance. It is well-focused on the mission at hand, that of assessing the ozone AQS. Moreover, it seems remarkably comprehensive although there are some gaps, the subject of comments that follow.

1.2 Accountability. The Draft does not address the cost-benefit tradeoff of ozone control with respect to primary standards although Chapter 9 discusses that issue for secondary standards. In particular, it gives no indication of the cost-benefits of current standards or principles by which future standards might be analyzed.

This seems surprising. Ever since 1971, Federal mandates have emphasized the importance of that issue and the Congress's 1993 Government Performance and Review Act covers all programs including those stemming from the Clean Air Act. Moreover, the EPA has estimated the costs of air pollution control ($500bi dollars for the 20 year period ending in 1990) and published studies relating to it (for discussion see the HEI Accountability Working Work). Even mortality was monetized. Therefore it is unclear to what extent this gap stems from lack of relevant knowledge and to what extent, other factors. Something on this issue in the Revision (or other document) would seem worthwhile, especially if changes in the AQS are to be recommended.

1.3 Chronic vs Acute Effects. Relating to 1.1, with respect to primary standards the Draft contains little about chronic effects as compared acute effects. In fact, only 11 pages in Chapter 7 address that issue (**Section 7.5)** and none from a cost benefit perspective. Yet undoubtedly chronic effects would lead to higher societal costs than acute.

With respect to secondary standards, **Chapter 9** does devote a whole section (**Section 9.8)** to economic analysis and presents quite a thorough comparative discussion of the two kinds of effects (see for example **Page 9-58, line 13**). Yet even here we find no comparison is found of the relative costs of the two types of effects.

Undoubtedly the omission in this case derives from lack of knowledge. However, it points to another potentially large source of uncertainty surrounding the benefits of controlling ozone that should be mentioned in the Revision (or related document).

1.4 Criterion metric. AQSs involve complicated criteria metrics (e.g. the 3 year running average of the second highest value per year of the daily maxima) that *de facto*, become the

guardians of health of welfare. Does the knowledge base suggest an appropriate metric? If so, the Draft does not seem to include the answer to this seemingly fundamental question.

1.4 The US ozone monitoring program. Although the regulatory program is based on the data provided by ambient monitoring and although the monitoring network now has a very large number of sites, the Draft does not offer any evidence that the monitoring network is adequate for its intended uses. [In fact, it is clearly inadequate for some, as in rural areas the authors had to resort to modeling (kriging) to overcome inadequacies of measurement (see **AX3, line12**).] At present non-scientific criteria play an important if not primary role in deciding the number of monitors in a region and where they should be placed. Yet given the advances in knowledge reported in the Draft, it seems surprising that a scientifically sound basis has not been developed.

More technical issues around this point are presented below but just to emphasize more fundamental issues, the Draft struggles between two conflicting goals for the monitoring data. One is implicit, that of serving the regulators. That in turn would argue for their placement in locations that would maximize the probability of non-compliance. Hearsay evidence suggests that CTMs have been used to help identify the ``hot-spots''. If indeed, that were true, then the resulting network might well be ideal for that purpose.

However, an entirely different goal is explicit in the Draft, that of ``characterizing'' the ozone field (see for example, page **3-1, line 25)**. The ideal here would not be well served by the design best serving regulatory goals for it would be biased since the measured concentrations would be upwardly biased and give a misleading characterization of the ozone field, making the estimated ozone concentrations too large. Here the ideal would be some sort of purely random distribution of monitors, stratified by urban-rural, elevation, etc.

Yet there is a still another purpose for a network, that of assessing risks. Then the ideal network would have monitors split evenly between hot - spots and cold - spots to maximize contrasts. That network would not be optimal for either the purposes above but might provide the highest power for tests of association.

Given sufficient resources, networks could be designed to address all three objectives. Moreover, the non - scientific component of the site selection process might well mean the current network serves all three purposes adequately, albeit in a sub - optimal way. In any case, the Revision should include an assessment of the monitoring program and its ability to meet the needs of the ozone regulatory program. Can it detect non-compliance with a reasonably high probability and if so how likely is it to produce ``false positives''?

