

1 Dear Administrator Jackson:
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3 The Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel met on May 20,
4 2011 to provide advice on EPA's *Integrated Science Assessment for Ozone and Related*
5 *Photochemical Oxidants* (March 2011). We provide detailed comments in the attached
6 responses to eleven charge questions and highlight key points in this letter.
7

8 We take note that this draft Integrated Science Assessment (ISA) covers a wide range of
9 scientific data and that the data base is complex and extensive. Nonetheless, the first draft ISA
10 does a good job of capturing the remarkable wealth of information available regarding ozone, its
11 atmospheric formation and the potential for health and welfare effects. There is substantial new
12 evidence since the 2006 Air Quality Criteria Document. CASAC continues to support the use of
13 EPA's framework for causal determination that was first used in the ISA for particulate matter.
14 This framework provides a comprehensive and transparent approach for evaluating causality.
15 Based on long-standing approaches in public health as brought together in a recent National
16 Academy of Sciences (NAS) Institute of Medicine (IOM) report¹, the framework employs a two-
17 step approach that first determines the weight of evidence in support of causation and then
18 characterizes its strength in a standard scheme for causal classification. The second step further
19 evaluates the quantitative evidence available regarding concentration-response relationships and
20 the duration, level and types of exposures at which effects are documented. EPA's adoption of
21 this framework has greatly improved the consistency and transparency of its assessment as
22 compared to the approach of past reviews. We note, with appreciation, the ISA provided a
23 helpful comparison between current findings and the conclusions found in the 2006 Criteria
24 Document; and in this letter, we provide CASAC's comments on changes in the findings of
25 causal determinations and on other issues as well.
26

27 The ISA's coverage of Policy Relevant Background (PRB) ozone concentrations is still a work
28 in progress in this first draft ISA. The PRB is the concentration that would occur in the U.S. in
29 the absence of anthropogenic emissions in continental North America. The PRB includes
30 contributions from natural sources everywhere in the world (wildfires, biogenic emissions,
31 lightning) and from anthropogenic emissions outside of North America. The PRB calculation is
32 critical because it defines the extent to which ozone concentrations can be reduced by U.S.
33 regulations or through international agreements with neighboring countries. We concur with
34 EPA that PRB will need to be calculated with models; however, EPA needs to provide a more
35 specific and precise description of how the PRB will be calculated, especially given the biases in
36 modeled ozone concentrations in comparison with measurements. To deal with those issues, an
37 approach must be devised that is clearly articulated through analysis of model uncertainties..
38

¹ / National Academy of Sciences Institute of Medicine. *Improving the Presumptive Disability Decision-Making Process for Veterans*. National Academy Press, 2008.

1 The ISA provided useful information on human exposures to ozone and the evidence relating
2 human exposure to ambient ozone concentration and the errors associated with exposure
3 assessment; however, the characterization of the temporal and spatial variability of ozone could
4 be improved. A critical claim of the ISA is that there is “low spatial variability” in ozone
5 concentrations at an urban scale, and that correlations in ozone exposure and ambient
6 concentration are strong enough to support a conclusion that central site monitors provide
7 relevant time series data for health effects estimates in epidemiological studies. However, as
8 noted elsewhere in the ISA, ozone is not spatially homogeneous in urban areas because of
9 titration with nitrogen oxides (NO_x) near roadways. Furthermore, the temporal correlations are
10 described as “moderate” but only become strong if the averaging time is increased to several
11 days. Given that the current standard is based on an 8-hour averaging period, the relevance of
12 daily average or four-day average correlations is not established. The ISA should more critically
13 address the adequacy of central site monitors for use in epidemiological studies and perhaps
14 more fully address potential biases that could result from assuming that they are representative of
15 spatial homogeneity and temporal trends. Descriptive characterization of ozone at lower levels
16 (40 – 60 ppb) will need more attention as the primary ozone NAAQS is reevaluated and the
17 secondary (W126) standard is implemented.

18
19 With respect to the ISA’s characterization of short-term health effects, the ISA highlights the
20 broad scope of human chamber studies, toxicology studies, and new epidemiologic findings.
21 This ISA covered the new evidence on the relationship between ozone and all-cause (non-
22 accidental) mortality and concluded that there is “likely to be a causal relationship” between
23 ozone and all-cause mortality. This is an elevation of the classification of the evidence over the
24 previous conclusion from the 2006 Air Quality Criteria Document that the evidence was “highly
25 suggestive” of ozone contributing to all-cause mortality. This upgrading was well justified by
26 new multi-city studies and new studies examining potential confounders (co-pollutants and
27 seasonality) of the ozone-mortality relationship. CASAC also agrees with the ISA’s finding of a
28 “causal” relationship between ozone and respiratory effects. New toxicological studies support
29 the ISA’s finding of a “suggestive of a causal” relationship between ozone and cardiovascular
30 effects. New toxicological evidence also demonstrates an impact of ozone on the brain and
31 behavior; hence the ISA’s finding of a “suggestive of a causal” relationship between ozone and
32 central nervous system effects is justified.

33
34 Similarly, with respect to long-term health effects, CASAC concurs with the strengthening of
35 causality determinations from the 2006 Air Quality Criteria Document. In this ISA, evidence
36 from new epidemiologic and toxicology studies supports the finding that the effects of ozone on
37 long-term respiratory effects are “likely to be causal” and the evidence on the effects of ozone on
38 the central nervous system are “suggestive “ of a causal relationship. Similarly, new
39 epidemiologic and toxicological studies support classification for cardiovascular, reproductive,
40 and central nervous system effects as “suggestive of a causal relationship.”

41

1 The evidence on short-term effects of ozone exposure is relevant to interpreting some findings on
2 long-term exposure to ozone. For the short-term effects, there is a deep literature from
3 epidemiological studies, human clinical, animal toxicological, and mechanistic studies. The
4 links between this literature, as it contributes to the biological plausibility of chronic effects,
5 should be strengthened in the ISA, where appropriate. For example, the evidence for respiratory
6 effects on mortality is strengthened by the evidence for respiratory morbidity. As the ISA
7 correctly notes, EPA concluded in the 2006 review that associations between short-term ozone
8 exposure and respiratory health effects are causal, and new evidence since that time supports this
9 claim.

10
11 This ISA uses a broad definition of “susceptible populations” as individual and population-level
12 characteristics that increase the risk of ozone related health effects. This definition conflates
13 intrinsic or biological factors (such as genetic background, birth outcomes, race, sex, and
14 lifestage) with extrinsic factors (such as socioeconomic status and time spent outdoors). While
15 CASAC has previously concurred with EPA’s broad definition of “susceptible subpopulations”
16 as those that have a greater likelihood of experiencing health effects related to exposure, it may
17 be useful to consider classifying the factors that define susceptibility somewhat arbitrarily as
18 intrinsic (e.g., genetic background, gender, age, and pre-existing disease) and extrinsic (e.g.
19 socioeconomic status). WeTO BE DISCUSSED In any case, additional
20 refinement of the definition of susceptibility is still needed.

21
22 The ISA maintains its support for the conclusions from the 2006 AQCD that ozone reduces
23 vegetation growth, alters vegetation reproduction, causes visible foliar injury, alters leaf gas
24 exchange in vegetation and reduces the yield and quality of agricultural crops. These causal
25 relationships continue to be well-established scientifically. The ISA recognizes the key effects
26 and pathways by which ozone impacts vegetation at all scales, although the coverage of effects
27 on insect and mammal herbivores due to changes in vegetation is rather brief due to a lack of
28 research on these subjects.

29
30 Compared with the 2006 AQCD, the ISA draws stronger conclusions for the effects of ozone on
31 radiative forcing and climate change. The stronger conclusions are well-supported and largely
32 drawn from the 2007 Fourth Intergovernmental Panel on Climate Change Assessment (IPCC)
33 Report which ranked ozone as the third most important greenhouse gas after carbon dioxide
34 (CO₂) and methane (CH₄). The discussion of climate forcing due to ozone relative to that of
35 carbon dioxide (CO₂) and methane (CH₄) is scientifically sound; however, more attention should
36 be given to CH₄ as the only ozone precursor for which control would effectively reduce climate
37 forcing. We also recommend that more attention be given to the recent Representative
38 Concentration Pathways (RCP) scenarios of the IPCC Fifth Assessment Report (AR5), since
39 these scenarios will provide the core of future assessments of climate forcing for emissions
40 relevant to air quality and they present a very different picture than the older emissions scenarios.
41 Given the complex feedback loops between various ozone precursors (a decrease in NO_x
42 emissions could lengthen the lifetime of CH₄ in the atmosphere whereas a decrease in CO or
43 VOC emission should shorten the lifetime of CH₄), we echo the ISA’s call for research to
44 determine the optimal mix of emissions reductions that would act to limit future climate change.

45

1 Finally, we were asked whether the ISA, at 996 pages, is too long. A highly useful ISA must
2 clearly explain the key studies that facilitate decision-making with regard to the NAAQS as
3 required by the Clean Air Act. The encyclopedic nature of this 996 page ISA can be a
4 weakness, making it hard to focus on the most relevant information. While some panelists
5 thought that the length was appropriately reflective of the scope of evidence, others offered
6 suggestions for shortening the document. All agree that clarity of presentation is of paramount
7 importance and suggestions for enhancing the packaging and presentation of the evidence may
8 be found in abundance in the attached individual comments. In particular, we underscore a
9 recommendation that the text should focus on findings, only discussing methods and models
10 when necessary to describe the findings. We also underscore the need for an Executive
11 Summary. Currently the “Integrative Health and Welfare Effects Overview” (Chapter 2) is a 66
12 page overview that mirrors the other sections of the ISA rather than integrating across the other
13 sections on concentration, exposure, dosimetry, mode of action, and health and welfare impacts.
14 Moreover, each section is written for an expert audience in a narrow domain, and thus for most
15 readers, it remains incomprehensible. Hence, an Executive Summary, not to exceed 10 pages, is
16 needed to communicate to a broader audience and highlight findings of greatest import. Finally,
17 tables are needed to succinctly lay out the details of the important findings, regardless of the date
18 published. Then the ISA can succinctly refer to these tables and reserve space in the text for in-
19 depth consideration of the far fewer studies that will influence the setting of the NAAQS.

20
21 As a separate and final point, It is important that the ISA give the time point at which input from
22 new evidence was suspended. Moreover, EPA should say what was done, if anything, regarding
23 potentially important information received after that time.

24
25 We look forward to our continuing work with the Agency on this review of the ozone NAAQS.

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Consensus Responses to Charge Questions

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2
3 **1. This first external review draft O₃ ISA is of substantial length and reflects the copious**
4 **amount of research conducted on O₃. EPA has attempted to succinctly present and**
5 **integrate the policy-relevant scientific evidence for the review of the O₃ NAAQS. The**
6 **panel may note that per CASAC consultation on November 13, 2009, considerable**
7 **discussion has focused on older literature. The panel emphasized that important older**
8 **studies should be discussed in detail to reinforce key concepts and conclusions if they**
9 **are open to reinterpretation in light of newer data and where these older studies remain**
10 **the definitive works available in the literature. In considering subsequent charge**
11 **questions and recognizing an overall goal of producing a clear and concise document,**
12 **are there topics that should be added or receive additional discussion? Similarly, are**
13 **there topics that should be shortened or removed? Does the Panel have opinions on**
14 **how the document can be shortened without eliminating important and necessary**
15 **content?**
16

17 This charge focuses on length. Length is an important consideration for the ISA, but not
18 nearly as critical as clarity of presentation of a large and complex literature that is being used
19 for regulatory purposes. Thus, our comments focus on four approaches to present the
20 knowledge of O₃ more effectively and succinctly, without regard to number of pages.
21

- 22 • The text should focus on findings, only discussing methods and models when necessary
23 to support or describe the findings. The model descriptions in Chapter 3, while
24 necessary, may be simplified. Also, there may be too many figures in the Chapter
25 Appendix. The number of examples may be trimmed down without any significant loss
26 in understanding.
- 27 • It is not possible, nor desirable, to eliminate duplication, but a reduction would be
28 helpful. In particular, the duplicative summaries within the chapters and in Chapter 2
29 need significant revision. In addition, the mode-of-action (MOA) section of Chapter 5
30 has significant duplication to the effects chapters (6 and 7), and, more importantly, this
31 artificial separation inhibits a clear understanding of the biological plausibility for some
32 of the effects.
- 33 • The health-related chapters have no tables setting out exposure-response relationships,
34 except for some of the epidemiology studies. As a result, the text is crowded with
35 information on exposures (species, concentrations, durations, responses, levels of
36 exercise, and air quality, and cities studied, for example). This makes for difficult reading
37 that inhibits understanding of concepts and key findings. In many cases, the information
38 necessary for understanding (e.g., was exercise used in a certain clinical study, what was
39 the exposure duration of a certain animal study) was not provided at all. For clarity, it is
40 essential to provide tables of all the literature that should be considered. While this
41 would result in many new pages, the text could be reduced by referring to the tables for
42 several design details.
- 43 • The separation between old and new studies causes duplication and restricts cohesive
44 understanding. Furthermore, this distinction is artificial because the NAAQS is based on
45 all pertinent information, independent of what year it was published. Having tables and

1 utilizing them optimally would avoid this problem. For example, complete tables on a
2 particular endpoint would facilitate identification of the relatively few key studies,
3 *independent* of date, which could then be described in the text with cross reference to the
4 tables. At present, some of the key studies are from the older literature. If these studies
5 have been superseded, they should be deleted from the tables.
6
7

8 **2. The framework for causal determination and judging the overall weight of evidence is**
9 **presented in Chapter 1. Is this framework appropriately applied for this O₃ ISA? How**
10 **might the application of the framework be improved for O₃ effects?**
11

12 Panel members were largely satisfied with Chapter 1 on a micro level, but have several
13 concerns at the macro level. First of these is a need to clarify the definition of “cause” and
14 put it in an operational form. The present definition (Pag4 1-14, lines 1-2) states that
15

16 “Cause” is a significant, effectual relationship between an agent and an effect on health or
17 public welfare.
18

19 We recognize the historical origins of this term, but question whether it fits with the
20 specific context of the ISA. This definition is ambiguous with respect to whether
21 “significant” refers to the size of an effect (perhaps as reflected in measure of statistical
22 significance) or its importance (as estimated by its impact on health or welfare). If it is the
23 former, something should be said about the level(s) of statistical significance that are used in
24 various places in the ISA; if it is the latter, something should be said about what type or level
25 of impact qualifies as significant. Panel members are concerned about any definition that
26 would label a small but clearly demonstrated effect as less than “significant”; it is certainly
27 important to the affected persons. Also, it is not clear what “effectual” means. Does it mean
28 that an effect has in fact been demonstrated? That such a relationship is possible?
29

30 Couching the definition of cause in counterfactual terms, as perhaps hinted at in line 5, is
31 arguably the most informative and most usable way to define the term. This approach
32 incorporates the notion of “all else being equal” and allows for its application when multiple
33 factors are in the causal chain, when there are parallel chains, or both. Clarification of the
34 definition of “cause” may have important ramifications in many other places in the draft ISA
35 and provide a clearer conceptual basis for the Risk and Exposure Analysis.
36

37 Panel members have some general concerns about the application of the so-called Hill
38 criteria for evidence evaluation. In general, we recommend that these criteria be regarded as
39 a guide to thinking about the data, to assure that relevant aspects of the data are adequately
40 considered and that they be taken as a whole rather than used as a checklist. It is noteworthy
41 that presence of exceptions to each of the “criteria,” except temporality, is still consistent
42 with causality. We recommend also that the criteria not be ranked in any way; their relative
43 importance will depend on the specific context and specific issue under consideration.
44

1 We believe that the ISA has misinterpreted one of the criteria: Does “specificity” refer to
2 one cause with many effects or to many causes with a single outcome? Despite examples to
3 the contrary (such as cigarette smoking) we believe that Hill’s original intent, and our
4 understanding of current use, is that specificity requires that a cause of interest has only one
5 effect, or perhaps several related effects. This definition of specificity is meant to screen out
6 certain kinds of bias that might cause an apparent increase in a broad range of outcomes.
7 Thus, this criterion should be used to direct attention to possible biases, not to diminish
8 attention to responses that many have many contributing causes, such as most chronic
9 diseases in older populations.

10
11 Coherence refers to findings across epidemiological study designs, not just between
12 epidemiological, toxicological and other experimental studies
13

14 Panel members expressed some concern about the paucity of data regarding the effects of
15 multi-day episodes of high ozone exposure. For example, do ten separated days of high
16 ozone have the same effect as a single ten-day stretch of elevation, or a greater effect, or a
17 smaller effect? There are ways in which any of these three outcomes might occur.
18

19 It is important that this document give the time point at which input from new evidence was
20 suspended, and that it says what was done, if anything, regarding potentially important
21 information received after that time. “Nothing” would be an acceptable answer, but it should
22 be here and if any studies are included following a specified cut-off, clear and specific
23 justification should be given.
24

25 The discussion of effect modification should define it (e.g., differences in the effect of
26 exposure [ozone] by differences in another factor) before launching into a discussion of how
27 it differs from confounding. Also, temperature is presented as a potential effect-modifier, but
28 it might be valuable (and less confusing) to contrast how temperature is also (and more
29 importantly) a potential confounder. Essentially, effect modification refines our
30 understanding of the effect of an exposure while confounding addresses whether an effect is
31 actually present, or what the size of that effect is, if present.
32

33 The shape of the exposure-response relationship is influenced by the degree of measurement
34 error, as touched on (1-23, line 8). Specifically, measurement error at lower concentrations
35 can obscure a threshold and make it appear that a linear relationship extends to lower
36 concentrations (Brauer M et al. Exposure misclassification and threshold concentrations in
37 time series analyses of air pollution health effects. *Risk Anal* 2002; 22: 1183-1193). This
38 might be a particularly important issue for interpreting risks of pollutants, such as ozone, that
39 exhibit large degrees of measurement error.
40

41 In concept, a population threshold should be equal to the lowest of all individual thresholds
42 in the population under study. Thus, it does not require that the population-wide data, taken
43 alone, present a clear signal about thresholds if other kinds of data, e.g., human exposure
44 studies, show that some person or group has lower individual thresholds than inferred at the
45 population level. If the ISA is to use a different conceptual framework for interpreting

1 analyses directed at thresholds, that framework and related definitions should be presented
2 here and defended.

3
4 The observation that publication bias in the case of ozone may not be so important (1-23, line
5 27) is contradicted by the work of Bell et al. showing substantial differences in ozone effect
6 estimates from meta-analyses of published studies and multi-city study effect estimates.

7
8 The discussion of susceptibility indicates that the term here will be used in a general sense to
9 include both susceptibility and vulnerability, terms that include both disease risk factors and
10 factors that increase exposure (1-23, line 36) and therefore risk. This usage should be made
11 explicit.

12
13 The discussion of adversity is appropriate to include here. There is no discussion, however,
14 of the types of endpoints that are more problematic in a discussion of adversity, such as
15 markers of inflammation or oxidative stress, for example.

16
17
18 **3. Chapter 2 presents the integrative summary and conclusions from the O₃ ISA with**
19 **detailed discussion of evidence in subsequent chapters. Is this a useful and effective**
20 **summary presentation? How does the Panel view the appropriateness of the causal**
21 **determinations?**

22
23 CASAC strongly supports the inclusion of a chapter that summarizes and integrates findings
24 from the ISA and that relates these findings to those from the earlier 2006 AQCD. The
25 CASAC had a wide ranging discussion regarding the form and placement of such a chapter,
26 offering several possible options. For the form of the chapter, options include: (1) a chapter
27 that integrates findings across the ISA sections (e.g., concentration, exposure, dosimetry,
28 mode of action, and health and welfare impacts), with relevant summaries placed at the ends
29 of Chapters 3-10, (2) a brief executive summary placed at the front of the document with a
30 subsequent chapter integrating findings, and (3) a chapter that combines the summary and
31 integration of findings as an “integrative overview” rather than as a detailed summary. For
32 the three options, the Committee suggested that the “integration” chapter be placed as either
33 Chapter 2 (as is currently) or at the end of the ISA. Independent of its form and placement,
34 the Chapter should be amended to provide a uniform and sharper focus, which would help to
35 minimize repetition and provide a more cohesive and integrated picture of ozone and its
36 health and welfare impacts.

37
38 **4. In relation to Chapter 3 and its associated appendix, to what extent are the atmospheric**
39 **chemistry and air quality characterizations clearly communicated, appropriately**
40 **characterized, and relevant to the review of the O₃ NAAQS? Does the information on**
41 **atmospheric sciences provide useful context and insights for the evaluation of O₃ effects**
42 **on human health, vegetation, ecosystems, and climate in the ISA?**

- 1 **a. Is accurate and appropriate information provided regarding techniques for**
2 **measuring O₃ and its components, and spatial and temporal patterns of O₃**
3 **concentration?**

4
5 Yes.

- 6
7 **b. Policy Relevant Background (PRB) O₃ concentrations are necessary to**
8 **estimate risks to human health and environmental effects associated with**
9 **exposures to O₃ concentrations attributable to anthropogenic sources of**
10 **precursors emitted in the United States, Canada and Mexico (i.e., to O₃**
11 **concentrations above PRB levels). As such, estimates of PRB are key to the**
12 **NAAQS process for O₃. Is the evidence related to estimation of and**
13 **uncertainty in PRB presented clearly, succinctly, and accurately? Are there**
14 **issues related to uncertainties in methods for estimated PRB concentrations**
15 **that have not been addressed or should be expanded?**

16
17 As expounded upon in individual comments, the discussion of the PRB needs to be bolstered
18 and a more specific and precise description added on how the PRB will be calculated for use
19 later in the NAAQS process. There are biases in the modeled ozone concentrations in
20 comparison with observations. EPA should devise an approach to deal with those biases that
21 is clearly articulated, along with capturing the uncertainties that arise from that approach. At
22 present, the discussion of uncertainties in the PRB estimation is limited. Important chemical
23 uncertainties that could affect model PRB simulations that require more discussion include
24 halogen chemistry (not just in urban areas but in the background), isoprene chemistry, and
25 the chemical evolution of fire plumes. Current models simulating the pre-industrial and early
26 20th century atmosphere greatly overestimate the observed concentrations at the turn of the
27 century. In comparing the modeled ozone with observations, EPA should include data from
28 additional PRB relevant long-term data that are not in AQS. There needs to be a more
29 quantitative analysis of the contribution of stratospheric O₃ to ground level O₃; this is only
30 noted in passing with a reference to Thompson 2007. That study may over-estimate this
31 contribution in part because 2004 was a relatively low O₃ season for the NE US. An
32 additional resource that should be considered is the "Canadian Smog Science Assessment
33 (2011). The chapter presents cogent arguments for the use of a chemistry-transport model
34 like GEOS-Chem to simulate the PRB time series. However, the tendency of a chemistry-
35 transport model to underestimate the upper extreme values like the annual fourth highest
36 value poses a significant challenge to describe the PRB based on the same metric relevant to
37 the NAAQS for O₃. This issue was not addressed in the chapter.

- 38
39 **c. Does the discussion of ambient O₃ concentrations adequately describe the**
40 **variability attributed to diurnal patterns, seasonal patterns, and spatial**
41 **differences in both urban and non-urban locations? Are the analyses and**
42 **figures presented in Chapter 3 and its associated appendix (section 3.7)**
43 **effective in depicting ambient O₃ characteristics?**
44

1 The current presentation is useful, but lacking. Much of the analysis concentrates on the
2 higher ozone levels. However, if the human response to ozone exposure is treated as linear
3 with no threshold, low levels are very important in the analysis. Consequently, ozone trends
4 and relationships at low levels (e.g., 40-60 ppb) are very important as these levels are more
5 prevalent than the higher levels. Further, as the standard is proposed for tightening at
6 present, more interest develops in levels of around 60 ppb. Thus, more attention should be
7 given to ozone levels at, and below, the likely range of a proposed standard.

8
9 **d. Is there additional information regarding oxidants, other than O₃, that**
10 **should be included, or is the current emphasis on O₃ adequate?**

11
12 The current version is adequate as the reader can refer to prior documents.

13
14 **5. Chapter 4 describes human exposures to O₃. Is the evidence relating human exposure to**
15 **ambient O₃ and errors associated with exposure assessment presented clearly,**
16 **succinctly, and accurately? Are the results of field studies evaluating indoor-outdoor**
17 **and personal-ambient exposure relationships, and factors affecting those relationships,**
18 **presented in a manner that is useful for interpretation of epidemiologic results? Is the**
19 **information on modeling O₃ concentration surfaces and population exposures**
20 **appropriate for evaluating the utility of these modeling approaches? Do the**
21 **characterizations of temporal and spatial variability of O₃ in urban areas provide**
22 **support for better understanding and interpreting epidemiologic studies discussed**
23 **later?**

24
25 Historical placement of central site monitors away from local sources has potentially resulted
26 in a buffered view from the monitoring network regarding ozone variability, given the
27 considerable variation induced by NO_x titration near or immediately downwind from busy
28 roadways or other substantive sources of NO_x. Further, studies have shown central site
29 monitors to be relatively poor proxies of personal ozone exposures, especially for individuals
30 living in poorly ventilated environments or who spend little time outdoors. Thus, the chapter
31 should more critically address the adequacy of central site monitors for use in
32 epidemiological studies and be more forthcoming about potential biases that could result
33 from assuming central site data are representative of spatial homogeneity, temporal trends,
34 and personal exposures. Discussion is provided about models and factors affecting various
35 microenvironmental relationships, but a focused, decisive, and succinct summary of the
36 results of applying the models is lacking.

37
38 **6. The dosimetry and modes of action of O₃ are discussed in Chapter 5. The primary**
39 **focus of the dosimetry discussion is to highlight factors that might lead to differences in**
40 **dose between individuals and between species. Some potential modes of action that may**
41 **underlie a number of health outcomes and that may contribute to the biological**
42 **plausibility of health effects of short- and long-term exposures are described in detail.**
43 **Is the review of basic dosimetric principles of O₃ uptake presented accurately and in**
44 **sufficient detail? What are the views of the Panel on the approach taken in Chapter 5 to**
45 **characterize modes of action for O₃-related effects?**

1
2 The dosimetry and modes of action of O₃ are discussed in Chapter 5. The primary focus of
3 the dosimetry discussion is to highlight factors that might lead to differences in dose between
4 individuals and between species. Some potential modes of action that may underlie a number
5 of health outcomes and that may contribute to the biological plausibility of health effects of
6 short- and long-term exposures are described in detail.

7
8 **Is the review of basic dosimetric principles of O₃ uptake presented accurately and in**
9 **sufficient detail?**

10
11 With regard to factors that influence O₃ dosimetry (e.g., airway geometry, gender and age),
12 the chapter does a good job. However, there is little discussion of dosimetric principles and
13 their application to the interpretation of data and to extrapolation modeling. Also, there is an
14 insufficient explanation of essential dosimetry variables (i.e., flux, absorbed fraction,
15 absorption efficiency, inhaled dose and net dose) and the interrelationships among these
16 factors.