2. Chapter 3

page&line

3-31, line 19. This line goes to the adequacy of design question raised in the general remarks. One issue that has not been explored in the Draft concerns the role of the urban intersite correlations in support the use of a single hourly value for risk assessment. For one thing the

hourly (and daily maximum) ozone concentration field does not have a Gaussian (or multivariate t) probability distribution making it unclear how well correlation actually describes the intersite stochastic dependence.

Much of that correlation comes from temporal patterns in the data, for example, diurnal variation. However, that variation is associated with a number of things such as temperature, a competing health risk factor. Ideally, it would be desirable to separate the ozone and temperature components of the signal and determine the flatness of their individual fields. At the very least, prefiltering the temperature and ozone series by removing the low frequency components would help separate the two series for acute health risk analysis. But that would likely lead to a drop in the spatial correlations and uncertainty about the flatness of the ozone field.

Even if the hourly ozone concentration field were "flat" enough to make its mean level an adequate descriptor, a more relevant field for regulatory or epidemiological purposes would be the fields of daily maxima (or other metrics). The criterion metric itself involves even more extreme values (2nd largest daily maximum over the year). This raises some questions about the adequacy of the monitoring network not addressed in the Draft.

The issue can simplistically be phrased as follows. Suppose the criterion metric has been measured at each of the urban monitors in a given urban area. How well would the information provided by the existing network predict the value of that metric at say, an elementary school located say mid - way between two of those monitors?

For some insight into that issue consider Fig 1 below. Here we see the result of taking successive maxima over 1 hr, 24hrs and so on to 144hrs (6days) of (square root transformed) ozone concentrations for 19 selected sites represented in the AQS Database. Intersite correlations were computed for these successive maxima between site #1 and each of the remainder so 18 broken line plots are seen. Calculations were for a single ozone season (1997).

Most sites are in the Eastern USA and some pairs are quite close to each other.
The intersite correlations for a single hour are quite high (considering sites are widely dispersed) although not as high as might be seen in a compact urban area. The result of taking the successive maxima produces a variety of different results as seen in the graphs. For one pair we see a fairly steep decline in going to the daily maximum, yet an increasing trajectory thereafter (except for the last segment). For another we see a more or less monotone decline.

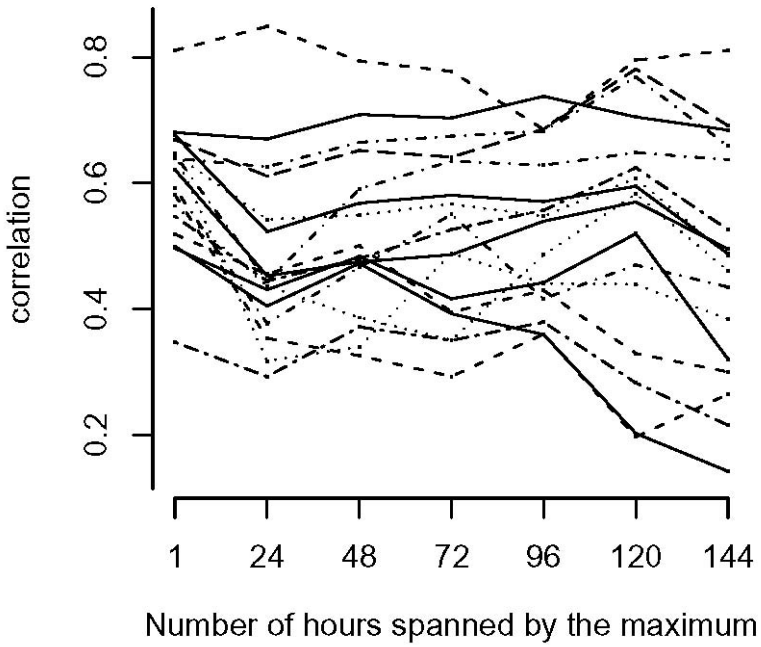

Fig 1. Intersite correlations between the site 1 and sites 2 to 19 for 19 selected sites from the AQS Database, 1997, all located in the Central and Eastern USA. The original concentration data were square root transformed to give the hourly values at least an approximately Gaussian distribution.