17
18 It is appropriate that ELF substrate reactions with O₃ have been emphasized in both the
19 dosimetry and mode-of-action (MOA) sections of this chapter. These reactions are a key
20 factor that links O₃ dose with biological dysfunction, cell damage, and physiological
21 responses such as altered pulmonary function. Some suggestions for improving the
22 integration of this material between the two parts of chapter 5 are given below.

23
24 There is limited discussion of species differences in nasal structure and lung morphometry
25 and the composition of the ELF together with the cellular composition in the major
26 respiratory tract regions (nasopharyngeal, tracheobronchial, and alveolar). Comparative
27 dosimetry linking human to animal studies needs to be expanded because many relevant
28 mechanistic studies exist primarily in animal models. For example, some effects of O₃
29 exposure, such as remodeling in small airways and other persistent anatomic changes, have
30 been demonstrated only in non-human primates and rats. Understanding these data is
31 essential because such information affects the strength of species homology and also
32 illustrates what needs to be taken into account in interspecies dosimetric extrapolations.

33
34 Given the importance of exercise on physiological responses to ozone, the chapter would
35 benefit from an expanded discussion of the relation between O₃ uptake and breathing patterns
36 during exercise (e.g., how a change from low to moderate exercise level is accompanied
37 primarily by a change in tidal volume whereas an increase in frequency becomes more
38 important when exercise increases from moderate to heavy levels). Transition from nose to
39 mouth breathing should also be discussed in the context of exercise.

40
41 **What are the views of the Panel on the approach taken in Chapter 5 to characterize**
42 **modes of action (MOA) for O₃-related effects?**

43
44 The MOA material is currently a combination of effects descriptions mixed with studies that
45 are more mechanistically oriented. The result is excess duplication with subsequent effect

1 chapters and a disjointed presentation. For example, understanding the MOA of an effect
2 described in the short-term effects chapter would require going back and forth between two
3 chapters. If the MOA for effects (other than the discussion of ELF reactions) were relocated
4 to the related effect in the effect chapter, more cohesive understanding (and fewer pages)
5 would result. The first part of the chapter on dosimetry seems disconnected from the second
6 part of the chapter on MOA. An implied link is O₃ reactions with ELF substrates that
7 simultaneously augment O₃ uptake as well as the production of toxic byproducts that can
8 reach epithelial cells. The MOA discussion overly relies on an assertion that free O₃
9 molecules cannot penetrate a lining layer depth greater than 0.1 μm, leading to the hypothesis
10 that O₃ effects throughout the respiratory tract must be mediated via secondary reaction
11 products. Since the surfactant film that covers almost all of the alveolar epithelial cells is
12 only about 0.02 μm in depth, this premise is not valid for the alveolar region.

13
14 If the purpose is actually to convey dose-response considerations, the chapter title should be
15 changed and the linkages between dosimetry and MOA should be better developed. The
16 chapter introduction would be improved by a version of Figure 5-6 expanded to depict the
17 main factors in dosimetry together with key events and pathways for the effects of ozone on
18 the respiratory tract to provide the reader with a perspective of the complexity of O₃ dose-
19 response relationships. The material on reactions of O₃ with ELF could be reorganized to
20 include a section focusing on issues that are primarily directly connected to dosimetric
21 aspects (e.g., the structure of kinetic rate equations, rate constant values of different
22 substrates, and diffusion-reaction models that estimate O₃ penetration into ELF). We also
23 suggest adding another section more concerned with issues that influence MOA (e.g.,
24 mechanisms of the O₃-ELF substrate reactions and the toxicology of the possible reaction
25 products).

26
27 Too little information from animal studies is brought into the MOA discussion. Throughout
28 the chapter, citation of key pre-2006 animal studies would strengthen the extension of MOAs
29 in support of the human findings. More interpretation and greater emphasis on the relevance
30 of key findings needs to be incorporated into the chapter. Discussion of the effects of O₃ on
31 other important preexisting conditions such as obesity and facets of metabolic pathways
32 could also be included. In addition, the MOA Overall Summary is weak; it does not convey
33 the strength and the importance of the findings discussed in the MOA subsections.

34
35 In toto, sufficient detail is presented in this chapter to serve as a background for a risk
36 analysis of health effects of ozone. The chapter does a reasonable job of including new
37 literature and integrating the research available from the 2006 ACQD. A major weakness is
38 the lack of continuity between the first part of the chapter on dosimetry and the second part
39 of the chapter on MOA and risk assessment. More interpretation/synthesis of key findings is
40 needed to identify scientific evidence that could potentially alter the current value of the O₃
41 NAAQS.

- 42
43 **7. Chapter 6 is intended to support the evaluation of human health effects evidence for**
44 **short-term exposures to O₃. To what extent are the discussion and integration of**
45 **evidence on the health effects of O₃ from the animal toxicological, controlled human**

1 **exposure, and epidemiologic studies, technically sound, appropriately balanced, and**
2 **clearly communicated? Does the integration of health evidence focus on the most**
3 **policy-relevant studies or health findings? What are the views of the panel regarding**
4 **the balance of emphasis placed on evidence from previous and recent epidemiologic**
5 **studies in deriving the causal determination for short-term O₃ exposure and respiratory**
6 **effects (in particular, additional epidemiologic evidence for lung function and**
7 **respiratory symptoms and new evidence for biological indicators of airway**
8 **inflammation and oxidative stress that previously has been largely limited to human**
9 **controlled exposure and toxicological studies)? The majority of new studies that**
10 **examine the association between short-term O₃ exposure and mortality focus on specific**
11 **issues that have been previously identified. Does the structure of the chapter adequately**
12 **highlight the breadth of studies (both older and new) that indicate an association**
13 **between O₃ exposure and mortality and provide the underlying rationale for the causal**
14 **determination? Are the data properly presented regarding the credibility of newly**
15 **reported findings being attributable to O₃ acting alone or in combination with other co-**
16 **pollutants and regarding the extent that toxicological study findings lend support to the**
17 **biological plausibility of reported epidemiologic associations in reaching a causal**
18 **determination? Are the tables and figures presented in Chapter 6 appropriate,**
19 **adequate and effective in advancing the interpretation of these health studies?**
20

21 Numerous clinical experiments from several laboratories have demonstrated that healthy
22 young adults exposed for several hours to O₃ during intermittent exercise experience
23 decrements in pulmonary function, respiratory symptoms, and lung inflammation.
24 Particularly for those studies below the current NAAQS level, it is important that the ISA
25 thoroughly discuss the details of the experimental regimens and the statistical as well as the
26 clinical significance of the results. A recent chamber study showed that 60 ppb O₃ causes
27 pulmonary function decrements in the lungs of exercising, young adult, healthy subjects,
28 with some subjects being more responsive than others. While the mean functional decrement
29 was significant statistically, it was not of a magnitude (<2%) that would be classified as
30 clinically relevant. However, the indicators of an inflammatory response (PMNs in induced
31 sputum) measured in a sub-set of the study population, were significant statistically, at a
32 magnitude (>8%) of clinical relevance, and with a greater response to ozone by the male
33 subjects. How much lower, if any, O₃ exposures could be and still induce pulmonary
34 function changes is open to question, particularly since the clinical chamber studies are using
35 exposures of long duration (i.e., 6.6 h) with exercise (i.e., increased minute ventilation) levels
36 that surpass those encountered by many occupational workers during a day of heavy to
37 severe manual labor and are well beyond those of most healthy individuals.
38

39 Pulmonary function, with or without ozone exposure, varies in a given individual as well as
40 between individuals. Most human clinical studies compare responses of volunteers exposed
41 to filtered air vs. responses after O₃ exposure. Thus, it would be helpful to include additional
42 information on the daily variability of pulmonary function responses of exercising
43 individuals to filtered air exposure. Since lower concentrations cause relatively small
44 statistically significant changes, it is important to explain all possible major sources of
45 variability.

1
2 Numerous factors have significant impacts on the results of experimental studies. They
3 include duration of exposure, pattern of exposure, concentration, exercise (ventilation rates),
4 age and gender of subjects, preexisting diseases of subjects, and species and strain of animal.
5 In too many cases, this information is not provided, but should be. The separation between
6 old and new studies in this chapter leads to a choppy presentation and weak integration. The
7 problem is especially troublesome in the case of short-term human clinical and
8 epidemiological studies since they will form the predominant bases of the O₃ NAAQS
9 review. Also, some important references to human clinical studies covered in Chapter 5 are
10 not included in this chapter. These shortcomings could be overcome by including tables that
11 summarize the human clinical or animal toxicology literature. Such tables would allow
12 brevity of the text and still provide a quick way to evaluate the weight of the evidence for
13 particular health effects.

14
15 The graphical presentation of the epidemiologic data (Figures 6-3 through 6-11) frequently
16 relies upon a single abscissa with multiple interpretations, depending on the endpoint used in
17 a particular study. A less confusing manner of presenting the data is needed.

18
19 The epidemiologic results of increased mortality (overall) are quite consistent in direction
20 (not in severity) over space, time, and a range of circumstances and study designs, although
21 there are some exceptions for single cities or other subgroups. Possible flaws in the evidence
22 being presented are adequately discussed. However, the discussion misses the point that a
23 remarkable combination of factors would have to affect the reported studies, each in different
24 ways, to decrease the estimated effect to be no more than “likely”.

25
26 In analyses of the short term effect of ozone on mortality, attention was given to confounding
27 by multi-pollutants (PM, SO₂). Although the chapter is already quite broad, a clearer
28 summation of the information on this sub-topic (co-pollutants, confounding, and mortality)
29 seems warranted.

30
31 Sub-topics of interest that could be considered for more emphasis under ozone and mortality,
32 include: (a) increases in mortality found to be higher in ethnic populations (page 6-155) and
33 how they interact and associate with economic factors (unemployment, education), (b)
34 primary users of outdoor public transportation, and (c) housing. These contributors to
35 potential exposure, also impact avoidance practices in vulnerable populations.

36
37 “Tolerance”, “adaptation”, and “attenuation” are used frequently and sometimes
38 interchangeably. These terms need to be defined initially and then used consistently,
39 throughout the document.

40
41 The discussion of severity of effects observed in humans should be expanded. The ATS
42 guidance on pulmonary function is referenced, but not explained. The document should
43 make clear what it means to have a certain percentage change in pulmonary function or an
44 increase in lung inflammatory markers in a healthy human or in an asthmatic child. This

1 chapter would also benefit from more integration with mechanisms of action and animal
2 toxicology studies.
3

4 The animal toxicological studies on respiratory structural changes are not adequately
5 discussed. When they are mentioned, the discussion is buried, too brief, does not allude to
6 supporting evidence, and does not discuss implications for severity of effects in humans.
7 There are dozens of references to effects below 0.5 ppm, down to 0.15 and 0.2 in non-human
8 primates, which are not included. Including them is important because the structural changes
9 are correlated with inflammation and (at higher levels) with functional changes. Such
10 structural changes cannot be measured in humans, but are very likely to occur if exposures
11 are sufficient. Such information contributes to understanding severity of the effects O₃.
12 Therefore, it is essential to add this information.
13

- 14 **8. Chapter 7 presents important new findings from studies published since the 2006 O₃**
15 **AQCD including studies that examine the relationship between long-term O₃ exposure**
16 **and new onset asthma in children, first childhood asthma hospital admissions,**
17 **increased asthma severity, bronchitic symptoms and respiratory-related school**
18 **absences. These studies provide evidence in this regard based on different genetic**
19 **variants. What are the views of the Panel on the conclusions drawn in the draft ISA**
20 **regarding the strength, consistency, coherence and plausibility of the evidence for**
21 **health effects for long-term O₃ exposure on respiratory morbidity? Limited new data**
22 **also suggest a link between long-term O₃ exposure and respiratory mortality; what**
23 **weight should be placed on this evidence in causal determinations? What are the views**
24 **of the Panel on the conclusions drawn in the draft ISA regarding the strength,**
25 **consistency, coherence and plausibility of the evidence for neurological effects resulting**
26 **from long-term O₃ exposure? Are the data properly presented regarding the credibility**
27 **of newly reported findings being attributable to O₃ acting alone or in combination with**
28 **other co-pollutants and regarding the extent that toxicological study findings lend**
29 **support to the biological plausibility of reported epidemiologic associations in reaching**
30 **a causal determination?**
31

32 *Strength of Causality*

33 Overall, the panel agreed with the causality conclusions in this chapter. The strength of
34 evidence for causality is perhaps weakest for mortality, for which EPA concluded a
35 “suggestive” relationship. This conclusion is largely based on a single epidemiological study,
36 with consistent supporting evidence from other lines of research, including toxicological
37 research. Further description of the mortality study, including its limitations, is needed. The
38 conclusion for evidence on all-cause mortality is appropriate, given the single study’s
39 evidence that the all-cause relationship is not robust to inclusion of PM. There is stronger
40 evidence for respiratory mortality.
41

42 The text on evidence for causality of long-term exposure to O₃ could be made stronger by
43 drawing on literature from other chapters that found consistent evidence for similar health
44 outcomes, albeit for a different timeframe of exposure. Specific examples are the findings
45 from epidemiology, toxicological, and human experimental studies on respiratory morbidity

1 for a range of health endpoints. These findings provide evidence of plausibility for the
2 conclusions in the long-term exposure chapter. The chapter could explicitly state the ways in
3 which there is and is not evidence for causality, such as whether the limitations relate to
4 sample size, lack of variability in study designs, etc. This should be done in the context of
5 evidence for causality, not research needs.

6
7 *Definition of long-term exposure*

8 Given the wide range of what “long-term exposure” may mean, this chapter would benefit
9 from a discussion early in the chapter on how this is defined. Throughout the chapter, the text
10 should specify the duration of exposure for each study. This is sometimes provided, but often
11 missing throughout the chapter. The exposure timeframe should be clearly specified in every
12 table, figure, and mention of a study. The “long-term” exposure timeframe in this chapter
13 ranges from a single day to many years. The inclusion of short-term exposure in this chapter
14 is inappropriate. This apparently relates to a decision to keep reproductive health outcomes
15 together; however, the remainder of the document clusters studies by exposure timeframe
16 (e.g., short-term versus long-term exposure for respiratory mortality) as opposed to clustering
17 by health outcome. This structure needs to be revisited to either divide the birth outcomes
18 literature by exposure timeframe to be consistent with the remainder of the ISA, or to have it
19 be its own chapter. There are some studies (e.g., 90-day exposures) that are included in both
20 the short-term and long-term exposure chapters. The beginning text of each chapter should
21 define the duration term.

22
23 *Co-Pollutants*

24 There should be more discussion and presentation of results on confounders, particularly PM.
25 This could be a table that presented side by side the effects of PM alone, ozone alone, and
26 their separate effects when they are both in the model.

27
28 *Wording choices and presentation*

29 In addition to the exposure timeframe issues mentioned above, there are several wording
30 choices that could lead to misinterpretation. One example is the use of “seasonal” in Section
31 7.2, which would be better defined as exposure over a few months, without using the word
32 “season.” There have been many “seasonal” studies of short-term exposure to ozone. A
33 second example of a poor wording choice is the sentence that “A 10-ppb increment in
34 exposure to O₃ elevated the risk of death from respiratory causes and this effect was robust to
35 the inclusion of PM_{2.5}” (page 7-20, with similar sentences elsewhere in Chapter 7). There is
36 nothing particular about the increment of 10 ppb. This needs to be reworded to note that
37 higher levels of ozone were associated with higher risk, or to add the numerical central
38 estimate so that the 10-ppb increment is meaningful. Another example is the vague use of
39 “relevant” exposure. A careful read and rewrite of this chapter is needed.

40
41 *Additional issues*

- 42 • A short discussion of why current findings differ from those in the previous review
43 would be useful. Are prior results fully consistent with current results, given the
44 differences in study methods, precision, etc.

- 1 • Asthma is a lethal disease, and death from asthma is sufficiently uncommon that it
2 might not show up in studies of total respiratory mortality. If the relative risk is high,
3 a relation to O₃ might be evident in a mortality analysis focused on asthma. Whether
4 this type of work has been done could be mentioned in the text.
- 5 • Many animal toxicology studies were omitted and some are misrepresented. For
6 example, page 7-54 summarizes the NTP O₃ cancer study in mice and rats. Although
7 the overall summary for mice is correct, the details provided are not.
- 8 • Many of the missing references were included in previous criteria documents and
9 could be easily incorporated.
- 10 • One way to include detailed information on a large number of studies would be to add
11 tables.

12
13 **9. Chapter 8 is a discussion of potential susceptibility factors. Are the characteristics**
14 **included within the broad susceptibility categories appropriate and consistent with the**
15 **definitions used?**
16

17 Epidemiological, clinical, and animal toxicology studies have made clear that many intrinsic
18 and extrinsic factors contribute to inter-individual variation in multiple ozone response
19 phenotypes. In fact, the NAAQS are designed to protect the most susceptible. Thus,
20 defining the term susceptible and then addressing the elements in a consistent manner is
21 crucial. The chapter defines the term broadly to include such diverse factors and genetics and
22 the extent of exposure. There was substantial discussion among the CASAC members as to
23 whether the definition of susceptibility put forward was appropriate. For example, tolerance
24 distributions are founded on the recognition of innate biological differences that make some
25 individuals respond at a given dose while other persons do not. And, as the dose is increased
26 the tolerance distribution becomes narrower. Others argued that susceptibility and
27 vulnerability have very different meanings: susceptibility factors refer to innate
28 characteristics of the individual that contribute to the response to ozone (or other pollutants)
29 while vulnerability refers to factors that influence individual responses that are acquired such
30 as living near highways, nutritional status, pre- or co-exposure to ozone and/or other
31 pollutants, and socioeconomic status (SES). A suggestion was made that all of the factors
32 that define susceptibility could be classified somewhat arbitrarily as intrinsic (e.g., genetic
33 background, gender, age, pre-existing disease) and extrinsic (e.g. nutrition, SES, magnitude
34 of exposure and dose). In any case, the panel agreed that additional consideration of the
35 definition of susceptibility was necessary.
36

37 The authors then captured what are considered to be the most important known categories of
38 factors that may contribute to enhanced susceptibility to ozone-induced adverse outcomes.
39 The 13 major categories for discussion included pre-existing disease/conditions (8.1),
40 lifestage (8.2), sex (8.3), genetics (8.4), diet (8.5), body mass index (8.6), socioeconomic
41 status (8.7), air conditioning use (8.8), involvement in outdoor activities (8.9), race/ethnicity
42 (8.10), physical conditioning (8.11), smoking (8.12), and hyperthyroidism (8.13). Broadly,
43 the 13 categories could be considered intrinsic (8.1-8.6, 8.10, 8.13) and extrinsic (8.7-8.9,
44 8.11, 8.12, and a new section on exposure and dose) susceptibility factors, as suggested
45 above. Some of the categories could be collapsed to be more inclusive, e.g. involvement in

1 outdoor activities and physical conditioning; pre-existing disease/conditions and
2 hyperthyroidism and smoking.

3
4 This chapter does not (and should not) repeat all the studies on susceptibles contained in
5 earlier chapters. However, the rationale for those papers chosen for expanded discussion
6 here are not clear. A more concerted effort is needed to identify the definitive papers for
7 each susceptibility class and then proceed to describe them, with a very brief cross walk to
8 the larger body of information within the other chapters (hopefully contained within tables in
9 the revised ISA).

10
11 **Are there any key susceptibility factors that were not included and need to be added?**

12
13 Exposure and dose are included in the definition of susceptibility, but are inadequately
14 treated in the text. Exercise is only indirectly and too briefly treated in the sections on
15 children and on outdoor activities. At ambient exposure levels, exercise is the single most
16 important driver of the amount of ozone inhaled and the likelihood of causing effects in
17 individuals of any age or disease condition. As such, more discussion of the role of exercise
18 and exercise levels should be included in Chapter 8.

19
20 The Genetics section was well-written, and adequately considers recent genetic association
21 studies in human epidemiological and chamber investigations. It should be noted that, due to
22 small sample sizes, many of the chamber studies are limited to testing only those potential
23 candidate genes that have very high minor allele frequencies in order to obtain appropriate
24 statistical power. Other genes with potential impact on ozone-induced outcomes may be
25 important, such as those identified in some of the mouse models, but power considerations
26 have limited testing these genes in human populations.

27
28 It was a bit surprising that the discussion of toxicological studies did not include more
29 thorough consideration of potentially important genes other than those mentioned (e.g., Tnf,
30 Nqo1). Recent investigations in animal models have implicated additional candidate genes
31 for future investigations in human populations, including for example I110, Mmp9, Il6, Tlr2,
32 Marco, Hsp1a, H2-Aa, Ab1, Eb1, Eb2, Ea (histocompatibility genes), Lta, Nos2, and TLR4
33 and TNF signaling genes such as Myd88. A table should be created that identifies these and
34 other genes that have been implicated to be important in the pathogenesis (or protection
35 against) ozone-induced lung inflammation and injury.

36
37 The inclusion of diet as a susceptibility factor was timely and important. Given that this
38 factor was not considered in previous AQCDs, the authors should have the flexibility to cite
39 older papers to give appropriate context. In addition to vitamins C and E, vitamin A
40 deficiency has also been shown to have important consequences on ozone-induced
41 inflammation (see e.g. Paquette, et al, Am J Physiol 270:L475-82, 1996). Caloric restriction
42 (protein deficiency) was briefly mentioned, but this area could be better developed by
43 including additional studies such as Kari et al (Am J Respir Cell Mol Biol 17:740-747,
44 1997).

1 In general, the chapter would be stronger if evidence from animal toxicology studies were
2 included that provides support for the susceptibility characteristic under discussion. A good
3 example is Section 8.1.1 Influenza/Infections. The section is only a short paragraph about
4 findings in epidemiology studies. However, there are a number of animal studies showing
5 the ability of ozone to increase the incidence and/or mortality from respiratory infections,
6 even to exposures as low as 0.08 ppm O₃. Inclusion of such material would strengthen the
7 case for O₃ being able to cause similar effects in humans.

8
9 The chapter summary identifies older age groups as being one of the most susceptible
10 populations to O₃ exposure. However, the studies discussed in Section 8.2.2 (Older Adults)
11 do not give the reader this impression. For each type of effect discussed, both positive and
12 negative studies are typically available. This section also provides an example of how the
13 results from clinical and animal studies can provide biological plausibility for some
14 endpoints (see the discussion starting at line 33 on page 8-11). The evidence may be stronger
15 for some endpoints than for others, and this should be the bottom line carried forward to the
16 chapter summary.

17
18 **10. Chapter 9 describes effects of O₃ on vegetation and ecosystems. Are the major effects of**
19 **O₃ exposure on vegetation and ecosystems identified and characterized? To what extent**
20 **do the discussions and integration of evidence across scales (e.g., species, communities**
21 **and ecosystems) correctly represent and clearly communicate the state of the science?**
22 **Has the ISA adequately characterized the available information on the relationship**
23 **between O₃ exposure and effects on individual plants and ecosystems? Are there**
24 **subject areas that should be added, expanded upon, shortened or removed?**

25
26 **Are major effects of O₃ exposure on vegetation/ecosystems identified and**
27 **characterized?**

28
29 The ISA does a nice job of recognizing the key effects and pathways by which ozone impacts
30 vegetation at all scales. There is little additional, relevant literature since the last assessment,
31 however, and there has been very little research on the effects of ozone on ecosystems (e.g.,
32 watersheds).

33
34 New evidence obtained in chamberless exposure systems, including various FACE
35 experiments, supports the broad range of conclusions derived from earlier Open Top
36 Chamber experiments. For clarity, the discussion of this alignment of FACE and OTC data
37 could be consolidated.

38
39 The alteration of complex physiological systems, including gene expression, is too often
40 equated with direct effects on vegetation, and differences in sensitivity with mechanisms of
41 resistance. Responses may be more appropriately interpreted as symptoms of overall
42 sensitivity, reflecting lack of upstream defense.

43
44 **To what extent do the discussions and integration of evidence across scales (e.g., species,**
45 **communities and ecosystems) correctly represent and clearly communicate the state of**

1 **the science?**
2

3 The chapter does a reasonably thorough job of integrating effects across spatial scales, given
4 the limited literature about ozone impacts on ecosystems or landscapes. However, the
5 authors may want to consolidate the discussion into fewer, but more vertically integrated,
6 sections, with less repetition among them.
7

8 It is clear that stomata provide the principal pathway for ozone to enter and impact plants and
9 to influence water dynamics at plant, and potentially ecosystem scales. There are better
10 references for this than cited in the text. The stomatal and gas exchange discussions could be
11 consolidated with the discussion of gas exchange, water use efficiency, stomatal control and
12 impacts on water cycling and watershed-scale effects. The McLaughlin et al. watershed data
13 and Gregg et al. studies support arguments about loss of stomatal control, however, these
14 observations contrast directly with more frequently observed stomatal closure caused by
15 ozone. Further discussion of these discrepancies is required.
16

17 Arguments regarding measurement height are confused with arguments regarding the ozone
18 concentration to which stomata are exposed, and further with uncoupling of stomatal
19 conductance and high ozone periods. These are fundamentally different issues which should
20 be separated in the text.
21

22 The definition of ecosystem should be strengthened to indicate that ecosystems have
23 boundaries (defined by the investigator/study), and that physical exchange and the interaction
24 of biotic and abiotic are important defining parts of the ecosystem concept.
25

26 **Has the ISA adequately characterized the available information on the relationship**
27 **between O₃ exposure and effects on individual plants and ecosystems?**
28

29 The comparison of exposure-response relationships from the NCLAN and NHEERL studies
30 with recent SoyFACE and Aspen FACE results is particularly useful. It clearly confirms that
31 the approaches are complementary and provide similar results. Similarly, the meta-analyses
32 that have been performed since 2006 are quite important to this ISA and useful for showing
33 the new evidence.
34

35 The ISA appropriately concludes that ozone is perceived in many ways by plants and cells.
36 Ozone and its reaction products interact with ROS metabolism at several potential places.
37 However, it is inaccurate to state that ozone is sensed by specific apoplastic receptor proteins.
38

39 In Chapter 1, much is made of the concept of adverse responses. Yet, the ISA often cites
40 alterations without stating in what direction, or whether they appear to be adverse.
41

42 **Are there subject areas that should be added, expanded upon, shortened or removed?**
43

44 While it is clear that Ca⁺⁺ and MAPKs and many other signaling components are involved
45 in ozone responses, the entire signaling framework remains poorly characterized and need

1 not be described in this chapter.

2
3 The coverage of effects on insect and mammal herbivores due to changes in vegetation is
4 rather brief. There is inadequate consideration of the interaction between N deposition and
5 ozone response. There is no consideration in the ISA of the responses of nonvascular plants
6 (e.g., mosses), lichens or lower vascular plants to ozone. Mosses may be of particular
7 significance globally.

8
9 A more critical discussion and interpretation of model approaches and results is needed. The
10 draft ISA lists main conclusions from each of a number of studies. However, the models
11 discussed are very different in scope and complexity. A critical discussion of their strengths
12 and weaknesses is required, perhaps along the lines of that in the previous AQCD.

13
14 The consideration of ozone impacts on stomatal conductance and its ramifications at various
15 scales could be condensed and consolidated, both for brevity and clarity. A more critical
16 discussion of the differences in effects of ozone on transpiration from different models and
17 from different experiments is warranted, perhaps focused on likely effects at the watershed
18 scale, addressing the discrepancies.

19
20 **11. Chapter 10 provides a concise overview of key information regarding O₃ effects on**
21 **climate and UV-B exposure. Is there any information regarding the climatic effects of**
22 **domestically produced O₃ on climate in the U.S. that should have been included? Is**
23 **there important new information on UV-B effects or other welfare effects such as**
24 **materials damage that have been overlooked and should be incorporated into this**
25 **chapter?**

26
27 **What are the views of the Panel on the scientific soundness and usefulness of the**
28 **discussion in Chapter 10 on the role of O₃ in global climate change and changes in mean**
29 **global temperatures?**

30
31 This chapter is definitely useful in view of recent interest in chemistry-climate interactions
32 and in combining air quality and climate goals for environmental policy. The discussion was
33 strong on climate forcing due to O₃ relative to that of CO₂ and CH₄, as well as the way it
34 distinguished between long-term and short-term greenhouse gases. However, more play
35 should be given to CH₄ as the only O₃ precursor for which control would effectively reduce
36 climate forcing as well as emphasizing that O₃ itself can affect CH₄ concentrations
37 (feedbacks). It should also give more play to the recent RCP scenarios of IPCC AR5, since
38 these scenarios will provide the core of future assessments of climate forcing for emissions
39 relevant to air quality and they present a very different picture from the older SRES
40 scenarios. In conclusion, the chapter is correct in concluding that there is likely to be a
41 causal relationship between tropospheric O₃ and climate change.

42
43 Additionally, there may be important effects of O₃ at the regional or continental scale in
44 addition to the global scale, as discussed on pg 10-12. Could such regional impacts be
45 additional to the range of impacts on radiative forcing cited from IPCC? If so, this topic

1 warrants further discussion. There could also be effects of climate change on circulation, and
2 thus on mixing of stratospheric O₃ into the troposphere, although effects on surface-level O₃
3 might not be large.

4
5 Feedback effects involving vegetation are also important and emphasis on individual species
6 responses may be necessary to determine the effects of climate change on ecosystems. For
7 instance, individual species may be affected in different ways, reflecting differential
8 responses to climate change by these species, including species replacements, even though
9 total ecosystem productivity may not be as severely impacted. Thus, measuring or reporting
10 only total ecosystem responses, without regard to individual species responses, could
11 underestimate impacts.

12
13 Most models of pre-industrial O₃ overestimate those values. This has implications for
14 modelers, and more emphasis should be placed on determining if those overestimates are due
15 to inadequate parameterization, or missing chemistry. With respect to calculating recent O₃
16 trends, E. Henry Lee et al. compared trends in California back to the time when ethylene-type
17 ozone monitors were used and showed that they could reconstruct the O₃ trends for that
18 period, but this work was not cited in the ISA (2003, History of tropospheric O₃ for the San
19 Bernardino Mountains of Southern California, Atmos. Env. 37:2705-2747).

20
21 This chapter also pointed out the paucity of studies relating to how increasing tropospheric
22 O₃ will affect UV-B impacts and consequently most conclusions regarding these effects are
23 tentative. In conclusion, we agree with the ISA that there is likely to be a causal relationship
24 between tropospheric O₃ and climate change brought about through radiative forcing. We
25 also agree with the ISA conclusions that tropospheric O₃ impacts on human health through
26 climate change cannot yet be critically assessed within reasonable uncertainty. With regard
27 to welfare effects, the lack of published studies assessing UV-B impacts caused by variations
28 in the column of tropospheric O₃ reflects challenges in this area, and in fact, no conclusions
29 can be drawn about these effects at this time.

30
31 **Is there any information regarding the climatic effects of domestically produced O₃ on**
32 **climate in the U.S. that should have been included?**

33
34 The discussion of climate forcing due to tropospheric O₃ was relatively thorough, and except
35 for vegetation feedbacks (see above) was comprehensive in its scope and analysis.

36
37 **Is there important new information on UV-B effects or other welfare effects such as**
38 **materials damage that have been overlooked and should be incorporated into this**
39 **chapter?**

40
41 This chapter thoroughly reviewed the literature on health and welfare effects, and there did
42 not appear to be any significant literature that was overlooked or omitted.

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**Preliminary Individual Comments on the Ozone ISA (March 2011)
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1 **Mr. George Allen**

2
3 Revised Individual Comments for CASAC Peer Review of the March 2011 Draft Ozone ISA
4 George Allen, June 7, 2011

5
6 These comments focus on Chapter 3, specifically section 3.4 (PRB O3) and 3.5 (Monitoring).
7 Sections 3.2 and 3.3 are well written.

8
9
10 3.4.2: The discussion of PRB ozone is a critical part of the ISA. EPA should include data from
11 additional PRB relevant long-term data that are not in AQS. The UNH AIRMAP Mt.
12 Washington (NH) summit data are a very rich and unique resource that may be useful in
13 validation of GEOS-Chem. The summit of Mt. Washington is at 6300' and about 4500 feet
14 above surrounding terrain. Thus, although the elevation is not high relative to western high
15 elevation sites, it is a very good high-elevation site for the NE – no NE high elevation sites were
16 included in this analysis. These data could be parsed by transport regimes to get a better
17 indicator of PRB O3 bounds. These data show a spring peak, but no trend in means over a
18 decade (Figures 1 and 2). Two distinct spring intrusion events occur (Figures 3 and 4); ground
19 level ozone could be analyzed around the period of these events. Other long-term NE/Eastern
20 US rural sites worth consideration that are in AQS: Whiteface Mt. NY (summit 36-031-0002,
21 and base 36-031-0003, year round), and Shenandoah NP VA.

22
23 There needs to be a more quantitative analysis of the contribution of stratospheric O3 to ground
24 level O3; this is only noted in passing with a reference to Thompson 2007. That study may over-
25 estimate this contribution in part because 2004 was an unusual O3 season for the NE US due to a
26 cool and rainy summer, and thus the reported % ozone at ground level from stratospheric ozone
27 would be higher.

28
29 The spatial scale for urban area health effect studies is of concern; Boston has only one O3
30 monitor that represents the entire core urban area. Although well correlated, an offset of 9 ppb
31 exists between that monitor and one downwind 12 miles.

32
33
34 3.4.2.1, pg 3-31. Wood smoke in the eastern US and Canada has significant elemental mercury
35 concentrations, which is a potent interference for UV ozone analyzers. Assessment of ozone due
36 to wildfires needs to take this into account.

37
38 3.4.3

39 Pg 3-31, lines 20-24: Consider using CO as relatively conserved tracer of urban air masses.

40
41 Pg 3-31, lines 34-37, pg 3-31 lines 1-4: As noted above, there is a 10-year research grade O3
42 record at the summit of Mt. Washington, NH from the AIRMAP study that should be included in
43 this assessment: <http://airmap.unh.edu> . Data are publically available:

44 <http://airmap.unh.edu/DownloadData>

45 Daily plots of all available parameters: <http://soot.sr.unh.edu/airmap/archive/>

1

Daniel Jacob's group at Harvard may be able to run GEOS-Chem to assess its performance for the Mt. Washington site - a site that has a very large spatial scale, and thus does not need a small grid size to properly model.

Pg 3-33, line 24, and 3-38 and 3-39 tables: Include MtWash as eastern elevated site for this analysis. There are 8-10 years of research grade O₃ and relevant indicator data (CO, NO_y, particle # concentration, etc.) that would be very valuable for this purpose.

3.5.2: plots are hard to use - plot 95 %tiles?

3.5.3, page 3-46, table 3-4 Agree that O₃ specifications and FRM are seriously outdated.

3.5.5.2: I endorse the concept of changing the FRM for O₃ to the NO chemiluminescent method.

3.5.6.1 pg 3-52, line 23: NH₃ and HNO₃ are not measured at NCore sites. SO₂ is.

3.5.6.1 pg 3-52, line 30: PAMS sites measure NO_y, not NO_x ("NO-what"). Actually, they measure NO_w, since these historical measurements are not robust NO_y measurements.

3.6.2.1 pg 3-71, figure 3-25 and related discussion throughout this section: It should be noted that for the Boston CSA ozone sites, Blue Hill, the site 10 miles south of Boston (AQS ID 25-021-3003, "East Milton"), is quasi-high elevation relative to surrounding terrain, at 630 ft.

<http://www.hazecam.net/bluehill.html>

and often reads higher than most other Metro Boston O₃ sites. This site is not run year-round. Lynn (25-009-2006), 12 miles NE of downtown Boston, is run year round.

Also - the Boston C.S.A. is very large, including parts of RI and NH; it's unclear if this is an appropriate spatial scale to assess.

Pg. 3-85, line 11: Which sites are A and D for Boston?

3.6.3.2, pg 3-96, fig. 3-43: add similar plots with weekend and weekdays separated out. Are Mondays cleaner than Fridays?

General comment: The Canadian Government recently completed a large report titled: Canadian Smog Science Assessment (2011). Source: Environment Canada and Health Canada. The report is not yet public but is expected to be available upon request by the end of 2011 to:

Rosa.Wu@ec.gc.ca

There are two chapters that are relevant to the PRB discussion:

CHAPTER 3: Ambient Measurements and observations

and

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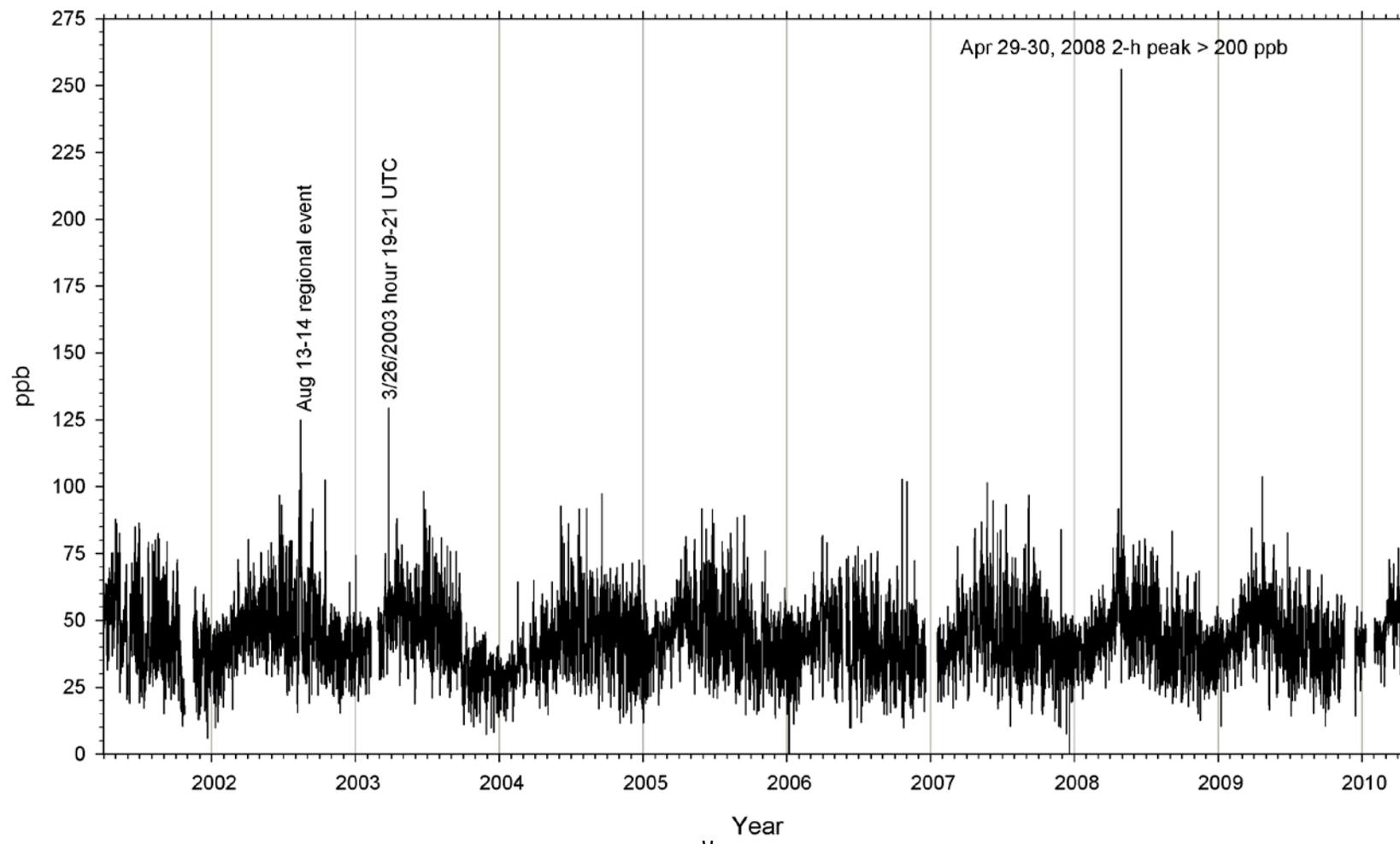
CHAPTER 7: Air Quality at the Regional and Local Scale: The What, Where, Why and How of Concentration Variations

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Figure 1.

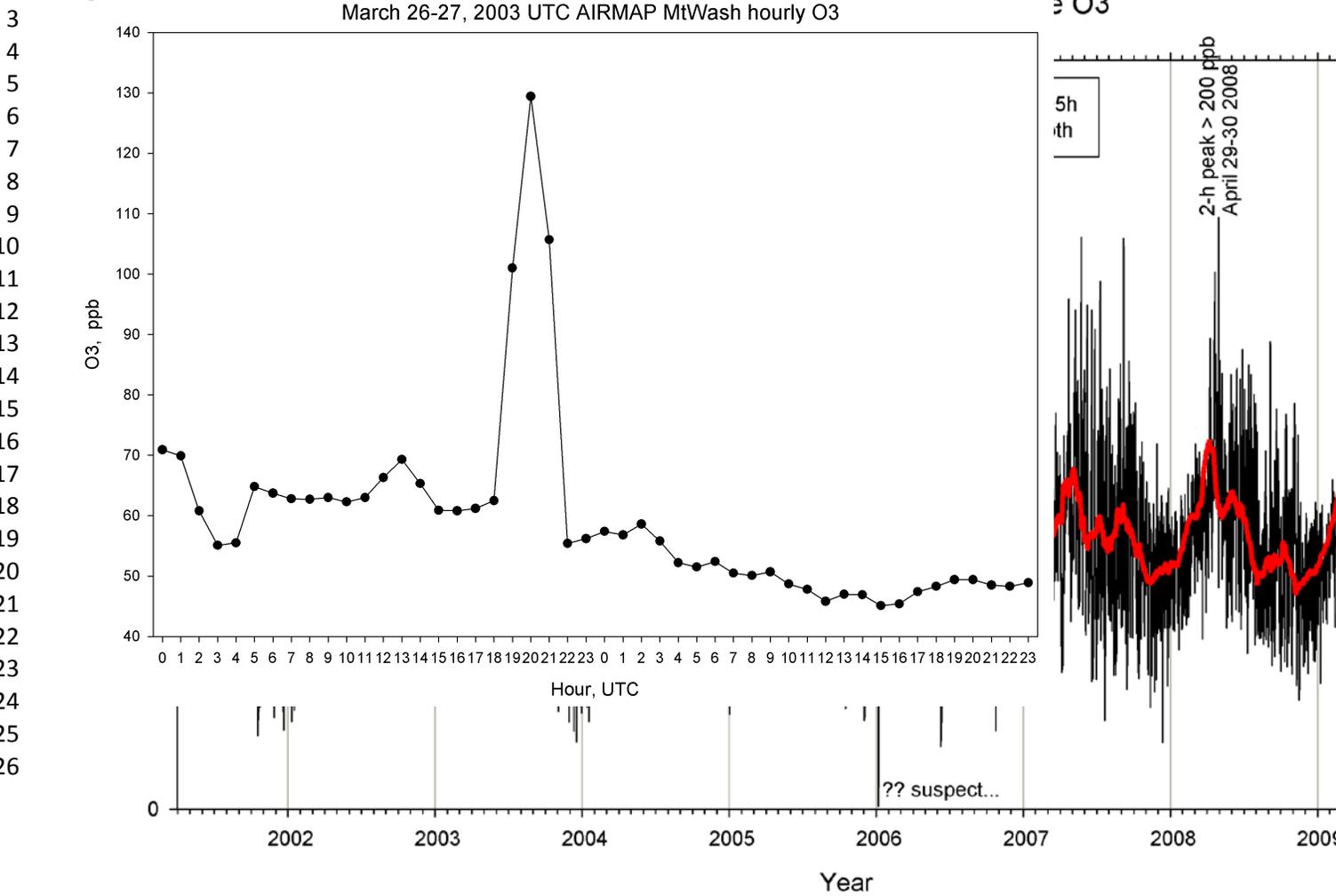
Deliberative Draft Letter to be discussed on July 6, 2011 Teleconference of the CASAC Ozone Review Panel. Do not cite or quote. This draft has not been approved by the chartered CASAC nor does it represent EPA policy. Updated 6-17-11.

AIRMAP MtWash 1-h O3

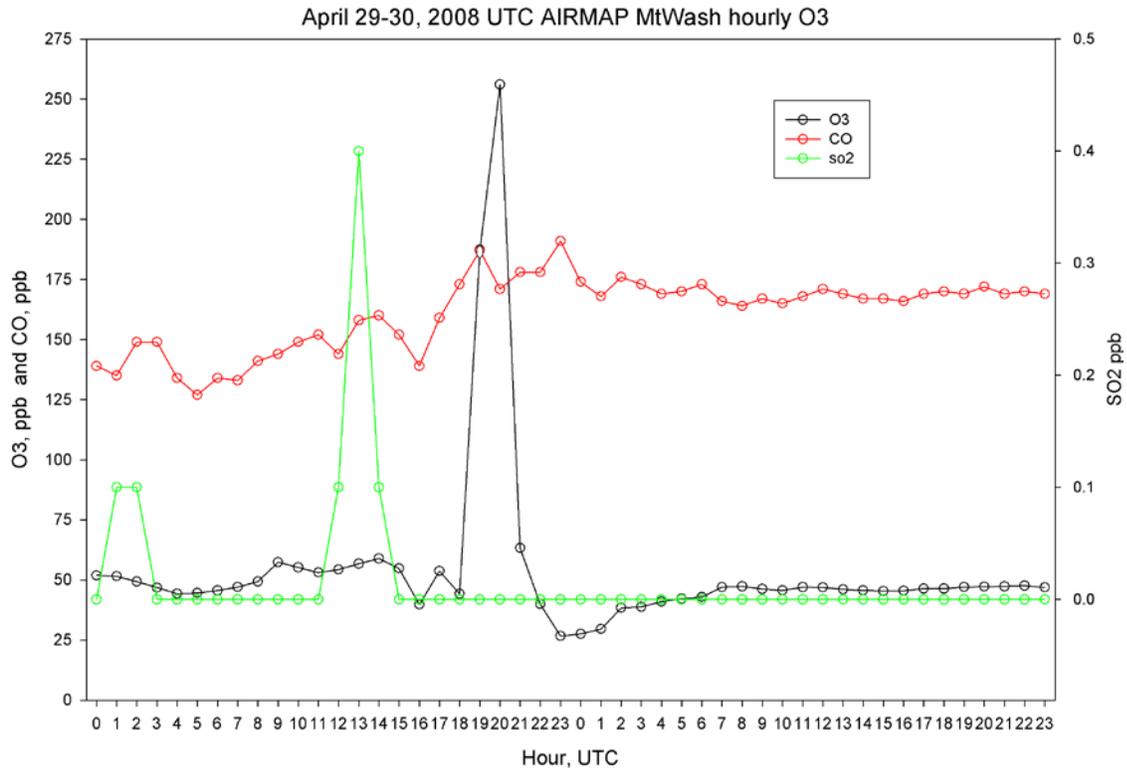


1 Figure 2.

2 Figure 3.



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1
2 **Figure 4**
3

1 **Mr. Ed Avol**

2
3 General Overview:

4 The breadth, weight, and size of the first external draft ISA O₃ document is testimony to the
5 wealth of information available regarding ambient ozone, its atmospheric formation, and the
6 potential for human and material exposure and detrimental effects. To be sure, this large
7 document represents a substantial summarization of a much larger body of published
8 information. That said, in my opinion, the document, is too large, still missing at least two key
9 chapters, and has a third key chapter mis-identified.

- 10
11 1) The document needs a Summary/ Conclusions section, to provide some determination of
12 what key points have been presented.
- 13 2) The document is missing a chapter identifying critical gaps/scientific needs. Is there
14 sufficient information to address critical topic areas, or are there key gaps in
15 understanding or research that need to be addressed? Specific guidance regarding
16 perceived critical gaps could help improve the utility and quality of subsequent reviews,
17 by motivating researchers to consider/address identified needs.
- 18 3) Chapter to chapter, the document is written in differing detail, layout, and approach. This
19 is not surprising, given the broad range of the overall topic and the fact that different
20 authors composed different chapters, but there should still be some harmonization of the
21 approach and layout. Chapter 5, for example, reviews the current state of understanding
22 in “Dosimetry and Mode of Action” by what had been reported up to the 2006 Review,
23 what “recent publications” (post-2006) have shown, with periodic summaries of what
24 each section presents, with an overall chapter summary (p5-61), and a “gaps in
25 knowledge” section (5-62) – could/should this serve as a useful template for each chapter
26 to review what was known as of the last review cycle, what is new, what we know think
27 we know, and what we still need to find out?

28
29 The section on Adversity (Sec1.6.6, p1-24) raises an important issue in assessment and
30 interpretation. With improved analytical capabilities, it is possible to detect much smaller and a
31 wider array of biological endpoints...but are they clinically significant, important, or “adverse”?
32 Some perspective on what constitutes adversity would seem useful.

33
34 Chapter 2, currently entitled” Integrated Health and Welfare Effects Overview” seems out of
35 place and not well defined. It currently brings together many different elements of our current
36 understanding of ozone, from the chemistry to the animal and human health effects to welfare
37 effects. If it is essentially an “Executive Summary” of the document, it should be shorter and
38 placed in the front of the document. If it is an integration of the document’s chapters, it should be
39 near the end of the document. Some decision needs to be made regarding its purpose, and
40 appropriate modifications to it should be accordingly made.

41
42 Chapter 1 (Introduction)

43 There are sections of the document that could be reduced in size, without loss of document
44 integrity.

1 In Chapter 1 for example, the discussion on Causal Determination (beginning on P1-12, Section
2 1.6 in general, p1-14, Section 1.6.3 in particular) is useful but overly detailed, and could be
3 summarized or substantively moved to an appendix attachment. The Summary paragraph (p1-25,
4 Section 1.7) lacks much substance – what specific conclusions can be drawn from the
5 information presented? There arguably could and should be concise statements based on what
6 was presented that represent essential elements to be carried forward.

7 Chapter 2 (Overview)

8 In Chapter 2, the discussion about Policy Relevant Background (PRB) concentrations (p2-5,
9 Section 2.1.3 and especially p 2-7, Section 2.1.3.4) provides some useful information but
10 meanders around the topic at hand. After laying the groundwork for how this is determined and
11 what affects it, what is the best current estimate of the PRB? Has it increased or decreased since
12 the last review? If so, why might this have occurred? These questions are addressed later in
13 Chapter 3 (p3-25, Section 3.4), but why doesn't the summary chapter present (just) summary
14 information?
15

16
17 (Specific Comment: The section on Exposure Measurement in Chapter 2 (p2-12, Section 2.2.1.1)
18 is misleading, in that it describes one passive sampler (a chemically-coated diffusion filter
19 sampler based on nitrite-to-nitrate oxidation) and describes this as if it were the ONLY passive
20 sampler technology available. While the commercial sampler described (but not identified by
21 manufacturer) may well be widely used, it likely is not the only passive sampler in use).
22
23

24 Chapter 3 (Atmospheric Chemistry)

25 The Chapter 3 discussion on Policy Relevant Background and estimating PRB (p3-25, Section
26 3.4) is interesting but perhaps too extensive for this focused summary. Could this be more
27 effectively summarized and defer some of these details to an appendix? (This is admittedly more
28 of a packaging and presentation issue than a factual or substantive one, but the important points
29 can get lost in pages and pages of discussion, citation, and discourse). In a similar manner, the
30 Chapter 3 section on Air Monitoring (p3-40, Section 3.5) contains a great deal of instrumentation
31 performance/specification data (for example, p3-44, Sections 3.5.2.1 and p3-46, Section 3.5.3)
32 that would seem more appropriate in an appendix. With respect to p 3- 48, Section 3.5.5.2, it
33 seems inappropriate to specifically review a specific manufacturer's instrument in this ISA.
34 Wouldn't a better approach be to discuss the class of instruments or measurement technique?
35

36 The Chapter 3 air monitoring section boxplots and figure representations of O₃ concentrations
37 are interesting, informative, and helpful. The figures on pp3-98 and 3-99, in Section 3.6.4
38 (Associations with Co-Pollutants) is especially insightful...but once again, at the end of the
39 chapter, there is no summary, no conclusions, no drawing together of key issues or identification
40 of critical gaps.

41
42 (Specific Comment: P3-4, Section 3.2, lines 9-16 discuss nocturnal low-level jets (LLJs), but to
43 the casual reader, this could be misconstrued to be aircraft rather than wind flow; a few more
44 words of clarification would help avoid confusion).
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Chapter 4 (Charge Question 5) (Exposure)

(A better summary is needed): The presented chapter is informative and well-referenced, but major sub-sections lack any focused summary, and the collective chapter lacks a concise set of conclusions. Section 4.6 (p4-21 to p4-25), which is entitled “Summary and Conclusions”, is itself almost four pages in length. Rather than rehashing what was previously presented, key perspectives should be brought forward into a short listing of objective findings.

For example, the one-and-one-half pages “summarizing” Exposure Measurement (Section 4.6.1, p4-21) could be arguably collapsed into six statements:

- (1) passive badges are widely in use and provide ppb detection levels, when appropriately used;
- (2) Small active samplers, either based on chemical oxidation or uv detection, are also available;
- (3) indoor/outdoor ratios are driven by air exchange rates (due to a general lack of indoor sources of ozone) and are generally in the 0.1-0.4 range;
- (4) personal exposure and ambient ozone concentrations are moderately well-correlated (0.3-0.8) and are related to activity patterns, housing characteristics, and season;
- (5) central-site monitor concentrations are representative of day-to-day changes in average personal exposure;
- (6) central site concentrations tend to over-report personal exposures, due to time spent indoors (and low indoor penetration of ozone).

In a similar way, Section 4.6.2 (p4-23, Exposure Modeling) might be summarized by presenting a short table, listing the various models (or model types) presented (stochastic, land-use regression, spatial, or APEX, SHEDS, etc) with a summary of application, strengths, and weaknesses.