While superficial, these results demonstrate the complexity associated with fields of extremes. Their behavior as seen in the plots reflects things as the direction of prevailing winds. Two sites along a prevailing wind direction might have an intersite correlation that is sustained over the calculation of successive maxima while two orthogonal to that direction might see it decline.

The field for the criterion metric would likely be even more variable than those considered above. Therefore it seems unclear how well that elementary school would be covered by the primary standard.

3-36, line 28. What's the mean conditional on? This should be explained.

3-40. Chen (2002) is not in the reference list.

3-41, line 16. From the point of view of health risk analysis where daily maxima are used, this definition of co-occurrence seems too restrictive. Different pollutants may reach their peaks at different hours and co-occur over the day.

3-44, line 5. A problem associated with CTMs is that of characterizing the uncertainty in their predictions. A method that overcomes this problem to some degree is described below (**3-46**).

3-45, line 3. The northern, southern hemisphere or both for “winter” and “spring.”

3-46, line 18. CTM simulated data versus monitoring data. These two kinds of data cannot be compared directly. The former come from models for large atmospheric scales while monitoring data represent micro-scales.

However, Fuentes and Raftery (2005) offer a non - naïve way of integrating these two kinds of data (“Bayesian melding") and demonstrate its application to CASTNET and Models – 3 data for hourly SO2 concentrations. They show how their conjunction can be profitably exploited in spatial prediction.

Their model assumes an unmeasured latent field, the “truth,” that connects the simulated and real data. The CTM is then seen as measuring the integral of the truth over grid cells (possible with additive and multiplicative bias). On the other hand, monitors measuring it with error at specific points. Their estimated CTM biases enable the simulated data to be adjusted to correspond to the measured SO2 concentrations. Moreover, both can then be used for spatial prediction.

Zidek and his co-investigators at the University of BC have been applying the same method to AQS data for O3 and output from the MAQSIP model. That unpublished work shows the CTM bias to vary by hour, day and location. Table 1 shows some of illustrative results computed by Zhong Liu.

Hour	Additive-bias	Multiplicative-bias
1	1.289	0.607
2	1.897	0.505
3	2.904	0.391
4	2.177	0.511
5	2.051	0.560
6	1.061	0.725
7	-0.004	0.953
8	0.521	0.946
9	1.202	0.883
10	-1.122	1.195
11	-3.013	1.715
12	-2.987	1.729
13	-3.985	1.721
14	-5.941	1.927
15	-8.102	2.102
16	-8.585	1.992
17	-6.662	1.591
18	-3.248	1.139
19	-1.104	0.919
20	-1.136	0.967
21	-0.088	0.881
22	-0.733	1.000

Table 1. Additive and multiplicative bias by hour for the MAQSIP hourly O3 simulation model for 1997 from unpublished work at UBC. Here 50 grid cells were used and 100 monitoring sites.

These results suggest for example, that MAQSIP overestimates the true grid cell values a factor of about 2 at around 3PM that day. Generally it appeared to overestimate the true values during the day and underestimate them during the night, relative to the monitoring site values.

In summary, a promising method does exist for combining CTM and monitoring data and that could lead to strengthened predictive estimates for hourly ozone concentrations. That option seems worthy of exploring.

3-49, line 8. This conclusion seems somewhat questionable since the two distributions do disagree where it really matters, i.e. for large concentrations in Jun-Aug.

3-51, line 25. Residential volume is a factor that affects indoor concentration but it is not explicitly mentioned.

3-57, line 22. Spatial prediction methods can be used to get Cout and thereby address another measurement error problem. That was done in conjunction with a SHEDS analysis for

Philadelphia for example, where concentrations were predicted down to the level of census tracts (see Burke et al 2001 in the Draft reference list; see also page 3-63, line 6) .

3-62, line 23. The construction of APEX (with its forerunner pNEM) have been major EPA achievements. SHEDS, the first such model to include parameter uncertainty, has been added to the arsenal but for reasons not made clear, the former will be used to analyze proposed new ozone AQS. The Draft gives a very clear description of the model, although it does not emphasize enough one of its principal features, no doubt the reason it was designed in the first place, that it can forecast exposures under hypothetical abatement proposals. As far as we know, this type of model would be the only way of estimating exposure benefits.