(POPULATION PROXIMITY TO OZONE MONITORS & SPATIOTEMPORAL

VARIABILITY): There is often a systematic difference in the nature of urban vs rural ozone exposures, due to local NO titration of ozone in urban areas. Ozone tends to be “peakier” in urban areas, and more broad and drawn out, in terms of sustained ambient levels, in more rural areas. This has exposure and dose implications for urban and rural populations. These issues are not captured in the current document, and are not likely to be, if the focus is only on the urban exposure.

(INTRA COMMUNITY VARIABILITY OF OZONE CONCENTRATIONS): The research and regulatory communities have generally considered ozone to be a regional pollutant, with minimal local variability, but our group’s studies (and many others) have repeatedly encountered the diminution of ozone levels caused by NO titration near busy roads and fresh combustion sources... could a finer spatially-resolved sampling approach identify biologically meaningful differences in ambient ozone levels, or is it purely an academic or engineering exercise in measurement performance?

1 The section/chapter summaries should be developed with a clear focus on how the information
2 provided or developed would be applied in interpreting epidemiologic studies. How does the
3 presented work improve our knowledge, or application of it? How would information, perhaps
4 currently identified as being “unavailable”, materially move the science and understanding of
5 that science forward?
6

7 Chapter 5 (Dosimetry)

8 This chapter has a great deal of information, organized in a somewhat different way from most
9 of the other chapters, but perhaps in an ultimately more useful one. Whatever the organizational
10 approach, there should be some consistency across chapters.
11

12 Chapter 6 (Short-Term Effects)

13 This chapter, which reviews the available information on short-term effects of ozone exposure,
14 covers a very large data base. Yet a different organizational approach has been used in this
15 presentation, organizing by successive sub-topics first (be it respiratory, cardiovascular, etc,
16 health outcome) and then integrating historical and recent information.
17

18 On p6-167, a section appears entitled “Adaptation”, referring to the blunted responses in some
19 individuals from repeated exposures to ozone. This re-opens a discussion that simmered over 20
20 years ago – is “adaptation” the correct description of the observation? Many at the time felt it
21 was not, and a better term was attenuation, toleration, or blunted response, since adaptation
22 implied some positive coping change, which this did not appear to be...since by the following
23 ozone season, the blunted responses had usually disappeared but could be re-developed with
24 repeated exposure (in some individuals). Therefore, the statement on line 1 of p6-167 is not
25 strictly accurate, since controlled exposures arguably did not demonstrate an adaptive response
26 for respiratory effects, but rather, a development of temporary toleration or blunted response.
27

28 One especially interesting and potentially valuable section in this chapter is on Confounding (p6-
29 144, Section 6.6.2.1). This is one of the few places where multi-pollutant exposures are
30 considered, albeit as a “confounder”. Should more be said about multi-pollutant exposures? How
31 is this issue being approached?
32

33 Chapter 7 (Long-Term Effects)

34 Long-term exposure effects are addressed in this chapter by evaluating the evidence for a wide-
35 ranging list of health outcomes. In this chapter, grouping is by systems – respiratory,
36 cardiovascular, etc. with mortality and morbidity as sub-sections. Could similar chapter
37 organization be used for both short and long-term effects (Chapters 6 and 7)? Many of the same
38 endpoints are reviewed...

39 A final conclusions section, summarizing what has been determined through the course of the
40 chapter (e.g., suggestive causal for all cause mortality, inadequate for cancer, suggestive causal
41 for CNS, suggestive causal for reproductive, etc) would have been helpful.
42

43 Chapter 8 (Susceptible Subpopulations)

44 This is an important chapter, addressing who among us are at greater risk to the effects of
45 ambient ozone. Based on previous work with other NAAQS, there ought to be an almost-

1 standardized list of characteristics or sub-groups who might be at increased risk, with some
 2 possible additions or deletions due to some specific attribute of the chemical being considered.
 3 The document would profit from the inclusion of a summary susceptibility factors table, such as
 4 Table 8-2 of the PM ISA (see below), to focus the reader on what is known or surmised.

Table 8-2. Susceptibility factors evaluated.

Factor	Collective Evidence (+/-) ²
Older Adults (≥ 65)	+
Children (<18) ¹	+
Pregnancy and Developmental Effects	+*
Gender	-
Race/Ethnicity	-
Genetic factors	
- Genetic polymorphisms	+
- Epigenetics	
Cardiovascular Diseases	+
Respiratory Illnesses	+
Respiratory Contributions to Cardiovascular Effects	-*
Diabetes	+*
Obesity	+*
Socioeconomic Status (SES)	+
Educational Attainment ³	+
Residential Location ³	+
Health Status (e.g., Nutrition) ³	+*

¹ The age range that defines a child varies from study to study. In some cases it is <21 years old while in others it is <18 years old (Firestone et al., 2007, [192071](#)). For the purposes of this exercise children are defined as those individuals <18 years old because the majority of epidemiologic studies consider individuals under the age of 18 children.

² This column identifies whether the "collective" evidence from studies evaluated found that a specific factor increased (+) or did not increase (-) a population's susceptibility to PM exposure (i.e., PM exposure to all size fractions combined). In instances where only a few studies were evaluated for a specific factor it was not possible to clearly assign a (+) or (-) as a result the direction of the preliminary evidence is identified along with (*) to represent that more information is warranted.

³ These factors are surrogates of socioeconomic status and are discussed within this subsection of the chapter.

5
 6 The definition of "susceptibility" still seems in evolution...It has been broadly defined here as
 7 essentially anything that increases the risk of O3-related health effects or anything that modifies
 8 O3 exposure...which seems too broad to me. Beyond the "innate biologicals" (disease status, age,
 9 genetics, etc), only SES comes to mind as a factor eligible for consideration under susceptibility
 10 (since SES is a marker for access to health care and a host of other health issues).

11
 12 How does "Air Conditioning Use" (p8-20, Section 8.8) come to be considered as a susceptibility
 13 factor, similar to genetics or age or sex or disease status? Notwithstanding the discussion about
 14 AC use as an indicator of SES or regional temperature, it seems somehow inappropriately placed
 15 here. Would "proximity to on-road traffic" be considered a susceptibility factor (since higher
 16 proximity would likely imply a reduction in O3 exposure)? Susceptibility seems to me to be
 17 more about involuntary or innate biological attributes, rather than operational circumstances that
 18 can be readily changed by human behavior to reduce or increase exposure.

19

1 In a similar manner, inclusion of “Involvement in Outdoor Activities” (p 8-20, Section 8.9) as a
2 factor *per se* seems incorrect. It seems like the “active agent” is the increased exposure or dose
3 *associated with being outdoors* rather than the act of participating in outdoor activities.
4

5 If this is the relevant definition of “susceptibility”, why not add other exposure-modifying
6 factors, such as (1) scarves, masks, or personal protective equipment, (2) time spent indoors, (3)
7 percentage of time spent oral or nasal breathing, (4) physical location (i.e., proximity to
8 combustion emissions), (5) use of personal hygiene products (which may chemically react with
9 O₃, affecting one’s “personal cloud”)...? The possibilities are seemingly endless...and untenable.
10 I suggest the definition of susceptibility be revisited and limited to innately biological or
11 involuntary phenomena (e.g., disease status, age, genetics, SES).
12

13 Chapter 9 (Environmental Effects on Vegetation and Ecosystems)
14 (Note that this is well out of my area of expertise, so I comment as a naïve reader)
15 This chapter begins well, with a summary table (p9-5, Table 9.1) to help guide the reader as to
16 current understanding, and (presumably) the chapter content. The section presentations initially
17 seem to follow the Table 9.1 tabular summary, focusing on the causal evidence for effects, but
18 then the chapter diverges into “Experimental Exposure Methodologies”, before returning to the
19 main topic. Some rationale needs to be provided to justify why the discussion of experimental
20 methodologies is even included here.
21

22 Chapter 10, Climate Change
23 (very interesting, relevant, and seemingly focused chapter; no specific comments).
24

1 **Dr. John Bailar**

2
3 **Comments on Charge Questions 2, 7, and 8: Integrated Science Assessment for Ozone and**
4 **Related Photochemical Oxidants**

5
6 The time available for the review of this assessment has not been sufficient for me to examine
7 any of the literature cited. Thus I have taken the descriptions of individual studies and their
8 findings as correct.

9
10 **Charge Question 2.**

11
12 *The framework for causal determination and judging the overall weight of evidence is presented*
13 *in Chapter 1. Is this framework appropriately applied for this O₃ ISA? How might the*
14 *application of the framework be improved for O₃ effects?*

15
16 Section 1.6.1 It is important that this document give the time point at which new input was
17 suspended, and that it say what was done, if anything, regarding potentially important
18 information received after that time. “Nothing” would be an acceptable answer, but it should be
19 here.

20
21 1.6.2 “Cause” is still not well defined. but should be defined in terms of the whole body of
22 evidence, not in terms of individual reports. (My own definition is that an agent is a cause if the
23 effect appears when the agent is present in some setting, and does not occur when the agent is
24 absent, all other things being equal, but there is no reason for you to adopt this if some other
25 definition works better in this ISA context. This requires only a little modification in more
26 complex situations such as synergy. My point is that I do not see a definition here that I could
27 apply in an unambiguous fashion.)

28
29 1.6.4 You give a nod to the S-G report on page 1-20, but I think that is not sufficient. It was
30 published some months before the Hill paper, and in my view deserves the credit. More
31 important, perhaps, is that “consistency” may well not be one of the most important criteria –
32 that depends on the context of other information. What is really critical is the whole body of
33 evidence, not any one criterion in isolation. You seem to misinterpret specificity. I have
34 understood Hill’s “specificity” to be non-restrictive -- to refer to a single *effect* (or a group of
35 closely related effects rather than a collection of effects that are not likely to have a common
36 cause), but not to require only a single *cause*, which would be extremely restrictive. Or have I
37 misunderstood you? You may want to look at Hill’s original paper on this, as well as the S-G
38 report. We may also not agree about lines 14/15 on page 20. For me, a failure to satisfy one or
39 more criteria can be as telling as meeting them. Again, the whole body of evidence is what
40 matters.

41
42 1.6.5, table re “not likely”. It is a truism that one cannot prove a negative with empirical data. I
43 would cast “not likely” in terms of probability *and* a specific effect size – e.g., “It is very
44 unlikely that X causes more than a 10% increase in Y.”

1 1.5.4.1 “Conditions” may include more than dose or exposure, duration, and pattern. One
2 example is simultaneous exposure to a synergistic agent.

3
4 A comment in this chapter that experimental evidence may be the strongest once more brings me
5 to comment on the need to interpret the whole body of evidence. Experimental evidence may
6 not be supreme.

7
8 It might be worth noting that, for the criteria as a whole, some refer to individual studies, some to
9 collections of studies, and some to the entire body of evidence. I see this comprehensiveness as
10 a strength.

11 **Charge Question 7.**

12
13
14 *Chapter 6 is intended to support the evaluation of health effects evidence for short-term*
15 *exposures to O₃. To what extent are the discussion and integration of evidence on the health*
16 *effects of O₃ from the animal toxicological, controlled human exposure, and epidemiologic*
17 *studies technically sound, appropriately balanced, and clearly communicated?*

18
19 I am not an expert on the health effects of short-term O₃ exposure, and time has not allowed me
20 to review the primary literature. Given my dependence on what EPA has presented in this draft,
21 it appears to me that the evidence for mortality as a result of short-term exposure to O₃ is
22 stronger than “likely”; it is compelling.

23
24 This view of the mortality data is guided by two broad principles: There can be no heterogeneity
25 in effects (interaction, synergy, or effect modification) unless there is some kind of effect to be
26 altered in at least some subset of the study population. And, any mortality effect cannot be zero
27 overall if there is an effect for some cause, however minor or for some subset of the population,
28 however small, unless there is a compensating effect in the other direction for some other cause
29 of death; I have not seen any evidence suggesting that O₃ exposure is protective against any
30 lethal disease. These principles hold even if overall mortality cannot be shown to be elevated; an
31 effect can be real but too small to be evident in overall mortality or broad categories of causes of
32 death.

33
34 The epidemiologic findings of increased overall mortality are quite remarkably consistent in
35 direction (though not in size) over space, time, and a wide range of circumstances and study
36 types, despite a few exceptions for single cities or other subgroups. This evidence seems to me to
37 be even stronger than the early evidence regarding cigarette smoking and lung cancer, prior to
38 the time “research” sponsored by the tobacco industry inserted a few negative findings. The
39 discussion of the possible flaws in the evidence is thoughtful and detailed, but seems to me to
40 miss the point that a remarkable combination of factors would have to affect the reported studies,
41 each in different ways, to decrease the estimated effect to no more that “likely”.

42
43 It is worth note that if a distributed lag model holds, the effect estimated for day X includes the
44 effect for day X-1 with a one day lag, that for X-2 with a 2 day lag, etc. This argues for an
45 analysis of periods longer than days to compare high vs. low O₃ levels (and there are other

1 reasons for this, including possible cumulative effects and, conversely, possible habituation or
2 delayed avoidance behavior). More generally, there should be something here about the
3 *combination* of daily averages, whether lagged or not. What is the cumulative effect of ten days
4 in a row, each with an RR of 1.01? Is adaptation important? Do RRs decline over a few days
5 because a susceptible sup-population has been depleted? (The text on page 1-167 should
6 mention the possibility of depletion or avoidance, which is suggested, though over a shorter
7 interval, by Figure 6-35.)

8
9 It would help to add a table showing, for each short-term mortality study, the crude effect and the
10 effect after adjustment for PM and any other factors in the reported study. In my experience,
11 when adjustment for confounders reduces a crude estimate of an effect by a substantial amount,
12 more and better information about confounders etc. (including additional items) is likely to lead
13 to a further reduction; if the initial adjustment has little effect, using more items and better data is
14 not likely to have much effect. The limited information on this in the present report suggests that
15 co-pollutants and other confounders do account for some, but not all, of the relation to O₃
16 measures in the crude measures of mortality.

17
18 *Does the integration of health evidence focus on the most policy-relevant studies or health*
19 *findings?*

20
21 This is clearly a matter of opinion, and in my opinion the focus is largely appropriate. However,
22 if the ISA concludes that there is a real, measurable mortality effect at the current exposure limit,
23 or that there is no effect near that limit, that finding is likely to drive any overall policy decision
24 about a change in regulatory standards for O₃. Thus I would reorganize the report to discuss
25 mortality first, and I would give it more weight in the various summaries.

26
27 An additional point is the need to consider how regulation should address joint actions that are
28 more or less than additive. For an artificial example, assume that agent A alone is innocuous,
29 with an RR of 1.0, agent B also has an RR of about 1.0, but the combination has an RR of 10.0.
30 How much of that increase should be laid on A and how much on B? The answer could have an
31 impact on regulation of one or both. While this is artificial, more complicated real-life examples
32 may not be rare. This matter should be addressed in the draft ISA report.

33
34 *What are the views of the panel regarding the balance of emphasis placed on evidence from*
35 *previous and recent epidemiologic studies in deriving the causal determination for short-term O₃*
36 *exposure and respiratory effects (in particular, additional epidemiologic evidence for lung*
37 *function and respiratory symptoms and new evidence for biological indicators of airway*
38 *inflammation and oxidative stress that previously has been largely limited to human controlled*
39 *exposure and toxicological studies)?*

40
41 Evidence is evidence, regardless of whether it was developed yesterday or a decade ago. I would
42 judge old and new by the same standards (though this may often mean that the new is better
43 because of advances in technology, bigger sample sizes, or other reasons). Also, it is likely that
44 many readers will not have ready access to the prior report(s). Thus I would argue for a more

1 complete statement of prior results when they contribute in an important way to the present
2 conclusions.

3
4 *The majority of new studies that examine the association between short-term O₃ exposure and*
5 *mortality focus on specific issues that have been previously identified. Does the structure of the*
6 *chapter adequately highlight the breadth of studies (both older and the new) that indicate an*
7 *association between O₃ exposure and mortality and provide the underlying rationale for the*
8 *causal determination?*

9
10 Avoidance behavior, when for a good medical reason (not just fashion or trendiness), is a health
11 cost. I would like to see new evidence about the extent and nature of avoidance behavior, but
12 even with what is now available, there should be a bit more emphasis in the summaries here.

13
14 *Are the data properly presented regarding the credibility of newly reported findings being*
15 *attributable to O₃ acting alone or in combination with other co-pollutants and regarding the*
16 *extent that toxicological study findings lend support to the biologic plausibility of reported*
17 *epidemiologic associations in reaching a causal determination?*

18
19 I believe that they are.

20
21 *Are the tables and figures presented in Chapter 6 appropriate, adequate, and effective in*
22 *advancing the interpretation of these health studies?*

23
24 In my view they are appropriate, adequate, and effective.

25
26 **Charge Question 8.**

27
28 *Chapter 7 presents important new findings from studies published since the 2006 O₃ AQCD*
29 *including studies that examine the relationship between long-term O₃ exposure and new onset*
30 *asthma in children, first childhood asthma hospital admissions, increased asthma severity,*
31 *bronchitic symptoms and respiratory-related school absences. These studies provide evidence in*
32 *this regard based on different genetic variants. What are the views of the panel on conclusions*
33 *drawn in the draft ISA regarding the strength, consistency, coherence, and plausibility of the*
34 *evidence for health effects for long-term O₃ exposure on respiratory morbidity?*

35
36 Page 7-6, lines 16/25. What did Clark et al. report finding, weak as that finding may be?

37
38 The evidence regarding genetics and asthma would be stronger if it did not rely so heavily on the
39 CHS.

40
41 Please add a short discussion of why current findings differ from those in the previous review.
42 Are prior results fully consistent with current results, given the differences in study methods,
43 precision, etc.?

44

1 *Limited new data also suggest a link between long-term O₃ exposure and respiratory mortality;*
2 *what weight should be placed on this evidence in causal determinations?*

3
4 Asthma is a lethal disease, and death from asthma is sufficiently uncommon that it might not
5 show up in studies of total respiratory mortality. If the relative risk is high, a relation to O₃
6 might be evident in a mortality analysis focused on asthma. Has this been done?

7
8 The section on infant mortality is not focused on asthma, and the few positive finding (among
9 many negative) might be accounted for by small biases in the data, multiple comparisons
10 problems, and post-hoc selection of subgroups.

11
12 Overall, I agree with the ISA that, overall, the evidence regarding mortality and long-term
13 exposure to O₃ is suggestive, but it is not as strong as that regarding morbidity. However, good
14 evidence of an effect on potentially lethal conditions adds to the strength of the findings on
15 mortality. The negative findings of the six-city study could be the result of having only six
16 points of observation with several potentially important confounders or modifiers, as well as the
17 narrow range of average O₃ levels, so that even a major effect could be missed. Other negative
18 human studies are in general lacking in statistical power, have narrow ranges of exposure, or do
19 not examine an appropriate set of causes of death.

20
21 *What are the views of the Panel on conclusions drawn in the draft ISA regarding the strength,*
22 *consistency, coherence and plausibility of the evidence for neurological effects resulting from*
23 *long-term O₃ exposure?*

24
25 This question appears to refer to Sections 7.4.8.2/3 and 7.5. The ISA concludes, “suggestive or a
26 causal relationship”, but I would add that the evidence includes only one human study and that
27 the animal evidence was all at exposures well above the current EPA limit

28
29 *Are the data properly presented regarding the credibility of newly reported findings being*
30 *attributable to O₃ acting alone or in combination with other co-pollutants and regarding the*
31 *extent that toxicological study findings lend support to the biological plausibility of reported*
32 *epidemiological associations in reaching a causal determination?*

33
34 This is a bit difficult me to answer because I have not had an opportunity to review the literature
35 that the ISA summarizes, but I am alert to problems of presentation and credibility, and I have
36 found no reason here to question any of the descriptions, findings, or conclusions, except as I
37 have noted elsewhere here.

38
39 I understand the effect on mortality of adding PM to the O₃ model, but what about the reverse? I
40 would like to see, side by side, the effects of PM alone, O₃ alone, and their separate effects when
41 both are in the model. That is that only way to understand whether the apparent effect of either
42 one is in part or totally a result of their co-occurrence.

43
44 Overall, I concur with the ISA that “there is likely to be a causal relationship between long-term
45 exposure to O₃ and respiratory morbidity”. I might even make the statement a bit stronger; the

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1 evidence is really pretty persuasive, though not as strong as for short-term effects. This
2 conclusion is based primarily on the epidemiologic evidence, but seems to be fully supported by
3 toxicological and human experimental findings.
4

1 **Dr. Michelle Bell**

2
3 ***Charge to the O₃ CASAC Panel***

4
5 *We ask the Panel to focus on the following questions in their review:*

- 6
7 12. *This first external review draft O₃ ISA is of substantial length and reflects the copious*
8 *amount of research conducted on O₃. EPA has attempted to succinctly present and*
9 *integrate the policy-relevant scientific evidence for the review of the O₃ NAAQS. The*
10 *panel may note that per CASAC consultation on November 13, 2009, considerable*
11 *discussion has focused on older literature. The panel emphasized that important older*
12 *studies should be discussed in detail to reinforce key concepts and conclusions if they are*
13 *open to reinterpretation in light of newer data and where these older studies remain the*
14 *definitive works available in the literature. In considering subsequent charge questions*
15 *and recognizing an overall goal of producing a clear and concise document, are there*
16 *topics that should be added or receive additional discussion? Similarly, are there topics*
17 *that should be shortened or removed? Does the Panel have opinions on how the*
18 *document can be shortened without eliminating important and necessary content?*

19
20 Although the O₃ ISA is of substantial length, I find the length of the ISA to be
21 appropriate in relation to the body of scientific literature on O₃ and the need to
22 summarize the evidence thoroughly and accurately. A significantly shorter summary
23 version is needed; however, the larger document serves to provide the underlying
24 evidence of ozone's impacts on human health and welfare. The role of Chapter 2 as
25 compared to an executive summary is a bit unclear to me as it doesn't so much integrate
26 as summarize the following chapters. In that sense it's largely repeating information that
27 is elsewhere and could be a separate summary document. Alternatively, this chapter
28 needs to be more integrative and does not need to revisit every main point of the
29 subsequent chapters. Whether it stays as a summary or is made more integrative, it could
30 probably be shortened to less than its current 66 pages.

31
32 The text on the history of the NAAQS for ozone may have too much detail. In particular,
33 the need to include issues that were raised in court but resolved (e.g., unconstitutional
34 delegation of legislative authority) is unclear. (Chap. 1)

35
36 The method by which scientific studies were identified is well described overall, with the
37 exception of the incorporation of non-peer reviewed studies. For example, see page 1-7
38 "Typically, only information that had undergone scientific per review and had been
39 published or accepted for publication were considered. . ." This is vague, but central
40 relating to the quality of studies. (Chap. 1)

1 The section on estimating policy-relevant background concentrations implies that the
2 approaches used are identical to those used previously (see first sentence of 3.4.3). A
3 better way to state this would be that the methods used are still the state-of-the-art
4 approaches, and to present only the new estimates, without this level of detail. This
5 section could be shortened (Section 3.4.3).
6

7 In comparison to its importance and length of other chapters, Chap. 3 is far too long, with
8 figures and tables that are not particularly useful for the underlying messages of the ISA
9 and lengthy appendices. As an example, there are 15 figures comparing observed and
10 GEOS-Chem estimates for ozone, but the discussion on these figures only relates to the
11 model, not to our understanding of ozone and health or welfare effects, or the underlying
12 science behind ozone formation. The point of these figures is not clear. The meaning of
13 this chapter is unclear, especially given its 203 pages. At the very least, a substantial
14 number of tables and figures from this section need to be cut. This chapter is
15 disproportionately long compared to its importance.
16

17 Section 3.3 could be cut entirely or greatly reduced. The importance of regional air
18 quality modeling to the ISA needs to be better described, including its relation to the rest
19 of the document. It seems odd to have an entire section on a tool rather than on
20 underlying principles (i.e., our understanding of the chemical and physical transformation
21 of ozone and its precursors). The ISA does not have primer sections on other tools and
22 methods (e.g., biostatistical modeling) that apply our scientific understanding, but has a
23 very large section on atmospheric modeling. This section also presents a somewhat
24 narrow view of air quality modeling, with heavy emphasis on CMAQ and almost no
25 discussion of how well CMAQ actually estimates ozone levels.
26

27 *13. Chapter 7 presents important new findings from studies published since the 2006 O₃*
28 *AQCD including studies that examine the relationship between long-term O₃ exposure*
29 *and new onset asthma in children, first childhood asthma hospital admissions, increased*
30 *asthma severity, bronchitic symptoms and respiratory-related school absences. These*
31 *studies provide evidence in this regard based on different genetic variants. What are the*
32 *views of the Panel on the conclusions drawn in the draft ISA regarding the strength,*
33 *consistency, coherence and plausibility of the evidence for health effects for long-term O₃*
34 *exposure on respiratory morbidity? Limited new data also suggest a link between long-*
35 *term O₃ exposure and respiratory mortality; what weight should be placed on this*
36 *evidence in causal determinations? What are the views of the Panel on the conclusions*
37 *drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of*
38 *the evidence for neurological effects resulting from long-term O₃ exposure? Are the data*
39 *properly presented regarding the credibility of newly reported findings being attributable*
40 *to O₃ acting alone or in combination with other co-pollutants and regarding the extent*
41 *that toxicological study findings lend support to the biological plausibility of reported*
42 *epidemiologic associations in reaching a causal determination?*
43

44 I agree with EPA's assessment of the degree of evidence on causality for long-term
45 exposure to ozone and respiratory effects ("likely to be a causal relationship") and central

1 nervous system effects (“suggestive of a causal relationship”). For readers who are
2 unfamiliar with this literature, key questions will relate to the reasons for the lack of
3 stronger evidence. The ISA O₃ could discuss these issues relating to whether more
4 conclusive evidence would need to rely on larger sample size, different types of studies,
5 further research, evidence across multiple study designs, etc. (in Section 2.4.2 and Chap.
6 7) This text could refer to the guidelines used to assess causality in Chap. 1.
7

8 The text on the relationship between ozone exposure and birth outcomes in Chapter 2
9 could be misinterpreted to indicate that there is a lack of studies, whereas there have also
10 been some studies that did not identify an association (e.g., for ozone and low birth
11 weight). A more clear way of describing this evidence would be to note that studies are
12 inconsistent, rather than list the limited studies with evidence in Section 2.4.2.3. This is
13 done in more detail in Section 7.4.
14

15 There have been additional recent articles that review and summarize methodological
16 issues on air pollution and birth outcomes that could be referenced in Section 7.4, page 7-
17 27 (e.g., Woodruff TJ et al. 2010).
18

19 Assessment of the biological plausibility of effects for long-term O₃ exposure can gain
20 information from the evidence for short-term effects of related health endpoints. This
21 could be further discussed and highlighted in the ISA in Chapter 7. As an example, the
22 evidence for respiratory effects on mortality is strengthened by the evidence for
23 respiratory morbidity. As the ISA correctly notes, EPA concluded at the 2006 review that
24 associations between short-term O₃ exposure and respiratory health effects are causal,
25 and new evidence since that time supports this claim. This includes a range of study
26 designs (epidemiology, animal models, controlled human exposure). Although that
27 research is for short-term exposure, it contributes to biological plausibility of respiratory
28 impacts from long-term exposure, especially as a range of health responses have been
29 noted (airway inflammation, decline in lung function, respiratory symptoms, hospital
30 visits, emergency room visits). In general, the causality of long-term exposure could
31 borrow information from the studies of short-term exposure, where appropriate, to note
32 consistencies or inconsistencies.
33

34 Given the wide range of what “long-term exposure” may mean, this chapter would
35 benefit from discussion early in the chapter on how this is defined. The long-term
36 exposure section considers exposure over several months, or spatial comparisons across
37 cities that have different annual O₃ levels. The wording used to describe exposure
38 timeframe and the lack of specifications is a large problem in this chapter. The
39 underlying analysis of causality seems appropriate, but it will be difficult for most readers
40 to assess and compare the evidence without knowing the exposure periods.
41

42 Throughout the chapter, the text should specify the duration of exposure for each study.
43 This is sometimes provided, but missing in several places. For example, the first sentence
44 of 7.2.3 does not indicate whether children’s lung function was assessed in relation to
45 their lifetime exposure, recent years, or some other timeframe. Another example is on

1 page 7-13 where “chronic exposure” is discussed. There are a few examples where the
2 timeframe of exposure is not specified at all (e.g., Section 7.2.7, Section 7.3.2). The
3 exposure timeframe should also be specified in tables or figures (e.g., Table 7-1 and
4 Table 7-7); this is done nicely in Tables 7-2 to 7-5.