How good are APEX forecasts? Some assessments have been made of pNEM, but we are unaware of any for APEX. However, in an application to PM2.5, McBride et al (2004) did assess a cousin of APEX, pCNEM. The latter described by Zidek et al (2000, 2005) emulates pNEM in concept so we would expect APEX to work at least as well. [PCNEM was built as a WWW platform that is freely available to remote users for application to any pollutant they specify for which they have the requisite parameter estimates and data files (that can be uploaded to the host server online). The program is run online with results downloaded to a spreadsheet on the user's PC for further analysis.]

McBride et al (2004) built a PM2.5 model on the pCNEM platform and ran it repeatedly to get an estimate of the population predictive distribution for seniors living in Baltimore. NHAPS time - activity patterns were used in the model but neither these nor the model parameters were tuned to suit the 15 subjects whose personal monitor estimates gave exposures against which the distributions were compared (over 27 hours). These distributions proved pretty well calibrated, surprising since the seniors were in a retirement facility, not a typical group of seniors.

A related question concerns the potential benefits APEX might provide in health risk assessments as a way of reducing the bias in the estimated transfer coefficient. Again, the Draft provides no information on that issue. Moreover, Shaddick and Zidek have done the only relevant work we are aware of. (It is unpublished but accepted for presentation at the 2005 ISEE conference.) They show that the association between daily PM10 concentrations and mortality among London seniors (for respiratory and cardiovascular causes separately) goes from insignificant using ambient data to marginally significant using pCNEM predictions. These results make APEX seem a very promising tool for health risk analysis.

One shortcoming of APEX and models like it lie in their inability to produce simultaneous exposure predictions. This is needed to address counterfactual issues that arise when abatement is planned. What really happens to the field of pollutants when ozone is reduced by regulatory measures? The answer lies well beyond current knowledge. Related to that issue, the Draft does not describe how an abatement scenario is implemented in APEX and inclusion of some detail would be desirable since this is critical in the analysis of new AQS.

AX3-2, line 26: A clear description of the two common scales is given here. However, the Draft seems to say which is preferable in terms of predicting adverse health or welfare effects although one might expect the requisite knowledge to be available.

A more basic issue concerns the appropriate transformation if any is needed of the "raw" concentration scale. That issue does not seem to have been considered very much and in any case is not mentioned in the Draft. Ott (1990) gives physical grounds that might suggest putting concentration on a log scale (like acidity). The resulting measure would then be additive in a certain sense and make the result have an approximately Gaussian distribution (by the "central limit theorem" of probability). Empirical evidence suggests a square root transformation to achieve an approximately Gaussian distribution for ozone at least.

However, the substantive issue involved here is biological. Loudness has been measured on the logarithmically scale (decibels) to reflect the way the human ear reacts as loudness increases. A step change in decibels corresponds to a step change in what is actually heard, although that jump was actually exponential in size measured on a loudness meter. Both the log and square root transformation would mean going from 50 to 60 ppb would have a greater impact than going from 100 to 100 ppb in terms of health impacts.

In their reanalysis of Burnett et al (1994), Zidek et al (1998) used the log concentration scale and found positive associations between Ontario ER visits and ozone as well as sulfate, each appropriately lagged in agreement with the earlier findings. However, resulting model has a different the interpretation. No doubt other transformations could have been used as well. The question is does new knowledge point to a natural scale for measuring ozone? Do any of the experiments described in the Draft point to an answer?

AX3-5, line 31: This line suggests the rationale for the exposure indices that have been chosen for assessing human health and vegetation effects can be found in Section AX3.10 and Chapter 9. The latter does give some rationale for the choices but neither explains why they might be the best suited in terms of explaining human health responses to ozone.

Related to that issue is the one about averaging time. Longer times mean reduced measurement error but lower resolution of the temporal field-changes may be obscured. Has any of the new knowledge point to the need to revisit that question?

AX3-30, line 6. How is the “expected number of days” computed?

AX3-38, line 24. While point estimates obtained by kriging might well be comparable to those obtained by other methods now available for spatial interpolation, more precision might be achievable by using multi-pollutant models. In any case, the predictive error bands are likely to overestimate the accuracy of those predictors.