5
6 Some of the infant mortality studies do not present an exposure timeframe at all (see
7 Section 7.4.9.4) and the inclusion of exposure timeframes of a single day in the long-term
8 exposure chapter is very confusing (see Table 7-6). I recognize this is a challenge EPA
9 has confronted in previous summaries of research on ozone and other pollutants, but the
10 current structure needs improvement. The lack of specification of what “chronic” and
11 “long-term” exposure means contributes to this problem.

12
13 The causality evidence for long-term exposure to ozone and mortality may be the
14 weakest endpoint as it is based on a single study, so I think the “suggestive of a causal
15 relationship between long-term O₃ exposure and all-cause mortality” (page 7-62) is
16 appropriate; however, another study found no association (see Section 2.4.2.6, Section
17 7.3.2). More description of these studies study would be useful to help evaluate causality
18 given the heavy weight on a single study.

19
20 For Table 2-3, word “no studies” as “no studies at that time” when referring to the lack of
21 evidence for the previous O₃ AQCD.

22
23 The use of “seasonal” in Section 7.2 would be better defined as exposure over a few
24 months, without using the word “season.” There have been many “seasonal” studies of
25 short-term exposure to ozone. Although the document notes that “the term seasonal was
26 used in these studies as a measure of a long-term exposure of several months,” there
27 appears no benefit to adding potential confusion by using the word seasonal to refer to
28 exposure over several months. The broad range of “long-term exposure” definitions in
29 this chapter adds to this potential confusion as the chapter does include short-term
30 exposures.

31
32 In this chapter, distinctions between cross-sectional studies and other studies is very
33 useful. More emphasis could be placed on the cohort studies as opposed to the cross-
34 sectional studies. The CHS has information on the study subjects’ individual-level
35 exposure, not just community information, so the 2nd sentence of 7.2.3, showing results
36 by community-level ozone, may not be the best presentation of results.

37

1 **Dr. Joseph Brain**

2

3 Answer to Charge Question 6 (Chapter 5)

4 General Comments:

5 This chapter, like the entire document, is encyclopedic. There are a large number of references.
6 Most of the relevant ozone publications in the last 5 years are here. Surely, the multiple authors
7 of this document need to be congratulated for being inclusive. At the same time, this
8 encyclopedic feature is sometimes a weakness. It is hard to focus on evidence which might
9 ultimately alter the recommended value for the ozone standard.

10 I am ambivalent about the use of having a section entitled “Recent Publications.” One the one
11 hand, it is convenient to have them here and segregated from the earlier literature. On the other
12 hand, it is unfortunate that these new references are not better integrated into the historic
13 literature. Especially, these sections appear to be an annotated bibliography. They list the
14 references and say a bit about each article, but rarely do they indicate a particularly important
15 paper and explain why it’s important. There is not enough integration and critical analysis.
16 It would be valuable if each “Recent Publications” section would end with a brief comment on
17 how these recent publications make a difference. For example, I applaud the sentence at the
18 beginning of 5.1.3.2 which concludes that the studies reviewed are in agreement with previous
19 studies and “do not change the dosimetry conclusions of the last document.” That kind of critical
20 analysis is very helpful. These same suggestions apply to comparable sections later in the
21 document entitled “New Cellular and Molecular Insights.” A clear statement of conclusions at
22 the beginning or at the end of each section with this title would be helpful in putting the literature
23 into perspective.

24 I appreciate the way in which the list of references and in the text itself, every reference has an
25 identifying number which permits the reader to locate it. That makes this document more useful.

26

27 Major Comments:

28 1. I draw attention to section 5.2.9.5, Adaptation. One of the hallmarks of oxidant injury,
29 especially ozone, is the phenomenon of adaptation. There are levels of ozone, or hyperoxia,
30 which produce serious injury or even death in naïve animals. However, in animals chronically
31 exposed to lower levels of ozone or oxygen, there is morphologic and biochemical adaptation.
32 Subsequent exposures to ozone produce a far lower response. This is important in understanding
33 ozone toxicology in humans as well. It also relates importantly to different patterns of ozone
34 exposure. Citizens, who rarely see significant ozone levels and then suddenly have a two to three
35 day episode of high ozone, may be much more affected than those who enjoy steady state ozone
36 exposures all the time.

37 2. Another component which should be better developed is the one dealing with co-exposures
38 with particulate matter, 5.2.9.6. Yes, there is some evidence for PM modulating ozone responses.
39 This section should be broadened to co-exposures of ozone with a variety of other pollutants,
40 such as oxides of nitrogen and oxides of sulfur. We need to better understand responses to ozone
41 per se compared to responses to ozone, plus other pollutants.

42 3. In response to Charge Question 6, I believe Chapter 5 does a good job of describing
43 differences in retained dose of ozone among different individuals and among species. They also
44 do a good job of describing generic mechanisms which make measured short and long-term
45 effects of ozone biologically plausible. Yes, I believe that the basic dosimetric principles of

1 ozone uptake are presented accurately and in sufficient detail. The document does not take a
2 clear position as to what is the ideal and most appropriate dosimetric approach. Is it the local
3 absorption/retention of ozone or is it the generation of ozone related by-products which are the
4 mediators of injury.

5 Finally, I believe Chapter 5 does link these biochemical changes to associated phenomenon of
6 inflammation and other types of organ injury. An area which could receive more attention is
7 extra-pulmonary effects of ozone. What other organs are affected? Do these responses alter our
8 understanding of dose response effects in humans?

9 4. “Gaps in Knowledge” is the title of 5.2.11. I would propose two other bullets. The first would
10 be

11 -Interacts with co-pollutants

12 -Is altered by adaptation and the time course of ozone exposure

13

14 Minor Comments:

15 Page 51, Line 17-19

16 I’m concerned about the phrase “cells protruding from the ELF and surface macrophages.” This
17 seems to imply that these cells are not covered by the alveolar lining layer (ELF). Electron
18 microscopic images clearly show that the extracellular lining fluid is continuous and covers these
19 cells.

20 Page 5-9

21 When discussing the nasal pharyngeal removal, the initial sentence sounds far too certain. The
22 precise percentages are significantly influenced by exercise and especially by the choice of
23 pathway. At least, the considerable variability among individuals should be acknowledged.

24 Also, is there additional information as to how pulmonary uptake and dose is modified by nose
25 breathing versus mouth breathing?

26

1 **Dr. David Chock**

2
3 **CHAPTER 4. EXPOSURE TO AMBIENT OZONE**
4 **CHARGE QUESTIONS**

5 Chapter 4 describes human exposures to O₃. Is the evidence relating human exposure to ambient
6 O₃ and errors associated with exposure assessment presented clearly, succinctly, and accurately?
7 Are the results of field studies evaluating indoor-outdoor and personal-ambient exposure
8 relationships, and factors affecting those relationships, presented in a manner that is useful for
9 interpretation of epidemiologic results? Is the information on modeling O₃ concentration
10 surfaces and population exposures appropriate for evaluating the utility of these modeling
11 approaches? Do the characterizations of temporal and spatial variability of O₃ in urban areas
12 provide support for better understanding and interpreting epidemiologic studies discussed later?
13

14 The Chapter describes clearly and generally quite accurately the understanding to date in the
15 relationships between human exposure to ambient ozone and errors associated with exposure
16 assessment. The results of field studies evaluating indoor-outdoor and personal-ambient
17 exposure relationships, and the factors affecting those relationships, are well described, but there
18 are issues that need further elaborations and modifications (See below). These results are useful
19 in the design of epidemiological models. The Chapter describes the modeling of concentration
20 surfaces and of population exposures adequately, but there remains a lack of sufficient data to (1)
21 properly evaluate the concentration surface models at spatial scales that are less than inter-
22 monitor distances, and (2) refine activity patterns to build more robust exposure models. The
23 descriptions of temporal and spatial variability of ozone represent our current knowledge well
24 and should help ascertain the scope and design of epidemiological studies and help interpret their
25 results. There are more detailed, specific issues that are presented below.
26

27 Ozone in the lower troposphere is a secondary pollutant, predominantly formed by
28 photochemical reactions between hydrocarbons and oxides of nitrogen in a time scale of a few
29 hours or longer, depending on the reactivity of the hydrocarbons involved. Therefore, we expect
30 it to be rather uniform in a spatial scale on the order of, say, 10 or more km. But ozone is also a
31 rather reactive oxidizing agent. It reacts quickly with NO, and contributes to aging of materials
32 and living things. So, unlike the less-reactive secondary PM_{2.5}, there are significant reductions
33 of ambient ozone concentrations at and downwind of major roadways, with a spatial scale of
34 meters to maybe hundreds of meters or more, depending on the emission rates of NO and wind
35 velocities. And indoors, ozone would be scavenged rather quickly unless the air exchange rate
36 with outdoor air is high. So, even though both ambient PM_{2.5} and ozone are secondary
37 pollutants, their spatial concentration patterns need not be similar in a populated urban
38 environment with spatially uneven NO sources. For ambient ozone, one can envision a relatively
39 flat terrain punctuated by many trenches and valleys along different roadways whose depths and
40 extents depend on the NO emissions from the vehicular traffic and local wind fields. One also
41 needs to note that increasing the averaging time would increase the smoothness of the spatial
42 pattern of ozone concentrations. In this connection, a 2010 paper by Sarnat, et al. (385852)
43 concluded that PM_{2.5} and ozone are spatially more homogeneous and thus the health effects are
44 less sensitive to the choice of ambient monitors, as compared to primary pollutants like CO and
45 NO₂. First, note that a large portion of NO₂ concentration comes from the titration of ozone by

1 NO near the emission sources. But equally if not more important, the authors used different
2 averaging times to characterize the pollutant concentrations, 24 hours for PM_{2.5}, 8 hours for
3 ozone, and 1 hour for CO and NO₂. This would inadvertently and preferentially increase the
4 smoothing of the spatial distributions of PM_{2.5} and ozone relative to those of CO and NO₂.
5 Nevertheless, the value of the paper is not diminished because the paper in effect smoothes out
6 the intra-day spatial variability in order to study the health effects of ozone concentrations based
7 on their inter-day variability.

8
9 Because of the rather complicated ozone spatial pattern in the urban environment, information on
10 the activity and location patterns of individuals, the proximity of their homes to major roadways,
11 and the indoor-outdoor air exchange rates of their homes become relevant to reliably determine
12 their ozone exposures. The Chapter indicates that indoor ozone concentrations are generally
13 considerably smaller than outdoor ozone concentrations. But it reports only one correlation
14 number, 0.58, which is from a study in the Los Angeles area conducted by Avol, et. Al. (018270)
15 (page 4-4, line 34). It would be great if the authors include more of such correlations from
16 studies in other cities. The Chapter describes quite thoroughly the observed relations between
17 ambient ozone concentrations measured at monitors and people's exposures to ozone. The
18 correlations between ambient ozone concentrations and personal exposures of ozone vary
19 considerably, but are generally in line with expectations. In particular, the correlations with
20 ambient ozone concentrations increase from subject-specific exposure, to pooled-group exposure
21 to community-averaged exposure even though the actual ozone exposures are generally
22 significantly lower than the ambient concentrations. This finding indeed supports the use of
23 ambient ozone concentrations as a surrogate for average personal ozone exposure, a finding that
24 is critical to establishing the relevance of community health effects studies.

25
26 In the description of personal-to-ambient ozone ratios, the authors need to include the work of
27 Suh and Zanobetti (677202), which indicates extremely low slopes between 24-hour personal
28 and ambient ozone concentrations for both fall and spring in Atlanta. Also, in the description of
29 the correlations between personal exposure of ozone and of co-pollutants, the Chapter authors'
30 attribute the paper's finding of a higher correlation coefficient of 0.14 between personal ozone
31 and personal PM_{2.5} to the regional nature of ozone and PM_{2.5} (page 4-8, lines 8 to 12). But this
32 may be a bit of a stretch because the paper also shows a low and insignificant correlation
33 coefficient between personal and ambient ozone (no number given) and between personal ozone
34 and ambient PM_{2.5} (a value of 0.08).

35
36 The Chapter describes three approaches that have been used for concentration-surface modeling:
37 spatial interpolation including inverse-distance weighting and kriging; empirical-statistical
38 modeling including land-use regression; and chemistry transport modeling. The interpolation
39 approaches are useful only if the pollutant concentrations are expected to be spatially smooth.
40 This would not be the case for ozone concentrations near NO emission sources like major traffic
41 areas. The land-use regression approach could provide greater spatial granularity, but it would
42 require frequent retuning to fit different local conditions and emissions. Only the chemistry-
43 transport modeling has a more solid physical basis. However, the required rather detailed
44 emission inventories are generally not available presently, and the parameters used in the model,
45 like eddy diffusivity, may need to be retuned for the relevant grid resolution. Furthermore, the

1 predicted results may need to be rescaled to be consistent with the observed concentrations at the
2 monitors. The Chapter authors have done a good job describing the state of the art
3 developments. There is one minor point that needs to be removed. In describing the work of
4 Brauer et al. (156292), the authors include their own opinions, which was not validated by the
5 paper's authors, that the inverse-distance weighting approach would be expected be favored
6 since ozone is a secondary pollutant (page 4-13, lines 32 to 33). Note that ozone is a reactive
7 secondary pollutant that is sensitive to local NO emissions. This sensitivity cannot be ignored in
8 large urban areas.

9
10 The Chapter highlights the important developments of many exposure models by the EPA.
11 These models couple a human activity database with a concentration-surface model. The
12 Chapter highlights two main sources of uncertainty: activity pattern database, including
13 children's activities, and concentration surface model. In the latter, improved information on the
14 ozone concentrations near-roadways would be an important step forward, and this kind of
15 improvement need is best satisfied by chemistry-transport modeling. The Chapter authors also
16 highlight a very important point: the need for the deployment of high sensitivity personal
17 exposure monitors to shorten the sampling time and to lower the ozone detection limits for low
18 indoor ozone concentrations.

19
20 In the description of the exposure measurement errors, the Chapter authors indicate that the
21 association between heart rate variability (HRV) and either ambient or personal ozone or PM_{2.5}
22 were similar and attributed these similarities to the regional nature of both ozone and PM_{2.5} (page
23 4-17, lines 28 to 29). These conclusions ignore the finding of Suh and Zanobetti (677202) that
24 the associations were insignificant to begin with, which may be attributable to the possible lack
25 of a causal link between HRV and either ozone or PM_{2.5}, regardless of their spatial distributions.
26 But even regarding the latter, the insignificant associations between the HRV indicators and
27 PM_{2.5} are generally similar between ambient and personal exposure, but those between the
28 indicators and ozone are mostly of opposite signs between ambient and personal exposure. More
29 important, the actual correlation between personal and ambient PM_{2.5} reported in the paper is
30 0.63 and significant and that between personal and ambient ozone is insignificant and no value is
31 given. These results support the regionality argument for PM_{2.5}, but not for ozone, even though
32 it does not rule out the fact that ozone is a regional pollutant subject to varying degrees of local
33 variability.

34
35 In the discussion of spatial variability, the Chapter authors describe the finding of Sarnat et al.
36 (385852) that the choice of monitor may have little impact on the results of ozone epidemiologic
37 studies (page 4-19, lines 18 to 26). Note that, as mentioned earlier, the use of different averaging
38 times for ozone and for CO and NO₂ in the study may have contributed to this conclusion. If the
39 same conclusion is reached based on an identical averaging time for all pollutants of interest,
40 then the case presented by the paper's authors would be strengthened.

41
42 In the seasonality discussion, the Chapter authors present a cogent argument that studies
43 conducted during the ozone season in periods when communities are likely to have high air
44 exchange rates are likely to have less exposure error than those conducted during winter. (pages
45 4-20, lines 10 to 15).

1

2 The Chapter authors rightly point out that use of microenvironmental models in epidemiological
3 studies has a disadvantage of needing an independent comparison with measured exposure levels
4 (page 4-21, lines 11 to 16). In fact, it defies scientific principles to draw conclusions from a
5 statistical epidemiological model that is based on numbers generated from an unverified or
6 unevaluated model like a microenvironmental model. This kind of practice has indeed occurred.

7

8 In the Chapter conclusions, the authors again highlight the similarity of the associations between
9 HRV indicators and either ambient concentrations or personal exposures of ozone and PM_{2.5} in
10 the Atlanta study, and attribute this similarity to the regional nature of both pollutants. As
11 pointed out earlier, the description of the finding of the Atlanta study is inaccurate and the
12 attribution is misleading.

13

1 **Dr. W. Michael Foster**

2
3 Comments on ISA – specifically for Chapter 6 (assigned):

4
5 Overall there is a tremendous amount of information in this particular chapter and includes 176
6 pgs of text, 37 Figures, 45 Tables, and 27 pgs of References cited. Several
7 Chapters do not even include 50 pgs of text !

- 8
9 1) a fair amount of text description is devoted to the concentration pattern of controlled lab
10 exposures of human to ozone and whether a square-wave (S-W) or triangular (variable
11 concentration) format for ozone concentration was utilized (pgs. 6/6 - 6/7, Fig. 6-2). Of
12 equal importance is likely some text should be devoted to differences in controlled
13 laboratory exposures whereby the subjects are exposed in a walk-in chamber facility or
14 via a face-mask exposure system (ref. 093690). The face-mask system excludes any
15 scrubbing out of nasal inhaled ozone by the URT, and carries with it then, the potential to
16 delivery a high deposition fraction to the LRT. Any Figures in the chapter, where results
17 from these 2 delivery modalities were combined, should likely be footnoted, and/or the
18 results to exposures listed separately.
19
- 20 2) with respect to Fig. 6-2 (pg. 6/10 of the text), it is not obvious to me why a decrement in
21 excess of 10% in the FEV1 is being identified in the respective panels of ozone
22 concentration. The rationale for selecting a 10% change as a “threshold” for a response to
23 a given concentration of ozone should likely be expressed. For example if a decrement
24 greater than 15% is selected, the frequency of responder subject to a given ozone
25 concentration decreases considerably. The text provides 2 refs for the 10% rationale
26 (044889 and 626521) and suggests that changes in FEV1 \geq 5% are clinically meaningful;
27 discussion on the threshold for defining a functional response, may be helpful.
28
- 29 3) text refers frequently to children and adolescents as being highly susceptible to ambient
30 ozone due to lung size, and perhaps increased time spent outdoors. It would likely be
31 helpful to add to the text (pgs. 6/13 – 6/14 and 6/35) reference to controlled lab studies in
32 children to ozone: for example: Koenig JQ et al, 1985, 1998; McDonnell WF et al, 1985;
33 and Linn WS et al, 1997) as these would add validity to the supposition that children are
34 more susceptible to ozone.
35
- 36 4) to address the issues over male vs. female and sensitivity to ozone, the ref by Weinmann
37 GC et al, 1985, in a controlled lab exposure setting to ozone with longitudinal data set,
38 has been overlooked and should be added to the text (pg. 6/14). Likewise, to address
39 issues over subjects habituated to cigarettes and their sensitivity to ozone, the controlled
40 lab study with longitudinal data set ref by Emmons K et al, 1991, has been overlooked.
41
- 42 5) in description of repeated exposures to ozone in controlled lab studies, the report by
43 Foster WM, et al, 1996, and which identifies systemic outcomes (peripheral blood
44 monocyte activation state, serum a-tocopherol, respiratory frequency of the breathing
45 pattern, that during or following repetitive exposures to ozone do not adapt in response to

1 a variable ozone concentration (triangular), seems to have been overlooked. As well the
2 report by Frank R, Liu MC, et al, 2001, also appears to have been overlooked, and is a
3 helpful ref as substantiates that small airway functional changes persist during repetitive
4 ozone exposure in controlled lab setting.

5
6 6) at issue is whether CS treatment of asthma cohorts are protective in controlled lab
7 exposure studies (pg. 6/30), and a helpful ref that has been overlooked would be the
8 report by Holz O, et al, 2005 that was accomplished in healthy subjects (non-asthmatics)
9 and evaluated for protection provided by comparing inhaled and orally administered GC.
10 This is helpful as provides comparison of the GC in a respiratory tract free of
11 inflammation at pre-exposure.

12
13 7) at issue is the description in the text under a toxicology section (pgs. 6/41-6/42) that in
14 referring to rodent models where the provocative exposure concentrations in testing
15 scenarios may be in the 1-3 ppm range, that these “high” dose models are helpful for
16 mechanism for understanding perhaps airway hyperresponsiveness, but have
17 “questionable” relevance for extrapolation to airway responses in humans exposed to
18 ambient levels of ozone. Two issues arise: human subjects undergo increased MV due to
19 exercise during controlled exposures (which in fact may have durations of 50 min per hr
20 over several to 6 h periods of exposure), are required for initiating functional changes.
21 Given that the rodents are not exercised during exposures and thus do not elevate MV,
22 and that is well known that the deposition fraction of ozone in the rodent respiratory is
23 roughly 40-45 % (ref: Wiester MJ et al, 1988) where as in the human, 90-98 %, exposure
24 concentrations of 1-3 ppm in rodent models are highly relevant for translation to human
25 studies.

26
27 8) a topic that seems underserved in the text is the issue over airway neuronal effects that
28 occur during ozone exposure, either ambient or controlled lab settings. Thus text perhaps
29 should be devoted briefly to this area, and include refs from both the clinical and
30 toxicology literature; for example refs dealing with parasympathetic nerves (Beckett WS,
31 et al, 1985), Krishna MT, et al, 1997; Taylor-Clark TE, et al, 2010; Nishiyama H, et al,
32 1998; Graham RN, et al, 2001; Hazbun ME, et al, 1993; Zhou S, Sunday ME, et al, 2010;
33 Evans CM, et al, 2000; Coulson FR, et al, 2003.

34
35 9) with respect to descriptions of ozone exposure and general effects of the immune system
36 (pg. 6/73), the understanding of surface expression on lung macrophages of surface
37 receptors called toll-like receptors (TLRs), which can recognize foreign pathogen-
38 associated molecular patterns (PAMPs), has become a topic of high interest with
39 respect to ozone exposure, alveolar macrophage function, and innate immunity (refs:
40 Kleeberger SR, et al, 2000; Li Z, et al, 2010).

41
42 10) with respect to Fig. 6-19: % increase in respiratory-related hospital admission and ED
43 visits for all yr and seasonal analyses, it might be helpful to separate in the Figure the
44 listings of All subjects, from Senior aged, from children. A significant part of the text has
45 been devoted to acknowledge that children may be more susceptible to ambient ozone,

1 and thus to emphasize this, one would expect the hospital admissions, etc to be higher in
2 this group with respect to a health effect. As well it would seem that there should be
3 available more ref citations than those provided at this point in the text by Steickland
4 (ref. 624878) and Orasso (ref. 202800).

5
6 11) with respect to Summary and Causal Determination, section 6.2.9 (pgs. 6/97 – 6/100) a
7 concerns arises. The text states on 6/98, that “recent controlled human exposure studies
8 found functional response enhanced in subjects with elevated BMI” as such, this is an
9 overstatement, as the suggestion of higher risk to ozone in subjects with high BMI is
10 based, at this point, entirely on retrospective analysis (as correctly stated in the text on
11 pgs. 6/15 – 6/16) and not designed laboratory studies. Although attractive concept, at this
12 time a controlled human lab study is warranted.

13
14 12) with respect to ozone-induced effects on cardiovascular-related proteins, the report by
15 Weinmann GC, et al, 1995, demonstrated that fibrinogen titers were significantly
16 elevated in bronchoalveolar lavage fluids sampled at delayed time point following
17 controlled lab exposure ozone, and should likely be an addition the refs in this section.
18

1 **Dr. Christopher Frey**
2

3 **Charge Question 3: Chapter 2 presents the integrative summary and conclusions from the**
4 **O3 ISA with detailed discussion of evidence in subsequent chapters. Is this a useful and**
5 **effective summary presentation? How does the Panel view the appropriateness of the**
6 **causal determinations?**
7

8 An integrative overview is important and necessary. The integrative review will be read by most
9 persons who read the ISA and will serve as perhaps the sole point of contact between the reader
10 and the ISA. Thus, careful consideration should be given as to the audience. A key shortcoming
11 of this chapter is that each section is written for an expert audience in a narrow domain, and thus
12 for most readers, most sections of the ISA become nearly unreadable.
13

14 Since there are detailed chapters on specific points in other parts of the document, it seems
15 unnecessary to attempt to provide detailed technical information in the summary. A true
16 “integrative overview” should not be highly detailed, but rather should present the key findings
17 from other chapters. This draft misses the mark in attempting to provide detailed information
18 from specific studies, but without proper citation, and inexcusably sending the reader on a wild
19 goose chase for figures and tables in other chapters that are cited but not shown in Chapter 2.
20

21 Chapter 2 needs to be self-contained with respect to including whatever figures or tables are
22 central to the integrative findings. Furthermore, it is not necessary for the figures and tables that
23 could be included in Chapter 2 to be duplicative of figures and tables in other chapters. The
24 figures and tables themselves should also be integrative and provide an overview, rather than
25 details.
26

27 Section 2.1 seems to be of about the right length although I encourage attempts at shortening any
28 and all sections of this chapter. I appreciated an upfront statement of the key point at the
29 beginning of a section, which is not done consistently throughout the chapter. For example, in
30 Section 2.1.1.1, the key point that the photochemical processes are well understood as of the
31 2006 ACQD was helpful in setting the tone for the review given in this brief section.
32

33 Section 2.1.5 and its subsections make a lot of references to specific figures in other chapters,
34 which is frustrating for the reader. If the information in the other figures is important to the
35 integrative summary, then create figures in Chapter 2 that subsume (but not simply copy) the
36 information, and do so in an integrative manner.
37

38 Some sections seem to be data dumps with no particular effort at integrating the results to key
39 findings. For example, Section 2.1.5.1 discusses a few examples of correlations among monitors,
40 but no effort is made to generalize from the evidence regarding findings. For example, under
41 what situations are high correlations expected? Under what situations do low correlations occur
42 (e.g., titration of O₃ near roadways by primary NO?).
43

44 As a matter of style, I dislike having consecutive headers with no introductory or transition text,
45 as is the case in the cascade of Sections 2.2, 2.2.1, and 2.2.1.1. In an integrative summary, there

1 should be some theses statements given in the introductions to a given level of a section before
2 presenting supporting details.