While kriging has been a value tool in geostatistics where it developed, it is challenged by the dynamically changing space - time fields confronted in mapping continuously changing air pollution fields. In particular, since it is applied timepoint by timepoint, the benefits of using the full space - time dataset are lost. Although it gains robustness against the mis – specification of the temporal structure (e.g. autocorrelation, trends) that benefit comes at the expense of needing a lot of monitoring site data at any one time and the often unrealistic assumption of an isotropic

pollution field. Haas (1990) suggests a moving window adaptation to help circumvent that difficulty.

Kriging's underestimation of predictive uncertainty stems from unrealistically assuming initially a known isotropic covariance, determining the optimal predictor on that assumption and then plugging in estimates for the unknown covariance parameters as if known. Sun (1998) shows that underestimation can be substantial, at least in a comparison of Haas's (co-kriging) method with a spatial – temporal method of Le et al (1997, hereafter LSZ). The comparison is made using cross validation and NO3 and SO4 concentration data from the NADP/NTN acid precipitation network. Sun finds that the nominal 95% prediction intervals come in at 64% and 99%, respectively for the co – kriging and LSZ approaches. The comparable results for 99% intervals are 73% and 99%, respectively. To be fair, the LSZ approach unlike the other also incorporates data accumulated over time and some of its calibration superiority may be due to that factor.

Methods have been proposed for correcting that deficiency and these may be seen in Cressie (1993) although it is not clear that adjustment was made in the work reported in the Draft. It could lead to improved estimates of the prediction uncertainty depicted in **Figures AX3-11** and those following. As it is, these may give a misleadingly favorable impression of their accuracy.

Co-kriging referred to above extends kriging to incorporate co-pollutants in the predictive model. This extension, not carried out in the Draft, has two benefits. First, much of the health risk analysis reported in the Draft is based on the analysis of co-pollutant models and the methodology can allow predictions of their field down to local environments from ambient ones as a way of partially addressing the exposure measurement error problem. Although Zidek et al (1998) found that bias dominates imprecision in that application, spatial prediction, as a method of "regression calibration", can help correct the attenuation of transfer coefficients that error induces.

However, even when only a single pollutant like ozone is of concern, co – kriging or one of its multi-pollutant cousins should still be used. The reason is that that in predicting that pollutant, strength can be borrowed through its correlation with other pollutants. In their study, Sun et al (1998) use cross validation in a comparative analysis of the LSK multipollutant method (referred to above) against the same method applied one pollutant at a time for NO2, SO4, O3, and SO2 concentrations. For each of the pollutants they used a cross validation approach (with pollutants on a log scale) and computed the mean squared error of prediction of the method. The results can be seen in Table 2 that shows the greater accuracy of the multipollutant method.

Pollutant	NO2	SO4	O3	SO4
Multipollutant LSK method	0.19	0.14	0.05	0.62
Single pollutant LSK method	**0.28**	**1.27**	**0.13**	**0.76**

Table 2. Mean square prediction error comparison of a multipollutant method against its single pollutant counterpart. The greater accuracy of the first stems from the strength if borrows through correlation with other pollutants. From Sun et al (1998).

AX3-86, line 14. What does "completely different" mean?

AX3-123, line 6. What does "hourly average concentrations in the 0.030 to 0.050 range increased" mean exactly?

3. The charge Questions.
A1. The format is very helpful. However, the Annexes certainly have to read to gain the requisite level of critical understanding.

B1. Recent work is described above (page 3-49) for combining simulated (CTM) and actual (monitoring) data that might enhance both. That new methodology is now being used in climatology.

B2. Comments above elate in various ways to this issue, in particular, that relating to scaling, network design for characterizing the fields of central importance such as those for the maximum daily ozone concentration.

B3. A very good discussion of the issues involved. Comments above concerning APEX support its use both for regulatory scenario analysis as well as for epidemiological application (where surprisingly, it has not been used). An important issue not addressed there relates to the counterfactual issue: reducing ozone, as supposed in the scenario analysis, would in reality change co-pollutant concentrations as well. Thus, a multipollutant version of APEX with realistic abatement scenarios would be highly desirable but beyond the current knowledge base.

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Comments of the Draft Ozone AQCD, 2005
Chapter 7

Prepared by Jim Zidek
Revised May 9, 2005

Chapter 7. The document contains no discussion of the ecological effect as it relates to health risk analysis. This seems surprising given its importance and the fact that many of the studies are ecological in nature. During the Panel discussion it was pointed out that this is not such a problem in time series studies as it can otherwise be. That observation seems worth incorporating in the Revision.

Page&line
7-13, line 4. Transfer of effects. This phenomenon, described in the context of air pollution and health risk assessment by Zidek et al (1996) for the classical measurement error model and extended by Fung and Krewski (1999) for the Berkson model, where causality can be ``transferred'' from one risk factor to another. It can occur when the causative factor is correlated with another that is measured more precisely, when the latter is found to be significant. The Draft mentions that this phenomenon is well - discussed in the PM criteria document but does not indicate what specific implications, if any, it might have with respect to setting ozone standards. Is that gap due to one on in the state of knowledge?

In particular, during the Panel discussion, it was pointed out that the secondary fraction of PM2.5 is correlated with O3 in some areas and in some regions. Yet it may be poorly measured when the primary fraction is substantial. Thus, some of the significance ascribed to ozone may be a reflection of the importance of the secondary fraction of PM2.5.

7-7, line 18. Measurement error. This phrase is used 22 times in the Draft, reflecting the importance of concerns about it. Not surprising since it can have unpredictable implications for any risk analysis where the risk effect model is nonlinear, *i.e.* when the ``link function'' relating the risk factors to the health outcome mean function is not linear, An example would be the commonly assumed exponential link *exp[b*X]*, b being the impact transfer coefficient and X, the value of the factor (e.g. pollutant). The analysis of Zidek (1997) demonstrates a competition between bias and imprecision (error variance). High levels of the latter relative to the former mean the transfer coefficient will be overestimated (away from the null), otherwise underestimated as indicated in the study referred to in this line. In accord with the finding of Zidek et al (1998), studies cited in Chapter 7 point to bias as the dominant factor. In other words risk is underestimated. That knowledge is comforting from a testing perspective - rejection of the null would lead to valid conclusion of association. However, this underestimation is undesirable from the perspective of adverse health outcome estimation, a point that is glossed over in the Draft and needs more emphasis in the revision. In any case, it is hard to judge the importance of uncertainty due to measurement error relative to the various other sources described in the Draft.

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Dr. Barbara Zielinska

Comments on the Draft Ozone AQCD, 2005
Chapter 3

By Barbara Zielinska

General Comments:

Although Chapter 3 presents extensive new information, I found it to be rather scattered and not very well written. Many sections are not clear and seem to need more careful editing and more focused approach. Detailed comments below address some of these issues.

<u>Answers to charge questions from Dr. Grant's memo of April 21, 2005</u>

Question A1: To what extend is the document format restructuring useful and desirable? Can the restructuring be further improved? If so, how?

To have the descriptive materials presented in annexes and the main chapters of the document focused on evaluative/interpretive aspects is a very good idea. However, as far as Chapter 3 is concerned, the main chapter does not really do a good job in presenting the integrated, conclusive information. Some Tables (such as Table 3-2, 3-3 and 3-5) are too long and should be moved to the Annex, whereas some other information is much better presented in the Annex. In my opinion this chapter should be revised with more attention directed towards conveying clearly summarized and concise information.

Question B1: Does Chapter 3 appropriately and sufficiently characterize the science supporting the basis for estimates of policy relevant background? In particular, is the approach for determining PRB ozone concentrations outlined in Section 3.7 and in AX3.9 based on the best available methodology?

I'm not an expert in PRB, but an approach that considers both observations and models, not only model calculations alone, seems more reasonable to me. I would like to recommend the extensive public comments regarding PRB estimation, for example submitted by Jon M. Heuss, Air Improvement Resource, Inc., for EPA consideration.