3
4 As an example of reader difficulty in reading this chapter, Section 2.2.1.2 comes across as a bit
5 of a data dump confounded by use of informal jargon that loses the reader. For example, the term
6 “slopes” is undefined. Slope of what versus what? It is also not very clear what the point is of
7 this section. Is the goal here just to list a bunch of results without integrating or synthesized to
8 some key points? Examples of possible findings here would be explaining conditions under
9 which there are strong correlations with other pollutants, and conditions under which there are
10 weak correlations.

11
12 Rather than including a lot of data from multiple studies in long paragraphs, please consider
13 summarizing the studies in tables or graphics and using the text to infer/synthesize key trends or
14 other supportable generalizations. If the data do not support (or falsify) a hypothesis, it is also
15 useful and okay to explain that the data are inconclusive.

16
17 In Section 2.2.3, the term “exposure error” should be defined. Consider the audience. If this is an
18 integrative overview chapter, it will be read by persons of varying expertise, and not all readers
19 will have expertize in all areas.

20
21 The first sentence verges on being a run-on sentence, and is debatable. Ozone cannot possibly
22 have “relatively low spatial variability across an urban area” if it is subject to titration from
23 primary NOx emissions, especially from large roadways. Whether there is variability depends on
24 the spatial resolution over which differences are being evaluated. Given that there is typically a
25 significant population living, working, or going to school near such roadways, there is the
26 potential for significant micro-scale variability.

27
28 I am not a fan of paragraphs that are 30+ lines long. In rewriting this chapter, I recommend that
29 consideration be given, for each section, to what are the key points to be made, with at least one
30 paragraph per key point, and with at least one paragraph that is truly integrative.

31 As the reader gets to pages 2-18 and 2-19, there is a sea of very dense text with few paragraph
32 breaks. What are the key integrative overview points? Details are in the other chapters.
33 Some points are made but then dropped. For example, page 2-22, lines 23-24 raises what seems
34 like a potentially important point of avoidance behavior in response to air quality advisories.
35 However, there is no discussion of the implication of this statement. For example, if this
36 behavior is occurring, then it would tend to reduce the strength of the concentration-response
37 relationships inferred from epidemiological studies not because of absence of health effects, but
38 because the air is so bad that people are avoiding it. This could lead to bias and
39 mischaracterization.

40
41 Some specific comments:

42 Page 2-5, line 7 “condensed” mechanisms is not very clear. “simplified” mechanisms may be
43 better.

44 Page 2-13, line 10: what is the averaging time upon which the correlation of 0.58 is based?

1 Page 2-13, line 39: what is meant by “central –site monitors are representative of day-to-day
2 changes” The more specific finding appears to be that relative changes in central site monitor
3 concentrations are correlated with relative changes in exposure concentrations. This could be
4 made more clear.

5 Page 2-17, line 21: replace “challenged with” with “exposed to”
6

7 **Charge Question 5: Chapter 4 describes human exposures to O3. Is the evidence relating**
8 **human exposure to ambient O3 and errors associated with exposure assessment presented**
9 **clearly, succinctly, and accurately? Are the results of field studies evaluating indoor-**
10 **outdoor and personal-ambient exposure relationships, and factors affecting those**
11 **relationships, presented in a manner that is useful for interpretation of epidemiologic**
12 **results? Is the information on modeling O3 concentration surfaces and population**
13 **exposures appropriate for evaluating the utility of these modeling approaches? Do the**
14 **characterizations of temporal and spatial variability of O3 in urban areas provide support**
15 **for better understanding and interpreting epidemiologic studies discussed later?**
16

17 Overall, this chapter was useful and contained appropriate and relevant material. I especially like
18 Section 4.2 and the clear derivation of the relationship between exposure and ambient
19 concentration.
20

21 In terms of technical issues, perhaps the key point in this chapter is a claim that there is “low
22 spatial variability” in ozone concentrations at an urban scale, and that moderate correlations in
23 ozone exposure and ambient concentration are strong enough, to support a conclusion that
24 central site monitors provide relevant time series data for health effects estimates in
25 epidemiological studies. However, as mentioned in various places in the document, ozone is not
26 spatially homogeneous in urban areas, such as because of titration with NOx near roadways.
27 Furthermore, the temporal correlations are described as “moderate” but are relatively weak (if
28 you plot data that have a 0.58 correlation, for example, the pattern will appear to be fairly
29 random), and only become strong if the averaging time is increased to several days. Given that
30 the current standard is based on 8-hour averaging, the relevance of daily average or four day
31 average correlations is not established. The chapter should more critically address the adequacy
32 of central site monitors for use in epidemiological studies and perhaps be a bit more forthcoming
33 about potential biases that could result from assuming that they are representative of spatial
34 homogeneity and temporal trends.

35 As with Chapter 2, there are some stylistic improvements needed that would enhance readability.
36 For example, there is a paragraph that is 36 lines long starting on page 4-6. Surely, the authors
37 can organize the thoughts better than this, by identifying some key points and writing shorter
38 paragraphs to address each of the key points.
39

40 Section 4.3.3.2 has a horrible introductory sentence that gives the reader very little idea of the
41 points to be made in this section. What follows appears to be a data dump of studies. Here again,
42 organizing the idea into key points, with one paragraph per key point, would help. Putting data
43 into summary table would be easier on the reader. Before diving into details, provide a thesis
44 statement or some indication to the reader of the topic or point to be made.
45

Deliberative Draft Letter to be discussed on July 6, 2011 Teleconference of the CASAC Ozone Review Panel. Do not cite or quote. This draft has not been approved by the chartered CASAC nor does it represent EPA policy. Updated 6-17-11.

- 1 The discussion of micro-environmental models is generally good, and section 4.4.2 appropriately
- 2 identifies that one of the key limitations of these models are related to individual activity data.
- 3 The summary and conclusions section should be rewritten. There should be text between headers
- 4 to introduce the purpose and content of each section and provide appropriate transitions. This
- 5 section should be shorter, avoid repeating points, and more crisply state the key findings and
- 6 conclusions. Thus, there should be less emphasis on summarizing and more emphasis on
- 7 synthesizing.

1 **Dr. Judy Graham**

2
3 **GENERAL COMMENTS NOT SPECIFIC TO A CHARGE**

- 4 1. I am very impressed by this draft. I have several comments, but they do not detract from
5 all the excellent parts and the hard work that went into developing this document.
6 Congratulations to all involved, including scientists, engineers, assessors, managers,
7 editors, and production staff.
- 8 2. HERO is fantastic. I understand that copyright laws inhibit providing full access by
9 everyone. However, some papers are particularly important (e.g., the key references used
10 by OAQPS, the ATS definitions of clinical significance of pulmonary function changes,
11 any unpublished papers used). Please consider the possibility of obtaining copyright
12 permission to make these publically available.
- 13 3. The database for O₃ is extremely large and complex, requiring an unusually high degree
14 of insight to describe and interpret well. I am concerned about whether this draft has had
15 adequate external input and peer review. Eight of 27 authors are external; 1 of 11
16 contributors is external; and 10 of 35 reviewers are external. This should not be
17 interpreted as a criticism of the EPA staff involved. I know many of them and fully
18 recognize that while several of the EPA staff are internationally recognized experts in O₃,
19 most do not have scientific expertise in this area. Thus, external experts play a major role
20 for insuring the quality of the ISA. I also know several of the extramural scientists
21 involved and have great respect for them. The CASAC Ozone Review Panel has a
22 collection of experts, but the magnitude of the database is quite large and, at least for
23 myself, I don't claim knowledge of the details of every key toxicology paper. A broader
24 collection of external experts would offer greater assurance that the original papers have
25 been critically interpreted correctly. This is even more important due to the brevity of the
26 descriptions of many of the papers. As a first step, I recommend listing the authors,
27 contributors, and reviewers according to the chapter they addressed, as was done for the
28 2006 AQCD. It was clear in the 2006 AQCD that the authors, contributors, and
29 reviewers represented an array of world-class experts (EPA and external). As a second
30 step, I recommend using additional external experts to assist in making revisions to the
31 ISA and reviewing the next draft prior to the document being reviewed again by CASAC.
- 32 4. The O₃ database is unique because of the concordance of human clinical, epidemiology,
33 and animal toxicology at ambient or near-ambient exposures. This makes the O₃
34 database especially compelling about health risks, particularly for susceptible
35 subpopulations. This ISA attempts to bring all these study approaches together in the
36 organization and summaries. However, the animal studies are not given sufficient
37 attention to contribute to a fuller understanding of the severity of effects. Each approach
38 has its strengths and weaknesses. Animal toxicology is strong because it is causally
39 linked and can study effects (e.g., lung morphology) not measurable in humans. Its
40 weakness is that extrapolation to humans is required, and this has quantitative limitations.
41 However, these limitations are outweighed by the strengths. I will offer specific
42 comments in the following comments that expand on this point.

43
44 **CHARGE QUESTION 1:** *This first external review draft O₃ ISA is of substantial length and*
45 *reflects the copious amount of research conducted on O₃. EPA has attempted to succinctly*

1 *present and integrate the policy-relevant scientific evidence for the review of the O₃ NAAQS.*
2 *The panel may note that per CASAC consultation on November 13, 2009, considerable*
3 *discussion has focused on older literature. The panel emphasized that important older studies*
4 *should be discussed in detail to reinforce key concepts and conclusions if they are open to*
5 *reinterpretation in light of newer data and where these older studies remain the definitive works*
6 *available in the literature. In considering subsequent charge questions and recognizing an*
7 *overall goal of producing a clear and concise document, are there topics that should be added or*
8 *receive additional discussion? Similarly, are there topics that should be shortened or removed?*
9 *Does the Panel have opinions on how the document can be shortened without eliminating*
10 *important and necessary content?*

11 12 **General Comments**

- 13 1. Any collection of knowledgeable reviewers will have different opinions about what to
14 add or subtract. Thus, there is no “correct” answer to this charge question. At best, we
15 can only offer suggestions.
- 16 2. This charge focuses on length. Length is an important consideration, but not nearly as
17 important as clarity of presentation for the various audiences using the document for
18 various purposes, particularly regulatory purposes. Thus, although there are several
19 opportunities for shortening, they have little value per se. In some specific cases, to be
20 noted later, I will recommend some targeted shortening and lengthening in my comments
21 related to charge questions.
- 22 3. It is *extremely important* to add tables of effects to this ISA. This draft ISA has no
23 human clinical or toxicology tables. There are several very good epi tables/figures, but
24 some of the existing ones only have exposure information, without an indication of the
25 effects. The text is quite complex due to the number of studies. The text often represents
26 a good, but very inadequate, attempt to describe study parameters and outcomes. When
27 the text is complete (e.g., species, strain, sex, age, ppm, exposure pattern, time of
28 examination, parameters, lowest concentration showing effects), the findings and
29 interpretation are obfuscated. A table would permit the text to be more qualitative. Also,
30 when a number of studies with different details and different outcomes are presented, it is
31 extremely difficult to get a handle on the weight of the evidence. Tables would reduce
32 this problem. Having all the studies (old and new) in a table (ranked by exposure rather
33 than by date of publication) enables a shorter integration of the body of work in the text.
34 The human clinical sections of chapter 6 offer an excellent argument for this. There are
35 several dozens of studies at very relevant concentrations with very relevant response
36 measures and effects. There is a lot of information that contributes to susceptibility
37 factors and exposure-dose-response, but it is buried. In some cases, such information is
38 missing (e.g., 6-43 L32ff) due to the overly brief summary of the studies in the 2006
39 AQCD. In many cases, one would need to look at the underlying references to get an
40 understanding. Tables would solve this major problem. Page 6-134ff provides a good
41 example; the one paragraph talks about CNS effects in the older study, without providing
42 any information at all on exposures (except for a concentration regression from one
43 epidemiology study). The epidemiology sections of Chapters 6 and 7 have tables. Some
44 are extremely useful (e.g., the ones showing the outcome and study details). Some
45 should be expanded. For example, Table 6-9 on p6-33 only has study characteristics

1 without indicating results. The results are buried in the text. Making this change would
2 require significant effort. Probably, the easiest approach would be to expand the tables
3 from older AQCDs. If you do this, please be aware that the 2006 AQCD is missing some
4 important studies cited in the 1996 AQCD. Also, after the tables are created, it is
5 important for them to be in reasonable proximity to the text discussion of the papers cited
6 there. For example, the tables should *not* be in a separate document or separate chapter.
7 I appreciate that the authors are under a great deal of pressure to keep the number of
8 pages down. Tables would increase the number of pages. But, they are fundamental to
9 clarity and understanding. Imagine a research paper in which there were no tables or
10 figures of data. The paper would either be very long because the same information was
11 spelled out in the text or the paper would be useless.

- 12 4. Throughout, the old studies (i.e., those presented in previous documents) are summarized,
13 and the new studies are discussed in more detail. The goal of this artificial separation
14 was to keep the length of the document under control, but unfortunately this ISA does it
15 at the expense of understanding the exposure-response effects of O₃. EPA regulations
16 need to be based on key studies, underpinned by supporting evidence. In some cases, the
17 key studies are buried because they are old, and less important studies get space just
18 because they are new. A preferred approach is to include tables of *all* the high quality
19 and relevant studies and use the text to discuss the key studies fully with a shorter
20 discussion of the supporting studies, independent of their year of publication.
- 21 5. One approach is to delete all discussion related to research needs. At present, such
22 discussion is spotty throughout; sometimes saying nothing for major needs, sometimes
23 saying something about minor needs. Such research needs should be a separate effort.

24 25 **Specific Comments**

- 26 1. In my opinion, there is excessive duplication, especially with the summaries. Also, there
27 is excessive duplication between discussions of MOA, effects, and susceptible
28 populations. Some of these overlaps are necessary. None do any real damage. However,
29 the length of the document is affected. Examples and suggested changes follow:
 - 30 a. The purpose of Chapter 2 is not clear. It is well-written, but duplicates
31 subsequent summaries exactly. Because it has an inadequate discussion of
32 exposure-dose-response, no references, tables, or much specificity, it is not useful.
33 Chapter 2 could be deleted because of its exact duplication to chapter summaries
34 or entirely revised.
 - 35 b. In some cases, the attempt at brevity can cause misunderstanding and be a show-
36 stopper to some readers. This typically happens when human studies are
37 described with an concentration but without an indication of whether exercise was
38 involved (e.g., 2-17. L20). Add the exercise statement with an adjective (e.g.,
39 moderate, heavy). In many cases, animal studies are described with no indication
40 of the exposure duration (e.g., 2-26 L8; 2-46 L22). Minimally, the term acute,
41 subchronic, and chronic should be used.
- 42 2. One approach to shortening is to have a major editing effort to catch minor duplications.
43 I won't cite them all here. One such example is on p1-18 in which there is excessive
44 duplication in the area between L3 and L24. Another example is 5-7 L35-38; true, but
45 generic and already said in introductory sections.

- 1 3. One approach to shortening is to focus more on results than the tools (e.g., methods,
2 models) used to obtain the results. Indeed, the tools need to be described, but in some
3 cases (especially chapter 3) the discussion focuses on the tools (models), with very little
4 discussion of the modeling results.
- 5 4. One approach to shortening is to delete the artificial separation between “old” studies of
6 previous documents and the “more recent work”. Actually, my greater concern is that
7 such an artificial separation makes the ISA intellectually “choppy”, hard to understand,
8 and does not provide the full picture of exposure-dose-response. This is a far greater
9 problem than length. In virtually all cases, it is necessary to compare the old with the
10 new, causing reiteration of the basis of comparison. There could be value in identifying
11 those conclusions that are changed or unchanged from the previous document. If
12 unchanged, a sentence or 2 would suffice. If changed, then a more rigorous discussion
13 would be needed. Some examples of problems are:
 - 14 a. 5-6 under “recent publications” discusses older work L34ff. Mudway and Kelly
15 (1998) are in both places.
 - 16 b. 5-14 L26 is in the “old” section, but contains a 2007 study. 5-15 L4 is in the new
17 section but discusses “past studies”
 - 18 c. 5-20 L1-16 (new section) is a study by Tsujino et al, 2005, described in some
19 detail, including the statement on L13 that the model is limited in such a way that
20 I think it has little (or no) value to the conclusions. Thus, some valuable old
21 studies are truncated, but new studies are described in detail, sometimes beyond
22 their value.
 - 23 d. 5-40 is “new” material. However, older studies are included.
- 24 5. Chapter 5 contains BOTH dosimetry and MOA. There is no reason to put them together.
25 The MOA should be integrated with its related concept/item. For example, MOA of
26 interaction of O₃ with ELF would stay in dosimetry, but MOA of inflammation would be
27 in the effects chapters. The MOA section 5.2 has several instances of describing effects,
28 rather than MOA, as well as instances of having to describe the effect which is discussed
29 later (i.e., duplication). In some cases, the effect referenced is not discussed later in the
30 appropriate effect chapter. I recognize that this is very difficult to untangle because some
31 MOAs (e.g., inflammation) are a pathway to several effects. Some examples follow:
 - 32 a. 5-8 L1-2 This is a very important concept, but no details are provided here under
33 dose. The reader is then referred to the MOA section for these details.
 - 34 b. 5-30 L35 ff. Over half a page is devoted to effects of O₃ on sRaw, with emphasis
35 on effects. It’s a stretch to see why this is in the MOA section. Many, but not all,
36 of the references are in Chapter 6, leading to duplication.
- 37 6. When studies are cited in the text, important parameters to the outcome need to be
38 included, either in new tables or the text. For example, the text should always indicate
39 whether the humans were exercising or not, and if so, whether it was light, heavy, etc.
40 (p3-37 L2 and several other places it doesn’t).

41
42 **CHARGE QUESTION 2:** *The framework for causal determination and judging the overall*
43 *weight of evidence is presented in Chapter 1. Is this framework appropriately applied for this O₃*
44 *ISA? How might the application of the framework be improved for O₃ effects?*

1 Specific Comments

- 2 1. 1-10 L6ff. These statements that animal studies are normally very high is generically
3 true for toxicity testing, but NOT for O3. Most of the O3 effects of concern are observed
4 in animals at <0.5 ppm; many are observed <.2ppm. Considering dosimetric differences,
5 these are roughly equivalent to human ambient exposures. The text (L8) goes on to say
6 that “Such studies” (i.e., those are very high concentrations) were considered. Earlier (1-
7 9), the text has a better description of the use of animal studies. The bottom line is that
8 O3 animal studies at environmentally relevant concentrations are fundamental to
9 causation and the range of effects. Thus, I suggest L-7 sentence (“Due to...response) be
10 deleted.
- 11 2. 1-24 L21ff. This whole subsection is “Concepts in evaluating adversity.” This is one of
12 THE most important sections of the document and further explanation would be helpful
13 to users. Specifically, please explain the ATS official statement about adversity, as
14 relevant to O3, in some detail.

15
16 Minor Comments for EPA’s consideration, but not needing discussion at the meeting

- 17 1. 1-15 L22. Consider adding “and ethical constraints”. This change covers the limitations
18 discussed in the immediately following text.
- 19 2. 1-18 ff This section reduces the value of animal toxicology studies, relegating it to
20 insights and MOAs.
- 21 a. L4. Consider making this paragraph more relevant to O3 by adding “the effects
22 of O3 on” before “human physiology” and deleting “putative” on L5.
- 23 b. Add a thought somewhere in this area about being able to detect and describe
24 effects that can’t be measured in humans, such as morphological changes, birth
25 defects, and tumors. This contributes significantly to understanding severity of
26 effects.
- 27 c. L 10-13 The limitations of animal-to-human extrapolation are correctly described,
28 but the strengths of such extrapolation are not even mentioned. For example, a
29 discussion of homology should be included.
- 30 d. L12 and L17. What “hormonal regulation”. Maybe there are new studies I’m
31 not aware of or the ISA has a different definition. It’s easier to just delete it and
32 add “respiratory tract biochemistry”.
- 33 3. 1-23 L38 Add “activity patterns” and “exercise levels” to the list of factors that influence
34 exposure. These are quite important and likely to be more important than some of the
35 others listed.

36
37 **CHARGE QUESTION 3:** *Chapter 2 presents the integrative summary and conclusions from*
38 *the O₃ ISA with detailed discussion of evidence in subsequent chapters. Is this a useful and*
39 *effective summary presentation? How does the Panel view the appropriateness of the causal*
40 *determinations?*

41
42 General Comments

- 43 1. Whether it is useful and effective is dependent on the audience. As mentioned in my
44 response to Charge Question 1, I believe much of this chapter is highly duplicative,

1 doesn't describe exposure-dose-responses, has no research references, and therefore
2 should be deleted or revised significantly.
3

4 Specific Comments (Note: Since much of Chapter 2 is an exact duplication of material in the
5 main chapters, the problems identified below are also relevant to their correlated chapters)

- 6 1. 2-2 L5-7 This language refers strictly to concentration-response but then goes on to
7 include and exposure duration, which is NOT part of concentration and ignores exposure
8 patterns/dose rate. Both concepts need to be clarified. The inclusive language on L5
9 would be to say "exposure-dose-response". The expanded form would define each term
10 and include the concept of delivered dose and exposure pattern/dose rate. Another
11 example of this problem is on 2-34, L22 which starts as C-R, but then adds C-V-D.
- 12 2. 2-16 L24 and many other places. Respiratory tract anatomy and dosimetric regions are
13 not defined consistently. "Deeper" has no scientific meaning. Create a standard
14 terminology and stick to it (RT, URT, NP, LRT, NP, TB, A or P), going into more detail
15 when needed (e.g., PAR).
- 16 3. 2-31 Section 2.5.1 on "potentially susceptible populations". Where is the discussion of
17 exercise and greater exposures (as a function of activity pattern) as factors? It is implied
18 with the statement of "air conditioner use", but these two factors are probably greater
19 susceptibility factors than genetic polymorphisms. Susceptibility of children has less
20 than one line, which is way too little.
- 21 4. 2-29 L29ff This sentence talks about dietary deficiencies. It is too "summarized" and
22 sounds stronger than the data. An additional sentence referring to the database (e.g.
23 deficient and then supplemented).
- 24 5. 2-36 Table 2-3. For airway hyperresponsiveness. Why aren't human studies mentioned
25 for the 2011 ISA. As is, it appears that the newer data refute the older conclusions on this
26 important point.
- 27 6. 2-36 Table 2-3. Symptoms are not discussed in the preceding text of Ch 2.
- 28 7. 2-44 L15 I see no evidence that animal tox and human clinical data support mortality in
29 epi studies. Even the chronic animal studies have no mortality at reasonable
30 concentrations. This is too big a stretch.

31
32 Minor Comments for EPA's consideration, but not needing discussion at the meeting

- 33 1. 2-2 L25. Delete "potential". The effects are real.
- 34 2. 2-16 L16-28. Please add a sentence or two about extrapulmonary effects.
- 35 3. 2-18 L19. Delete "may" and insert "of laboratory animals" before may. There is no
36 doubt about it in animals.

37
38 **CHARGE QUESTION 5:** *Chapter 4 describes human exposures to O₃. Is the evidence relating*
39 *human exposure to ambient O₃ and errors associated with exposure assessment presented*
40 *clearly, succinctly, and accurately? Are the results of field studies evaluating indoor-outdoor*
41 *and personal-ambient exposure relationships, and factors affecting those relationships,*
42 *presented in a manner that is useful for interpretation of epidemiologic results? Is the*
43 *information on modeling O₃ concentration surfaces and population exposures appropriate for*
44 *evaluating the utility of these modeling approaches? Do the characterizations of temporal and*

1 *spatial variability of O₃ in urban areas provide support for better understanding and*
2 *interpreting epidemiologic studies discussed later?*

3
4 Specific Comments

- 5 1. 4-10 L9-10. This cites Anderson and says that “these [referring to previous lines]
6 reaction products may have health effects in addition to, or greater than, those from O₃
7 itself.” Firstly, the Anderson studies used simulated indoor air chemistry of VOCs and
8 studied sensitization potential. They did not use O₃. Thus, this citation does not support
9 this sentence. The significant problem is that use of the words “in addition to or greater
10 than” implies either additivity or synergism or that these compounds have greater
11 potency. The Anderson paper does not support that. It could be changed to say that
12 many of these reaction products have effects themselves, opening the possibility of
13 interactions.
- 14 2. 4-14 L26ff. Why is this section so brief? It should be expanded to give some examples
15 of the results of applying the models. I realize that the OAQPS Exposure Assessment
16 will provide a great deal of such results, but this section could add a few figures or tables.
- 17 3. 4-17 L1-6. Why is this section so brief? The Georgopoulos paper is not discussed in the
18 previous AQCD, so it especially should be expanded here or criticized to provide a
19 rationale for dismissing it.
- 20 4. 4-17 L32 ff. This new exposure model by NERL sounds exciting. It is appropriate to
21 insert this clue at this draft stage if you expect it to be referencable at the time of
22 subsequent ISAs.
- 23 5. 4-16 Figure 4-2. This figure is not needed and could be deleted for brevity.
- 24 6. Please add a figure(s) that shows hourly personal exposure with variability—or
25 something that gives the reader a feel for exposure patterns.

26
27 Minor Comments for EPA’s consideration, but not needing discussion at the meeting

- 28 1. 4-15 L15. Delete the word threshold since this gets confounded with the whole risk
29 concept of threshold
- 30 2. 4-15 L38. Is a publication likely to be available during the draft life of this ISA.? If so
31 keep it.

32
33 **CHARGE QUESTION 6:** *The dosimetry and modes of action of O₃ are discussed in Chapter 5.*
34 *The primary focus of the dosimetry discussion is to highlight factors that might lead to*
35 *differences in dose between individuals and between species. Some potential modes of action that*
36 *may underlie a number of health outcomes and that may contribute to the biological plausibility*
37 *of health effects of short- and long-term exposures are described in detail. Is the review of basic*
38 *dosimetric principles of O₃ uptake presented accurately and in sufficient detail? What are the*
39 *views of the Panel on the approach taken in Chapter 5 to characterize modes of action for O₃-*
40 *related effects?*

41
42 General Comments

- 43 1. This chapter contains BOTH dosimetry and MOA. There is no reason to put them
44 together. In my response to Charge 1, I argue for the MOA being integrated with its
45 related concept/item. For example, MOA of interaction of O₃ with ELF would stay here,

1 but MOA of inflammation would be in the effects chapters. The current organization also
2 leads to excessive duplication (see my response to Charge #1). 5-27 L17ff is another
3 good example. It begins with effects and proceeds to talk about thickness of the ELF and
4 mechanisms of reactions, etc.

5
6 Specific Comments

- 7 1. The Dosimetry section is fundamental to understanding animal-to-human extrapolation
8 and intraindividual susceptibility. However, the figures are inadequate to display the key
9 points, and some key points are not discussed at all or too briefly. For example:
10 a. 5-12 L14ff. This section on interindividual variability is woefully inadequate in
11 its lack of attention to age (only about 2 sentences on 5-13, L29). This would be
12 the place to bring together concepts of preexisting disease states (e.g., asthmatics
13 ELF). For example, having a figure of age-related dosimetry would be more
14 useful than several of the other figures used.
- 15 2. In my view, Section 5.1.4 (5-16) “Species Homology, Sensitivity, and Animal-to-Human
16 Dose Extrapolation”, is one of THE most important sections in the ISA because it:
17 b. provides a scientific plausibility for human effects,
18 c. is fundamental to considering adversity in human studies,
19 d. is crucial to assigning causality,
20 e. and demonstrates a range of effects (e.g., chronic lung morphological changes)
21 that cannot be measured in humans.

22 Thus, I find it unacceptable that this section is only 3 ½ pages long (after I ignore the
23 figure that doesn’t add much). My recommendation is to expand it significantly;
24 independent of what year the pertinent research was published.

- 25 3. 5-1 L1ff The difference between concentration, exposure, and dose should be carefully
26 defined here, given the propensity of some to use them interchangeably. For example, in
27 L6 one definition of dose is actually concentration and this is not correct. Consider using
28 Zartarian, Bahadori, and McKone, JESEE, 2005:15, 1-5
29 <http://www.nature.com/jes/journal/v15/n1/abs/7500411a.html> . This paper is a summary
30 of a WHO effort that was also adopted by the International Society of Exposure Science
31 to standardize exposure terminology.
- 32 4. 5-1 whole page and throughout: Respiratory tract anatomy and dosimetric regions are
33 not defined consistently. “Deep” has no scientific meaning (e.g., L17). What are (5-11
34 L4) upper, central, and lower airways? Create a standard terminology and stick to it (RT,
35 URT, NP, LRT, NP, TB, A or P), going into more detail when needed (e.g., PAR). Fig 5-
36 1 on 5-3 could be modified to be clear on this. The current figure doesn’t add much.
37 Technically informed people already know it. Non-technical people would probably be
38 better off with an understanding of the total RT. For example, 5-10 has a header saying
39 “pulmonary O₃ uptake and dose”. Later “lungs” are referred to. Pulmonary is alveolar.
40 Lungs are LRT. This language must be more precise because some dosimetry studies
41 included the URT and some didn’t.
- 42 5. 5-13 L8ff. This says “Variability in local dose may be attributed to ...physiology”. This
43 is incomplete—variability is also significantly dependent on anatomy and biochemistry
44 of the epithelial lining layer.

- 1 6. 5-16 L5. Greater care has to be taken with citing effect studies. For example, Emmons
2 and Foster, 1991 is not cited in Chapter 6, but Frampton et al 1997 is.
- 3 7. 5-16 L17. This summary section talks about “major sources of variability in absorption
4 of O3.” However, the list does not mention surface area, which is an important concept
5 for deposition in children.
- 6 8. 5-17 L10-12. It is essential to add a reference here. Do you mean Gong et al. 1998? If
7 so, it was at 0.3ppm. The sentence seems odd since humans can’t really be exposed to
8 “very high” levels.
- 9 9. 5-19 Figure 5-5 adds nothing. It would be helpful to use a figure of exposure-responses,
10 comparing different species (including humans)---in Chapter 6.
- 11 10. 5-21 ff The MOA section 5.2 is VERY uneven in presentation of exposure characteristics
12 (i.e., male or female, animal species; concentrations, exposure patterns/durations).
13 Having all information for each study in the text would be far too distracting. Thus, there
14 should be a table with all the information and then a summary in the text (species and
15 qualitative description of exposure duration; adding details like sex when the study made
16 such comparisons).
- 17 11. 5-29 L6ff Please add comments on systemic possibilities. For example, consider adding
18 “and perhaps systemically” to the end of the sentence on L10.
- 19 12. 5-22 L3 ff. This is a discussion of attenuation, but why is it under Section 5.2.3
20 “Activation of Neural Reflexes”. Then p 5-38 L24 (under Section 5.2.4 (injury and
21 inflammation) goes on to discuss attenuation. These are other examples of the
22 confounding of effects and MOA. The major story of attenuation is that it occurs for
23 some effects, but not for others, may even contribute to effects, and is not long-lived. The
24 MOA is interesting and contributes to understanding, but is not THE story. Thus, it
25 belongs in Chapter 6. Virtually every section has similar examples, but I will not recount
26 them all here. Moving all the MOA (except that part dealing with dosimetry) to the
27 sections on effects will solve these problems.
- 28 13. 5-39 L1 ff regarding attenuation has some problems.
 - 29 a. The Tepper et al 1989 paper is cited. The next sentence says: “Thus, the
30 inflammatory response resembled that of the ...function...which was attenuated.”
31 The “thus” is not correct. Tepper reported that inflammation was NOT
32 attenuated. The abstract of his paper says “Acute ozone (O3) exposure in humans
33 produces changes in pulmonary function that attenuate with repeated exposure.
34 This phenomenon, termed adaptation, has been produced in unanesthetized rats.
35 Rats exposed to O3 (0, 0.35, 0.5, or 1.0 ppm) for 2.25 h for 5 consecutive days
36 showed an increased frequency of breathing and a decreased tidal volume on
37 Days 1 and 2 of exposure at all O3 concentrations. However, by Day 5 these
38 breathing responses to O3 were diminished in rats exposed to 0.35 and 0.5 ppm,
39 but not in rats exposed to 1.0 ppm. In addition, a flow limitation in smaller
40 airways was observed after the second day of exposure to 0.5 ppm O3 that
41 initially attenuated and then disappeared by the fifth day of exposure. In contrast
42 to these findings, a light microscopic examination of fixed lung tissue sections
43 from rats exposed to 0.5 ppm indicated a 5-day progressive pattern of epithelial
44 damage and inflammation in the terminal bronchiolar region. A sustained 37%
45 increase in lavageable protein was also observed over the course of the 5-day

1 exposure regimen to 0.5 ppm. Lung glutathione increased initially, but it was
2 within the control range on Days 4 and 5. Lung ascorbate was significantly
3 elevated above control levels on Days 3 and 5. These data suggest that attenuation
4 of the pulmonary function response to O₃ occurs in laboratory rats with repeated
5 exposure while biochemical and morphologic aspects of the tissue response
6 continue to progress.”

7 b. The text goes on to say what Christian et al, Hackney et al, and Horvath et al
8 found. Please recheck the accuracy of these summaries. I did NOT go back and
9 read the papers, but I think that the Christian et al one was quoted correctly. But
10 the Horvath and Hackney ones may not have been.

11 14. 5-43 L3-30. This is a good story. However, how does it relate to humans? Is there
12 homology? Please be explicit.

13 15. 5-24 L14ff. This asthma MOA story has a lot of references, some of which are NOT in
14 chapter 8 (I didn't check them all, but an example is Kreit et al 1989). *All* the effect
15 studies need to be in the effect chapters. If you retain the MOA story here in chapter 5,
16 so be it, but make sure the effect chapters are complete.

17 16. 5-57 L35 ff. This section on preexisting diseases doesn't discuss MOA. It discussed
18 sensitive subpopulations. It appears to be stretching for antioxidants, but it just doesn't
19 belong here.

20 17. 5-58 L27 ff. This section on lifestage is predominantly effects.

21 18. 5-60 L17ff. Adaptation is raised AGAIN in this chapter. The result is very disjointed.

22 19. 5-61 L1ff. This one-paragraph section on co-exposures doesn't belong here.

23 20. 5-62 Figure 5-6 This figure has some good and some questionable elements. A
24 schematic is often useful, but this one is not. Acute and chronic mechanisms can differ,
25 but this schematic says nothing about the exposure duration. This schematic has solid
26 and dotted lines to indicate “greater certainty” vs. “emerging interest”. The decreased
27 pathogen clearance leading to impaired host defense was part of the very first O₃ CD
28 (circa 1970), but here it is indicated as “emerging”. Inflammation and injury has a solid
29 line to immune system modulation. What is immune system modulation (parts would be
30 solid, but parts would be dotted). Also, why is it yellow. Also, one of the most important
31 effects is injury (remodeling), which is therefore deserving of its own box.

32 21. 5-62 L3ff. Delete “Gaps in Knowledge”. Research needs either need to be included
33 everywhere as appropriate or nowhere.

34
35 *Minor Comments for EPA's consideration, but not needing discussion at the meeting*

36 1. 5-2 L6. Do you really want to say adverse here and not lots of other places?

37 2. 5-19 L2. What is “overtly”?

38 3. 5-24 L5 The Long et al study is at odds with other studies. Why? Were methods
39 different? Or is it the species and higher concentration?

40 4. 5-28 L31ff. This is a summary paragraph that belongs on the next page under 5.2.2.1.

41 5. 5-76 Tepper et al 1989 is one of the most important papers in understanding the impact of
42 attenuation on health risk. HERO has the citation, but not the abstract or paper. The
43 abstract is available

44 <http://www.ncbi.nlm.nih.gov/pubmed?term=tepper%2C%20js%201989>

- 1 6. The structure of the MOA section is uneven within itself and compared to other sections.
2 Specifically, many subsections start with the “old” material, without such a label, and
3 then have a label for “new”.

4
5
6 **CHARGE QUESTION 7:** *Chapter 6 is intended to support the evaluation of human health*
7 *effects evidence for short-term exposures to O₃. To what extent are the discussion and*
8 *integration of evidence on the health effects of O₃ from the animal toxicological, controlled*
9 *human exposure, and epidemiologic studies, technically sound, appropriately balanced, and*
10 *clearly communicated? Does the integration of health evidence focus on the most policy-*
11 *relevant studies or health findings? What are the views of the panel regarding the balance of*
12 *emphasis placed on evidence from previous and recent epidemiologic studies in deriving the*
13 *causal determination for short-term O₃ exposure and respiratory effects (in particular,*
14 *additional epidemiologic evidence for lung function and respiratory symptoms and new evidence*
15 *for biological indicators of airway inflammation and oxidative stress that previously has been*
16 *largely limited to human controlled exposure and toxicological studies)? The majority of new*
17 *studies that examine the association between short-term O₃ exposure and mortality focus on*
18 *specific issues that have been previously identified. Does the structure of the chapter adequately*
19 *highlight the breadth of studies (both older and new) that indicate an association between O₃*
20 *exposure and mortality and provide the underlying rationale for the causal determination? Are*
21 *the data properly presented regarding the credibility of newly reported findings being*
22 *attributable to O₃ acting alone or in combination with other co-pollutants and regarding the*
23 *extent that toxicological study findings lend support to the biological plausibility of reported*
24 *epidemiologic associations in reaching a causal determination? Are the tables and figures*
25 *presented in Chapter 6 appropriate, adequate and effective in advancing the interpretation of*
26 *these health studies?*

27
28 General Comments

- 29 1. I only skimmed the epidemiology sections so my comments do *not* include them, except
30 as noted.
31 2. The causation statements are very well supported scientifically. Many have been well
32 established for many years. This answer leads to the key questions (focusing on
33 susceptible subpopulations) that require more attention, namely, what exposures are
34 sufficient to cause the effects of interest and what is the severity of the effects at these
35 effective exposures. I can find some answers to these questions interspersed in the text,
36 but clarity on these issues would be very helpful. I recognize that adversity has policy
37 implications vis-à-vis the CAA requirements. I am requesting a more extensive
38 discussion of clinical interpretation of the effects in the human clinical studies. The epi
39 studies are a bit easier to interpret (e.g., going to the ED or getting admitted to hospital is
40 a relatively clear estimation of the severity/impact of exposures).
41 3. Some important human studies cited in Chapter 5 (e.g., Bates et al, 2009 and Emmons
42 and Foster 1991 deal with smokers) are not cited here, but Frampton et al 1997, also on
43 smokers, is in Chapter 5 and 6. Why? I suspect it is due to the confounding of MOA in
44 too many places. I recommend comparing all the Chapter 5 MOA literature citations to
45 the citations in Chapters 6 and 7 and asking if some papers have not been fully used. The

1 optimal approach, as mentioned above, is to move all the Chapter 5 MOA to the relevant
2 effect chapters/sections.

- 3 4. With rare exception (some of the epi tables, e.g., Fig 6-3 supplemented with table 6-2)
4 the tables are wholly inadequate, the reason being that there are no tables for clinical and
5 toxicological studies. My comments in response to Charge Question 1 go into more
6 detail on this. But, here are a few examples out of many:
- 7 a. 6-7 L7. The Schelenge et al studies are quite important, but there is no indication
8 of whether exercise was used and if so, at what level.
 - 9 b. 6-18 Table 6-1 sets forth key attributes of several epi studies but, at least to me, is
10 deficient without another column of effects. This problem exists throughout.
 - 11 c. 6-43 L32 ff summarizes the 2006 AQCD material on human clinical studies on
12 pulmonary inflammation. A number of studies are referenced, with no indication
13 of C, D, or V.
- 14 5. The artificial separation between old and new studies and MOA and effects leads to a
15 choppy presentation and weak integration. My comments in response to Charge
16 Question 1 go into more detail on this. The problem is especially troublesome in the case
17 of human clinical and epi studies since they will form the predominant bases of the
18 NAAQS. It is important to understand the *whole* scientifically valid database which has
19 dependencies on C, D, and V. So giving details on new studies and just sweeping all the
20 older ones into a few sentences doesn't allow the needed integration.
- 21 6. The animal toxicological studies on respiratory morphological/morphometric changes are
22 not adequately discussed. When they are mentioned, the discussion is buried, too brief,
23 does not allude to supporting evidence, and does not discuss implications to severity of
24 effects in humans. There are dozens of references to effects below 0.5ppm, down to 0.15
25 and 0.2 in non-human primates that are not included. The result of this problem is that
26 the story of structural changes does not come through. It is correlated with inflammation
27 and (at higher levels) with functional changes. Such structural changes cannot be
28 measured in humans, but are very likely to occur, *if* exposures are sufficient. Such
29 information contributes to understanding of severity. Therefore, it is essential to add this
30 information. Most of these studies are older, so the easiest approach might be to identify
31 morphological studies discussed in the 1996 and 2006 AQCD that are not included here,
32 add the details to a table, and create a 2-3 paragraph discussion of the findings and their
33 implications to humans.

34
35 Specific Comments

- 36 1. (This comment is a duplicate to that under the next Charge question on Chapter 7.) There
37 is some confounding between Chapters 6 and 7 with regard to whether the studies were
38 short- or long-term. For example, some 90-day studies were in both places. Prenatal
39 exposure studies are in both places. The beginning text of each chapter should define the
40 duration term. In some cases, duplicate discussion may be of value, but this could be part
41 of the discussion (e.g., time trend for respiratory tract morphometric changes). The
42 whole of the literature on neonatal exposures should be in one chapter or the other.
- 43 2. 6-2 L6 Insert "non-asthmatic" before children (the original language conflicts with L35)
- 44 3. There are a number of problems with inconsistent use of terms. This leads to confusion.
45 Examples follow:

- 1 a. 6-2 L11. This is the beginning of a repetitive use of the terms tolerance,
2 adaptation, and attenuation as synonyms. The terminology is quite important
3 because full understanding is essential to interpreting the severity of repeated
4 exposures. One problem is that for O₃, the term tolerance has been used
5 historically to represent repeated low concentration exposures of animals that
6 protect against subsequent exposure to very high levels of O₃ or other selected air
7 pollutants. To avoid confusion, it is best to not use it. The use of the terms
8 adaptation and attenuation has some precise differences and has been contentious,
9 given the implications of the terms. It would be best to define them, and then use
10 these definitions consistently.
- 11 b. 6-6 L1 ff The terms square-wave and constant are used interchangeably. Also
12 this area uses the word dose to mean CxDxV. Other areas are more careful about
13 this. Continuing down, L22, the word “average” triangular exposure is used.
14 What is the definition of average? Is it CxD or CxDxV? Also address this issue to
15 Figure 6-2 on p6-10.
- 16 c. The term adverse or adversity is used in a few places (e.g., 6-138 L15). This
17 results in two problems: (1) If it is used in one place but not other places, it
18 implies that these other places are not adverse and we can ignore them; and (2)
19 adverse has not been defined here and in any case, isn’t it reserved to a policy
20 determination?
- 21 4. 6-2 L12. Add a new sentence to express the concept that attenuation does NOT occur for
22 other types of effects. This is important because the current text incorrectly implies that
23 successive exposures are no problem. Also, discuss the possibility that attenuation
24 contributes to the persistent changes by “allowing” more O₃ to penetrate and deposit to
25 sensitive lung areas (e.g. PAR when rapid-shallow breathing switches back towards
26 normal).
- 27 5. 6-2 L25. Consider changing “unknown” to “still speculative”. There are some
28 suggestions, so unknown is not proper. Also, what about the concept that repeated
29 respiratory infections might contribute to COPD?
- 30 6. 6-3 L22. This defines “O₃ induced” as “effects that have been corrected for...filtered air
31 exposures.” This is a significant problem because throughout the subsequent text, effects
32 and O₃-induced are both used. Thus, the L22 statement implies that when “effects” is
33 used, it has not been corrected. Also, why present any study results as “uncorrected for
34 FA responses” (6-98 L5)? Without FA controls, the results are very difficult to interpret
35 and use.
- 36 7. 6-4 L1. Add the concept that a shift to oronasal affects the pattern of deposition of O₃
37 dose, which could be quite important. The current text implies that the only difference is
38 a decrease in URT scrubbing.
- 39 8. 6-7 L18. This discussion of the Schelegle et al 2009 study is quite important because it
40 goes down to 60 ppb, at which no statistically significant group effects were observed.
41 Question: did EPA evaluate the quality of the statistics on this paper? Did the study have
42 adequate power to detect effects. What exercise levels were involved.
- 43 9. 6-7 L30ff. This paragraph, going over to the next page, is a summary of the relationship
44 between concentration and FEV₁, considering all the human clinical studies. It needs
45 further exploration. For example, since the importance of CxDxV is well established in

- 1 acute human clinical FEV1 studies, was there a difference in V or CxDxV in the studies
- 2 described? Perhaps the CxDxV differences were responsible for the lack of statistical
- 3 significance of the Schelengle study.
- 4 10. 6-5 Figure 6-1 is helpful. More such figures would be helpful. Look back at the 2006
- 5 AQCD for suggestions.
- 6 11. 6-10 L10 This defines “clinically meaningful” changes of FEV1, citing ATS 1991. The
- 7 public version of HERO does not have this paper. The reference in Chapter 1 also refers
- 8 to ATS definitions of meaningful, but cite 1985 and 2000 documents (also not in the
- 9 publically available HERO). This is quite important, so it is necessary to go deeper into
- 10 the discussion of clinically meaningful, preferably in summary sections.
- 11 12. 6-10 L14 This says that the data from these 2 studies are unavailable. The reason for the
- 12 Adams 1998 data unavailability was provided earlier. The reason for the Schelengle et al
- 13 2009 being unavailable to EPA should be stated also. Apparently, the OMB A110 rules
- 14 are not applicable, but what about the implications relative to the Information Quality
- 15 Act? If these studies are used as a basis of the NAAQS, they need to be publically
- 16 available and preferably peer-reviewed. If desired, there is precedence for having a
- 17 group of experts peer-review such studies.
- 18 13. 6-11 L17. An adjective is needed before “effects”. Consider “spirometric”.
- 19 14. 6-13 L19-20 The term “increased risk” is used. Explain why decreased symptoms in
- 20 these groups would lead to increased risk, especially considering the decreased effects of
- 21 O3 on the elderly. I can see why a lack/decrease in symptoms in children would result in
- 22 them not avoiding exposures that would lead to functional deficits.
- 23 15. 6-15 L2ff. This paragraph should be balanced with a discussion of the improvements
- 24 happening in people/animals that were dietary deficient originally.
- 25 16. 6-16 L7ff. Add Tepper et al 1989 to the end of the discussion since it is more definitive
- 26 of persistence of effects.
- 27 17. 6-39 L1-2. This one sentence is totally insufficient to describe the older literature. The
- 28 acute pulmonary function literature in animals is not especially important, but it adds
- 29 background to the human clinical studies. Referring to a table would suffice.
- 30 18. 6-40 L4 ff. This new study (Cremillieux et al 2008) is intriguing because of the types of
- 31 measurements (imaging); the intermittent vs. continuous exposure; and the finding of an
- 32 obstructive pattern of effects (rather than the expected restrictive pattern). I did not read
- 33 the full paper. Comparing the ISA text to the available abstract raised questions. The
- 34 abstract says no change in inspiratory capacity, but the ISA text says no effect on lung
- 35 capacity. Also, the ISA says that the effects of intermittent exposure were “more
- 36 prevalent and severe.” From the abstract, they were more prevalent, but the abstract
- 37 doesn’t mention severity. The abstract also doesn’t say whether the difference in
- 38 prevalence was statistically significant. Because all these differences from the abstract
- 39 and the relatively unique findings could be important the full text of the paper should be
- 40 rechecked with an expert in animal lung function and structure after O3 exposure and the
- 41 ISA text should be expanded a bit.
- 42 19. 6-41 L27ff. This section references the Depuydt et al. (1999) study. I checked the
- 43 abstract and it says that the exposure was for 4 hours so this should be added to the text.
- 44 I also checked the 2006 AQCD to see if it had more, but this study was only briefly cited
- 45 in the tables and even more briefly in the CD text. I strongly recommend that this study

- 1 be fully evaluated by an expert in such toxicology studies. I must question observing
2 such at effect at 0.05ppm for 4 hours. It is out of sync with other studies on this topic. If
3 it is a scientifically sound finding, the discussion needs to be significantly expanded. If
4 not, an appropriate critique should be added or the paper not used.
- 5 20. 6-42 L30ff. This discussion of adaptation needs a reevaluation.
- 6 a. L32 says “some adverse effects caused by acute exposure are absent after
7 repeated...” Do you really want to use the word “adverse”. Also, it is true, but
8 the story here is misleading because it does not go on to say that other effects
9 don’t adapt.
- 10 b. The whole paragraph is a rehashing of what is in the previous 2 pages and doesn’t
11 add anything.
- 12 c. The last sentence on this paragraph (6-43 L3) should be deleted because it is
13 wrong (and adds nothing). The interest in pursuing intermittent exposure
14 protocols dates back to UC Davis studies in the 1980’s. It’s important to give due
15 credit to the pioneers.
- 16 21. 6-43 Section on humans and inflammation. The Corradi et al 2002 study (0.1ppm for 2
17 hr causes increases in breath markers of inflammation) is cited in MOA, but why not here
18 also?
- 19 22. 6-43 L9. Reconsider the word “persist”. The time course of inflammation is very
20 complex during and after acute exposure, as is discussed on the next page. Persist
21 implies a steady state. Consider saying “is still observed for at least...”
- 22 23. 6-43 L32ff onto next page. This is a *very* unsatisfactory summary of the older literature
23 on human clinical studies of inflammation. It has no details at all. A new study has
24 details, with no ability to determine how it integrates with the older studies. Furthermore,
25 6-44 L4-5 emphasis is placed on the fact that inflammation responses “not elicit
26 significant spirometric responses.” First, it is correct to say that they were not *associated*
27 with spirometric changes. Elicit has a causation element. In any case, inflammation is
28 important in its own right (e.g., roles in host defense, pathogenesis), even in the absence
29 of spirometric changes.
- 30 24. 6-44 L7ff This discusses the time course of inflammation in humans. Consider using
31 figure 6-4 in the 2006 AQCD.
- 32 25. 6-56 L31. This quotes a study at 0.01 ppm. Please recheck the reference. The abstract
33 says 100ppb, which would be 0.1ppm. The EPA portal-HERO does not have the full text
34 of this paper.
- 35 26. 6-57 L3. The Vancza study is cited. The discussion should be expanded to include more
36 about the influence of age and sex. It is noteworthy that the researchers measured dose as
37 O18, allowing a better evaluation of dose differences in the groups. The age story is
38 complex, but important given the methods used.
- 39 27. 6-59 Section 6.2.4 This is the section on respiratory symptoms and medication use, but it
40 is only epi. Symptom responses in human clinical studies should be cross-referenced.
- 41 28. 6-71 L27ff. This emphasizes physical removal. The concept of bactericidal activity of
42 AMs needs to be incorporated here in the introduction (briefly since it occurs again on
43 the next page under AMs).
- 44 29. 6-72 Section 6.2.5.2 on AMs Bactericidal activity needs to be mentioned as one of the
45 primary functions.