Question B2: Does the discussion of ground-level O3 concentrations adequately describe the variability attributed to diurnal patterns, seasonal patterns and spatial differences in both urban and non-urban locations? Also, to what extend do the characterizations of temporal and spatial variability of O3 in urban areas provide support for better understanding and interpreting epidemiological studies discussed later? How might these characterizations be modified to help enhance such understanding and/or would other characterizations (as time permits) be useful in relation to later evaluations of various welfare effects? Is the summary of the effect of elevation on ozone concentrations sufficient to inform later evaluation of the representativeness of

elevated ozone monitors (e.g. rooftop) in relation to ozone levels in the breathing zones in children?

The presentation in Chapter 3 is somewhat scattered and lack the "punch line".

Question B3: Does Chapter 3 provide a sufficiently discussion of concepts and issues related to human exposures, applicable microenvironments, and modeling of O3 exposure to serve as a foundation for quantitative exposure analyses to be done in conjunction with Ozone Staff Paper. How might these discussions be improved?

In my opinion, these issues are covered relatively well in Chapter 3. The limitation of models should be emphasized.

Detailed Comments:

page&line

3-5, lines 8-22. This is a rather unclear paragraph. What is the point here?

3-27 line 29 through 3-28, line 18. This is very unclear, especially the last paragraph. There are no clear evidences supporting the ozone transport from Asia.

3-31, line 5. ad?

3-45, line 13. Please fix the references.

3-50, Figure 3-12. Something is wrong with Denali data. Instrument problems? Also, why is this figure shown? Not really discussed in the text.

3-53, Table 3-9. What are the regions?

3-57, line 1-4. How important are OH radicals indoors?

Appendix D – Additional, Consensus Review Comments from Selected CASAC Ozone Review Panelists on Chapters 9-11

After further reviewing our discussions at RTP on Wednesday and Thursday last week, the four of us (Allen Legge, Paul Hanson, Rich Poirot, and Ellis Cowling) offer the following two general recommendations regarding Chapters 9-11, and a number of specific suggestions for improvement of Chapter 9:

A) We believe that the Second Draft of the 2005 Ozone Criteria Document will be improved if NCEA will use the same "new-and-improved general format" for organization of information in Chapters 9-11 as was used quite successfully in developing Chapters 2-8 in the First Draft of the Ozone Criteria Document; and

B) We further believe that the revised Chapter 9 will be improved if it includes summaries of current scientific evidence that is relevant to the following questions:

1. Does available scientific information indicate that the present identical primary and secondary 8-hour standards for ozone provide adequate protection for crops, trees, and other vegetation in natural ecosystems against the harmful effects of ozone and other oxidants in various parts of the US?

   In this connection, we note that Chapter 3 of the 2005 Ozone Criteria Document includes extensive tables, charts, and maps that show ozone concentrations over various sites and time periods across the US. These information displays include both one-hour and eight-hour daily maximum ozone concentrations, and separately for the SUM06, W126, and other ecologically relevant exposure indices. But little information is now provided to allow assessments of how these human-health and plant-health-related indices relate to each other. Tables, maps, and/or scatter plot diagrams that compare the yearly 4th-highest 8-hour maximum ozone concentrations with the growing-season-long cumulative indices (such as SUM06, W126, and AOT40, etc.) across sites, regions, and years would also be very helpful.

   In this connection, we also note that the "Draft Ozone Health Assessment Plan" indicates that EPA will provide an "estimation of population exposures and health risks posed by ozone under existing air-quality conditions (as is" exposure and health risks) upon attainment of the current ozone primary NAAQS, and upon meeting various alternative primary standards in selected sample urban areas." Is there a possibility that EPA could provide in the soon-to be completed "Draft Ozone Environmental Assessment Plan," a similar assessment for ozone effects on vegetation, and/or include one or more of the ecologically relevant indices among the "various alternative standards" for which human health responses are estimated? For example, what would be the health benefits if a summer seasonal SUM06 of 25 ppm-hours was attained?

2. What magnitude of ozone- and other oxidant-induced losses in economic value of agricultural crops, managed forests, and aesthetic quality of vegetated landscapes are presently occurring in various parts of the US?

   We note that the relevant information in Chapter 9 on economic impacts is not very exhaustive. Thus, we expect that available exposure/dose-response information will support rigorous economic assessments for only a few crop species.

3. What concentrations of ozone or other oxidants have been shown to (a) cause visible economic losses in agricultural crops and managed forests, and (b) compromise the aesthetic quality of plants and vegetated landscapes?

   One possible way to show this is to include a Summary Table showing concentrations of ozone that were found to be injurious or economically damaging to various species of plants.

4. What are the durations of exposure to ambient concentrations of ozone that result in various types of injurious effects on various species and varieties of crop plants, forest or shade trees, and individual plants within natural ecosystems?

   This question is especially critical. We very much approve of the general focus within Chapter 9 on growth and productivity-based exposure-response indices. Relevant data are provided on page 9-188. But no comparisons were made to the current 8-hour ozone standard.

5. How do the concentrations of ozone and durations of exposure to ambient concentrations of ozone that cause visible injuries and economic damage to various species and varieties of plants compare to those that cause ill-health in people?

   In this connection, we were surprised to learn that it apparently is assumed from a public health perspective, that high ozone concentrations occurring at night (when most people are indoors) are just as harmful as high ozone concentrations occurring during daylight hours. Is it known whether or not plants that live their whole life out-of-doors are sensitive to high concentrations of ozone during nighttime hours? Musselman and Minnick's (2000) research on nocturnal conductance of ozone in stomata of plants is one of very few studies of this topic (see pages 9-170 and 9-171).

6. What specific indices of ozone exposure have been suggested as reliable means by which to protect vegetation and ecosystems from harm by ozone and other oxidants in various parts of this country and abroad?

   In this connection, we recommend that the perspectives and accumulated experience with various ecologically relevant ozone exposure indices and ozone flux experiments described in the following very valuable reports be analyzed and incorporated in appropriate sections of Chapter 9:

a) "Federal Land Managers' Air Quality Values Workgroup (FLAG) Phase I Report" (December 2000)" published by the U.S. Forest Service – Air Quality Program; National Park Service – Air Resources Division; and the U.S. Fish and Wildlife Service – Air Quality Branch. 177pp.
[See http://216.48.37.155/Flag2000.pdf].

b) "Federal Land Managers' Air Quality Related Values Workgroup (FLAG): Response to Public Comments on the Draft Phase I Report." 43 pp.
[See http://www2.nature.nps/air/permits/flag/Flagcommentresponse.htm].

c) "Effects of Ozone on Vegetation: Update in Support of the Canada-Wide Standards for Particulate Matter and Ozone" prepared for the Canadian Council of Ministers of the Environment, March 2003, Final Draft.
[See http://www.ccme.ca/assets/pdf/scrvw_oz_effects_vgttn_e.pdf].

d) "Assessment of Air Quality and Related Values in Shenandoah National Park"(2003), Technical Report NPS/NERCHAL/NRTR-03/090, Sullivan, T.J, B. J. Cosby, J. A. Laurence, R. L. Dennis, K. Savig, J. R. Webb, A. J. Bulger, M. Scruggs, C. Gordon, J. Ray, E. H. Lee, W. E. Hogsett, H. Wayne, D. Miller, and J. S. Kern.
[See http://www.nps.gov/shen/air_quality.htm].

7. Is the present monitoring system for determining ambient concentrations of ozone adequate for estimating ozone exposure of plants and ecosystems in urban, suburban, rural, and wilderness areas where ozone damage has been demonstrated?

8. What changes in the ozone monitoring systems in various regions of the US would be necessary to provide reliable information on ozone exposures to crops, forests, and natural ecosystems?

   Maybe answers to this question should be developed in the EPA Staff Paper on ozone rather than in the Criteria Document on ozone.

9. Is there available scientific evidence about whether adoption of a growing season-long cumulative secondary standard for ozone (such as SUM06, W126, and AOT40) might also provide an increased measure of protection against the injurious effects of ozone and other oxidants on public health?

10. What are some of the most important gaps in available knowledge that require future research in order to decrease uncertainties in present understanding of ozone effects on plants and ecosystems? Some research needs are discussed on pages 9-314 and 9-315, but this list could be augmented considerably and could profit from some prioritization in our judgment.

Thanks for your consideration of these questions and recommendations for inclusion in our summary letter to the Administrator of EPA regarding CASAC's current review of the First draft Ozone Air Quality Criteria Document. If you have any questions about any of these collective questions and recommendations, please let us know.

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.