- 1 30. 6-72 L2ff This area is a good example of excess detail on new studies and the difficulty
2 of summarizing old studies in such as way as to provide the range of effects. The
3 Weissbecker work cited on L24 should be deleted since it was in vitro with no
4 knowledge of comparable in vivo dose (in vivo, high concentrations are required to affect
5 viability). This work was not cited in the previous 2 documents, perhaps for that reason.
6 Other studies of value described in the 2006 AQCD (e.g., Bhalla 1996 on chemotaxis and
7 Cohen et al, 2001 and 2002, on superoxide anion production) were not included here.
8 The Cohen work could be correlated with the Hurst studies. The Dohm et al 2005 should
9 be deleted since it is on marine toads and extrapolation from rats and mice is difficult
10 enough. The Klestadt et al, 2005 should be deleted since it is an in vitro study with
11 unknown in vivo correlations and other in vivo studies on chemotaxis could be added
12 (e.g., Bhalla). The Mikerov et al. 2008 work should be examined further with a view
13 towards deletion because of the high in vitro exposure of surfactant proteins. It needs to
14 be tied in or deleted. Minimally, it should be described further. The Devlin et al 1991
15 study on AM phagocytosis should be expanded because it is in humans (and got fewer
16 lines of discussion than the toads).
- 17 31. 6-73 L29ff. This says “A relatively large body of evidence shows that O₃ increases
18 susceptibility to bacterial infections. The text then proceeds to summarize this large body
19 in 4 sentences, with no references, except for a “new” study at 2ppm. This is totally
20 inappropriate. As said on 9-74 L1 (with no reference), the lowest observed effect was at
21 0.08ppm. This is deserving of more discussion, references (Coffin et al 1967 and Miller
22 at al, 1978; see 1996AQCD for full reference), and a correct summary the increase in
23 mortality is in streptococcal-induced mortality, not just mortality. This is an egregious
24 example of ignoring the earlier work. For example, the Coffin et al was the basis for the
25 very first O₃ NAAQS (as O_x) and remains one of the lowest effective concentrations of
26 O₃.
- 27 32. 6-74 L3ff. For brevity, delete the work at 2ppm; it adds nothing.
- 28 33. 6-98 L6. This says “uncorrected for FA response.” This whole issue of uncorrected
29 needs to be more carefully presented. For example, 6-5 L3 (Adams 2006) does not
30 mention uncorrected, but 6-9 L20 (Adams 2006) does mention uncorrected. Also, one is
31 tempted to ignore research without appropriate controls. However, the discussion on 6-9
32 L23 makes comparisons showing that the uncorrected data are likely to be more
33 conservative. Throughout, every time uncorrected data are discussed, they should be
34 placed in context of whether they tend towards being more or less protective conclusions.
- 35 34. 6-100 L3. It says “continuum,” which is commonly defined as some kind of progression,
36 with A leading to B and B leading to C. However, he list of effects is not necessarily
37 progressive. Indeed, they are all observed (in multiple studies), but some are no
38 connected, as in lung function decrements and inflammation. Thus, delete “potential
39 continuum” and insert “understanding” or something like it.
- 40 35. 6-101 L4 This says O₃ is not transported “to extrapulmonary sites to any significant
41 degree.” This is at odds with Chapter 5 which basically says that O₃ doesn’t get beyond
42 the epithelium and may not even get to the epithelium. Thus, this section in Chapter 6
43 needs to be revised to be consistent.
- 44 36. 6-101 L24. The Fakhri et al 2009 study is discussed. This discussion should be revisited.
45 The text implies an antagonism between O₃ and CAPs and does not discuss the overall

- 1 HRV. The paper says: “The primary analysis, change in HRV indices between the start
2 and end of the 2-hr exposure period, yielded no consistent differences between the
3 exposure categories (Table 2). HF HRV showed a statistically significant increase for the
4 CAPs-only exposure ($p = 0.046$) and a similar trend for O₃ exposure ($p = 0.051$) when
5 compared with filtered air...However, when analyzing the CAPs mass concentration
6 relationship for exposures with O₃ (i.e., CAPs + O₃ and O₃ alone), there was a suggestion
7 of negative dose–response slopes (Table 3) between CAPs mass concentration and
8 several HRV indices.” In addition, they evaluated the asthmatics in their study, but this is
9 not mentioned in the ISA.
- 10 37. 6-102 Table 6-23 does not have Dockery et al 2005. Why not? In any case, the table is
11 not helpful since it doesn’t have results.
- 12 38. 6-128 L24 This sentence refers to CVS changes in humans “at very high O₃
13 exposures”... so caution must be used in interpreting animal studies “(Section 6.3.1)”. I
14 couldn’t find these studies here or in the 2006 AQCD. Even without knowing what
15 papers are being referred to, it’s fairly safe to assume that many of the animal studies
16 were at a higher concentration than the human studies. Not knowing of these human
17 studies, I am reluctant to agree with the conclusion offered in the text.
- 18 39. 6-128 L28. The Bloch et al dog studies are mentioned. This is an unpublished report and
19 in not contained in the publically available HERO. I know they were careful researchers
20 and perhaps some of the data are contained in other published reports with Trent Lewis as
21 the senior author. Thus, something needs to be done in keeping with the goal of only
22 using peer-reviewed studies. Perhaps the EPA report was peer-reviewed or could be
23 given to a panel of experts for peer-review.
- 24 40. 6-129 L1. This says “high concentration O₃...”, without providing the concentration.
25 Thus, this paper is, for all practical purposes, useless. Again, a table is needed.
- 26 41. 6-133 L18 says increase HR and L19 says bradycardia. L19 and 20 say it is “uncertain if
27 this effect is also observed in humans.” Please be more precise in the animal study
28 statements and the comparison to humans, especially.
- 29 42. 6-134 L29ff. This paragraph summarizing the 2006 AQCD on CNS is totally
30 insufficient. It talks about epi effects with no significant details, calling it “adverse”.
31 The rodent studies are described in 2 sentences with no indication of what the species, O₃
32 concentration, exposure duration, or specific endpoints were. Thus, there is no way to
33 compare them to the new studies to better understand the weight of the evidence. The
34 2006 AQCD refers to studies showing effects at 0.12ppm in animals, further indicating
35 the need for fuller presentation. This area is an excellent example of the need for tables.
36 As additional examples, all the Tepper et al (1982, 1983, 1985) papers should be
37 discussed because they found effects of 6-hr exposures to 0.12ppm in rats and 0.2ppm in
38 mice on running wheel behavior. The Tepper (and a few other) behavioral references can
39 be found in the 1996 AQCD (not in the 2006 AQCD). The discussion in the 1996
40 document discusses a potential MOA of avoidance of irritation, etc., without direct
41 effects on the CNS per se. Thus, this issue needs to be explored further.
- 42 43. 6-135 L32ff. This section discusses potential relationships between relevant O₃ exposure
43 of rats and Alzheimer’s. Thus, it is very important to discuss fully and precisely. This
44 section should therefore be revisited. Why are these studies “consistent with Alzheimer’s

- 1 incidence in the elderly”. Incidence is a frequency of new cases. There are still
2 significant questions beyond this word choice.
- 3 44. 6-137 L1ff. This paragraph discusses CNS effects on offspring of rodent’s exposure
4 during pregnancy. There is no discussion of the scientific issue of exposure, vis-à-vis
5 windows of susceptibility. One of the studies discussed here did not indicate when the
6 exposure was delivered. Also, the word “adverse” is used several times in this
7 paragraph.
- 8 45. 6-137 L13 and 6-138 L12. Both places say that “levels as low as 0.3 ppm” had CNS
9 effects in utero. The paper indicates that lower concentrations were not tested.
10 Therefore, there is no basis for the phrasing. For example, if they had tested 0.2ppm,
11 there might have been effects. Thus, just state the effective concentration used.
- 12 46. 6-138 L15. I agree with the conclusion “suggestive of a causal relationship”. However, I
13 am concerned about the use of “adverse” as an adjective for effects. What is adverse? Is
14 there some reference about clinical significance of these changes in rodents that could be
15 cited?
- 16 47. All the extrapulmonary sections need to be revisited for concordance of discussion of
17 MOA regarding extrapulmonary mediators. I don’t disagree with any particular sentence.
18 The problem is the differences in presentation throughout.

19

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

- 21 1. 6-6 L32. Adams 2006 is the reference, but there are 2, necessitating an a and b.
- 22 2. 6-8 L6 Please untangle the Kim et al study since it was statistically significant.
- 23 3. 6-8 L31 The McDonnell ref has a typo.
- 24 4. 6-12 L25 So far, this is the first time I noticed “in this well designed study...” Do you
25 really want to say that. What about all the others—were they not “well designed”.
- 26 5. 6-14 L34. There is nothing “pseudo” about it.
- 27 6. 6-15 L32. It says “better”, implying that the others were poor in some way.
- 28 7. 6-40 L4. The discussion of Farraj belongs under section 6.2.2.2 unless only the non-
29 sensitized animal are discussed here.
- 30 8. 6-40 L6-7. This last sentence should be deleted. It is true, but bears no relationship to
31 the preceding material.
- 32 9. 6-42 L5. This says, “Thus, recent ...monkeys, guinea pigs, and mice...” However the
33 preceding discussion of the recent studies does not mention monkeys.
- 34 10. 6-43 L6. Insert “increased” before “epithelial”
- 35 11. 6-58 L8. This is the only place I recall seeing in which the FA concentration (0.02) was
36 reported. Either do it for all or none, except if it was a key factor in the study itself.
- 37 12. 6-71 L15. Just say 0.2 and higher. Saying 1.0ppm is OK if you are sure there are no
38 studies at higher concentrations.
- 39 13. 6-73 L6 call 90 days subchronic.
- 40 14. 6-128 L15 Consider deleting “and other photochemical oxidants” because they are not
41 discussed here.
- 42 15. 6-133 L27 This summary says “leading to the reported cardiovascular pathologies.”
43 Pathologies is a very strong word; far too strong for this database in animals. Thus
44 change to “effects.”
- 45 16. 6-135 L30 specify that the increase in glutathione was in the brain.

1 17. 6-136 L24. Unless you calculated dose, change to concentration-dependent.

2 18. 6-138 L18 Insert “drug-induced” before sleeping time.

3
4 **CHARGE QUESTION 8:** *Chapter 7 presents important new findings from studies published*
5 *since the 2006 O₃ AQCD including studies that examine the relationship between long-term O₃*
6 *exposure and new onset asthma in children, first childhood asthma hospital admissions,*
7 *increased asthma severity, bronchitic symptoms and respiratory-related school absences. These*
8 *studies provide evidence in this regard based on different genetic variants. What are the views of*
9 *the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency,*
10 *coherence and plausibility of the evidence for health effects for long-term O₃ exposure on*
11 *respiratory morbidity? Limited new data also suggest a link between long-term O₃ exposure and*
12 *respiratory mortality; what weight should be placed on this evidence in causal determinations?*
13 *What are the views of the Panel on the conclusions drawn in the draft ISA regarding the*
14 *strength, consistency, coherence and plausibility of the evidence for neurological effects*
15 *resulting from long-term O₃ exposure? Are the data properly presented regarding the credibility*
16 *of newly reported findings being attributable to O₃ acting alone or in combination with other co-*
17 *pollutants and regarding the extent that toxicological study findings lend support to the*
18 *biological plausibility of reported epidemiologic associations in reaching a causal*
19 *determination?*

20
21 General Comments

22 1. I only skimmed the epidemiology sections so my comments do not include them, except
23 as noted.

24 2. I support the causality conclusions, with one However, I an expanded discussion the
25 animal toxicological data would offer more support to the conclusions and, more
26 importantly, assist in interpreting severity observed in human studies. In particular, the
27 first sentence on animal tox studies (7-14) dismisses all rodent data. This is wrong. In
28 particular, there are a number of excellent chronic animal studies not cited or discussed
29 too briefly that show numerous types of morphometric changes, some of which are
30 irreversible; findings that can't be measured in humans. Dosimetric comparisons of
31 these rat studies to humans are possible, but not done. The discussion of interspecies
32 homology is inadequate. The discussion on the effects of age and exposure pattern on
33 respiratory tract morphometry is inadequate, resulting in losing whole concepts about the
34 effects of O₃. See specific comments below for details of the foregoing.

35
36 The exception is (7-62 L19) “... the evidence is suggestive of a causal relationship
37 between long-term O₃ exposures and all-cause mortality”. I am not familiar enough with
38 the epi studies to comment on them. However, I know of no such evidence from the
39 human clinical and animal toxicology studies. Thus, it is important to expand
40 significantly on this part of the discussion.

41 3. The discussion of animal toxicology studies throughout is insufficient because so many
42 key studies were omitted and some are misquoted. For example, there are at least 3
43 major studies of seasonal effects, but only one is referenced. There are several on age,
44 but only 1-2 are mentioned. Thus, although I fully support the weight-of-evidence
45 evaluation that relies on animal studies, I support it based on what I know, not on what is

1 restricted to the references presented. More specific comments on this topic follow.
2 Briefly, it is essential to make sure *all* of the *key* animal tox studies of the 1996 and 2006
3 AQCDs are included here. This can be done with significant use of tables. I included the
4 1996 AQCD because it has some key studies not included in the 2006 AQCD.

- 5 4. As I have mentioned under all other charge questions I addressed, the separation between
6 old and new literature is artificial and results in a suboptimal understanding of the *whole*
7 of the findings.
8

9 Specific Comments

- 10 1. (This comment is a duplicate to that under the previous Charge question on Chapter6.)
11 There is some confounding between Chapters 6 and 7 with regard to whether the studies
12 were short- or long-term. For example, some 90-day studies were in both places.
13 Prenatal exposure studies are in both places. The beginning text of each chapter should
14 define the duration term. In some cases, duplicate discussion may be of value, but this
15 could be part of the discussion (e.g., time trend for respiratory tract morphometric
16 changes). The whole of the literature on neonatal exposures should be in one chapter of
17 the other.
- 18 2. 7-14 L14ff. This first paragraph is the introduction to the section of animal tox studies of
19 structure and function. The first few sentences generally dismiss animal studies. Indeed,
20 quantitative extrapolation is difficult, but qualitative extrapolation is generally accepted if
21 the database is strong enough. As a superficial general statement, subchronic and
22 chronic studies (<0.5ppm) from several laboratories of several species of mice, rats, and
23 non-human primates have shown similar morphometric changes, many of which would
24 be considered “adverse”, at least for that population studied. Given the similarities
25 among all these species and their similarities to humans, it is very likely that these same
26 effects could occur in humans, *if* exposure was sufficient. Homology is strong.
27 Quantitative extrapolation requires understanding of both interspecies dose and
28 sensitivity (e.g., repair mechanisms). Dosimetric extrapolation for rats is advanced and
29 could be developed for some of the key studies .
- 30 a. Thus, the first sentence is incorrect when it says that “considerable controversy
31 surrounds the extrapolation of data generated by rodent toxicology studies...”
32 This implies the studies are of no value. I don’t know of any “controversy”
33 among knowledgeable people (even with different points of view) about the
34 concepts of homology. Most informed people acknowledge the uncertainties
35 involved in quantitative extrapolation. So even the word “controversy” is wrong.
36 It would be accurate to discuss the issues of certainties AND uncertainties in both
37 qualitative AND quantitative extrapolation.
- 38 3. 7-15 L23 Add “where dosimetric models indicate the dose is higher” to the end of the
39 sentence. This is important because it adds evidence of the accuracy and value of
40 dosimetry models.
- 41 4. (NOTE: this comment could be made for virtually all of the sections including animal
42 toxicology descriptions) 7-14 ff. Many key studies are not cited in this section; and
43 according to HERO, they were not even on the list of considered but not used. I only
44 cross-checked a few. There probably are many more. The easiest way to check is to
45 compare this ISA text to the 2006 and 1996 AQCD. Unfortunately, the ones I identified

1 are also missing from the 2006 AQCD. It is NOT necessary to include each and every
2 paper in the text. It is necessary to include all relevant papers in tables and use the text
3 for papers that demonstrate key concepts of interest or suggested in humans (e.g., age,
4 seasonal exposures, daily patterns of exposure, irreversible effects, correlated endpoints,
5 and fibrotic changes). The few I identified to explain my point are (see 1996 AQCD for
6 full citations):

- 7 a. Chang et al (1991, 1992) rats; simulated urban pattern of a base of 0.06 O₃, on
8 which was superimposed a spike rising to 0.25; 78 wk exposure, with periodic
9 exams and post-exposure evaluation to assess recovery; advanced morphometric
10 methods. Shows complex pattern of time course of effects during and after
11 exposure ceases.
 - 12 b. Barry et al (1985) rats; 0.12ppm for 6 wk; Compared morphometry of 1-day old
13 and 6 wk old (at start of study). Some age effects.
 - 14 c. Pinkerton et al (1995) rats 0.12ppm, 20 mo. Epithelial and interstitial effects
 - 15 d. Tyler et al (1991) rats; 0.25ppm; “continuous” and “seasonal” exposure regimens
16 over 18 mo showing impacts of on-off exposure regimens, approximating the real
17 world of winter-summer sequence. In some cases, patterns equal (even with
18 lesser “dose”); in other cases, seasonal had different effects.
- 19 5. L23 ff. The Plopper studies of adult and infant non-human primates are described well
20 and are extremely important. Therefore, it would be of great value to add additional
21 references from different studies (in rats and non-human primates) that support many of
22 the findings. These supportive studies are provided in the 1996 and 2006 AQCDs. This
23 could be done briefly, with reference to tables that will be added.
- 24 6. 7-17 L7-26. This whole paragraph describes acute studies (on the order of hours),
25 although this is a long-term exposure chapter. These studies are already in Ch 6. The
26 goal of this paragraph was apparently to provide references to rodent studies of age to
27 buttress the Plopper studies. This could be done better by citing the several subchronic
28 and chronic rat studies that are not included here (see my comment earlier with
29 references).
- 30 7. 7-17 L27ff This is a summary paragraph. I fully agree with the first sentence. However,
31 I am concerned about the claim on L30 that the functional and structural changes are
32 “due to persistent inflammation.” Some animal studies show a time-course shift away
33 from acute inflammation and more towards interstitial changes (including increases in
34 fibroblasts). Any statement of “due to” is complex and dependent on an evaluation of
35 multiple studies, most of which are not even described here. The implications of the next
36 sentence (L31) are true, but not strictly correct because it refers to “these findings”,
37 referring to references of one excellent set of studies. If the reference were expanded as
38 recommended above, the sentence would be correct.
- 39 8. 7-19 L6. The phrase “protective adaptation” was used. The interpretation is that longer-
40 term seasonal exposures have no effect. The Carey study referenced had effects in both
41 the acute and seasonal group, so there were still effects of concern. This area goes on to
42 quote the Harkema study (L7) to 0.3ppm. I used the link to read the paper and the paper
43 was at 0.15ppm for 6 or 90 days (8h/day). The Harkema study showed effects at 6 days,
44 but not 90 days. There are all sorts of exposure duration/pattern studies not cited here, so

- 1 care must be exercised in only citing 2. Furthermore, the adjective “protective” needs to
2 either be deleted or justified.
- 3 9. 7-19 L8-10 The Schmelzer study is on BAL, whereas the paragraph is on nasal effects.
- 4 10. 7-20 L30ff. This is the summary and causal determination section for respiratory effects.
5 The summary of toxicological evidence is quite insufficient, probably because the base
6 offered in the text is weak (as opposed to the database, which is strong). In addition, the
7 summary should be fully integrated, rather than separating the old and the new for just
8 these 2+pages.
- 9 11. 7-25 L1. Briefly explain ApoE mice (i.e., model of atherosclerotic lesions) and the
10 strengths and limitations of this animal model.
- 11 12. 7-26 ff The whole section 7.4 on reproductive and developmental effects should be
12 reviewed by an epidemiologist expert in this area, if this has not already been done.
- 13 13. 7-26 L26-27 This causality statement refers to “relevant” exposures. What is “relevant”.
14 Also other causality statements don’t have such an adjective. Therefore, delete it to avoid
15 confusion.
- 16 14. 7-27 L37. This says that the studies didn’t identify specific pollutants and their
17 concentrations. Thus, why include them if there is no way to track to O3? Consider
18 deleting them.
- 19 15. 7-28 L1ff Studies of sperm counts and related indices are very difficult methodologically.
20 However, there is no discussion about the quality of the studies. Please add a discussion.
- 21 16. 7-29 L8 This says “...O3 was no longer significantly associated with IVF failure.” OK.
22 However the next sentence says that O3 had effects. This sentence therefore needs to be
23 deleted or the study results challenged.
- 24 17. 7-29 L21 This animal study on spermatogenesis should be moved over to the section on
25 sperm (p 7-27 7.4.1).
- 26 18. 7-34 L6. I did not read the entire epi section. When I look at this summary of studies
27 that are characterized as inconsistency, I fail to see evidence for the hypotheses of effects.
28 First, there may be no consistent effects. Where is the evidence for “decreased in utero
29 oxygen supply, ...changes in blood viscosity...” etc.?
- 30 19. 7-44 L23 ff. This was an interaction study with 1ppm O3 (intermittent for 1 month) and
31 0.48 mg particulate matter delivered intratracheally, repeatedly. The unrealistic nature of
32 this exposure regimen needs to be discussed and taken into account in the interpretation.
- 33 20. 7-54 L32ff This section summarizes the NTP O3 cancer study in mice and rats.
34 Although the overall summary(L36) for mice is correct, the details provided above are
35 not. There were differences between the “lifetime”-exposed and the 2 yr-exposed mice
36 that are not discussed. The same NTP study had rats (7-56, L3) but only Boorman et al is
37 cited (this is correct, just add the NTP reference). Because this is the most complete and
38 rigorous study on the topic, it should be discussed in more detail. The easiest approach
39 would be to add the information to a table (see the text and tables in the 1996 AQCD).
40 Also, this well-conducted study did not find effects on mortality, which should be stated
41 given the later conclusions about chronic O3 exposure and mortality.
- 42 21. 7-56 L32ff. This discusses the Kim and Cho studies and says that a 10% incidence of
43 oviductal carcinoma was observed at one point in time. The text raises questions about
44 this. Since these investigators used the same mouse strain as the NTP study, add a

1 reference to the NTP study which found no statistically significant increase in tumors at
2 any site other than the lung.
3

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

- 5 1. This chapter needs editorial "clean-up". Specifically, sometimes the text has a couple of
6 sentences describing a study, but doesn't give the ref and exposure information until the
7 end.
- 8 2. 7-20 L9 Insert "macrophage" after "alveolar".
- 9 3. 7-27 L5 Please clarify. For example, why "indirect effects on the mother's health".
10 What about direct effects on the pregnant or lactating woman's health that result in
11 indirect effects on the fetus/infant.
- 12 4. 7-29 L25. This summary statement needs to be its own paragraph. Furthermore, The
13 phrase "low doses" should be removed since they were concentrations, not doses, and
14 what is "low". Since the studies showing effects were at 0.8 and 1ppm, "low" is not
15 appropriate.
- 16 5. 7-44 L31. The Plopper studies should stay in the other sections where they were
17 discussed (e.g., 7.2.3). This section is on birth defects and deals with prenatal exposure,
18 which was not included in the Plopper studies.
19

20 **CHARGE QUESTION 9:** *Chapter 8 is a discussion of potential susceptibility factors. Are the*
21 *characteristics included within the broad susceptibility categories appropriate and consistent*
22 *with the definitions used? Are there any key susceptibility factors that were not included and*
23 *need to be added?*
24

25 General Comments

- 26 1. The definition of susceptibility (8-1) is very good. It includes susceptibilities related to
27 the magnitude/duration of exposure and health/genetic factors. However, the text that
28 follows does not seriously include the exposure side (see specific comments section
29 below). A specific exposure and dose subsection should be developed.
- 30 2. This chapter is extremely important because the "average," "healthy," "sedentary"
31 person is not at significant risk from "typical" ambient exposures. In contrast,
32 susceptible subpopulations are of significant concern. Therefore, having a clear
33 description of the following for each susceptibility "group" is crucial to interpretation of
34 risk (note: in many cases this information is provided):
 - 35 a. What is the prevalence of this group in the general population (this is especially
36 important for the genetic polymorphisms; and for different exercise levels).
37 Consider a table for this.
 - 38 b. What is the nature and severity of the risk. For example, where is the discussion
39 that even if COPD patients are not more affected in terms of % reduction in
40 FEV1, what is the impact of their having less reserves to cope with this "similar"
41 change in FEV1. What is the number of hospital admissions for asthmatic
42 children? What does a 5, 10, 20 % change in FEV1 in healthy exercising young
43 people mean to their well-being?
 - 44 c. What is the concordance of human clinical, epi, and animal tox data for this
45 group?

- 1 d. Does this group have characteristics that result in greater exposure and/or dose?
2
3 3. This chapter does not (and should not) repeat all the studies on susceptibles contained in
4 earlier chapters. However, the rationale for those chosen for expanded discussion here
5 are not clear. A more concerted effort is needed to identify the definitive papers for each
6 susceptibility class and then proceed to describe them, with a *very brief* cross walk to the
7 larger body of information within the other chapters (hopefully contained within tables in
8 the revised ISA).
9 4. I'm not clear about the criteria used for the discussion, vis-à-vis old and new. I strongly
10 recommend that the full story (not essential to have all the references, as per my
11 comments above) be provided for each susceptibility group, independent of date of
12 publication. For example
13 a. 8-6, L15-16 says "Recent epidemiological..." Is there old epi evidence on this
14 point? What's the story?
15 b. 8-6 L22 says "no recent evidence...controlled human...or toxicological studies."
16 It then goes on to discuss recent epi. What about supporting old evidence?
17 What's the story?
18 c. 8-7 L27 is about lifestage and overemphasizes new studies. What's the story?

19 Specific Comments

- 20 1. 8-3 L1ff. Please add a cross-reference to animal infectivity studies.
21 2. 8-3 L12. This says that asthmatics had no increased susceptibility.
22 3. 8-8 L31. This says comparable O3 doses. Please define dose.
23 4. 8-8 L38ff. This refers to dosimetry modeling by age. It should not be buried.
24 5. 8-23 L30ff. This summary identifies populations "that are most susceptible..." .
25 However, it includes older age groups and doesn't talk about younger age groups. Also,
26 why aren't those with higher exposure identified as a group?
27 6. 8-24 L13ff. This talks about "individuals involved in outdoor activities...in a recent
28 study...no effect modification was observed." The next line summarizes old studies that
29 disagree. So, what was the weight of the evidence. What study—what is meant by
30 "effect modification?"
31

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

- 33 1. 8-10 L 4This talks about senescent rats, but the section on older adults is below it.
34 2. 8-18 L20. This says "at more relevant doses". What were the irrelevant doses and if they
35 are irrelevant, why are they even included?
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1 **Dr. David Grantz**

2
3 **Charge Question #10; re: Chapter 9 (effects of ozone on vegetation and ecosystems)**

4
5 Note: Locations in the text are referenced as [chapter-page/line].

6
7 **Are major effects of O₃ exposure on vegetation/ecosystems identified and characterized?**

8
9 The ISA does a nice job of recognizing the key effects of ozone on vegetation at all scales. An
10 important point is made repeatedly, that new evidence obtained in chamberless exposure systems
11 supports the broad range of conclusions derived from earlier Open Top Chamber experiments. It
12 is therefore appropriate to pursue the analyses of ASPEN and SOY FACE experiments in the
13 context of the NCLAN- and NHEERL-derived C-R relationships for crops and trees. The
14 NCLAN studies imposed mostly chronic and relevant exposures, contrary to the implication in
15 the text (2-55/22-23). It may be preferable to conclude (9-56/25) that the new data "...lie within
16 the range predicted by the meta-analysis...", rather than that they "...support the meta-
17 analysis...". This overall conclusion appears to be contradicted at 9-56/20-21, where alternative
18 wording might be, "...enclosed fumigation systems or growth chambers. This did not appear to
19 alter the sensitivity as previously suggested for OTC exposures (e.g. McLeod and Long,
20 1999...".

21
22 For clarity, the various references to this alignment of FACE and OTC data could be brought
23 together in section 9.3.1 (9-18/19). For greater accuracy, it should be noted that for some crop
24 species, the NCLAN relationships are probably conservative, since current varieties in many
25 cases are more ozone-tolerant than those in production during NCLAN.

26
27 There is a tendency to equate alteration of complex physiological systems with direct effects.
28 Following from this is a tendency throughout the chapter to equate differences in the sensitivity
29 of various responses to mechanisms of resistance, as for the cutleaf coneflower (9-46/2),
30 symptomatic and asymptomatic leaves (9-40/28), and gene expression (9-31 to 9-32). These
31 responses are more appropriately interpreted as symptoms of overall sensitivity, reflecting lack
32 of upstream defense. This is correctly evaluated for sapling beech trees (9-32/25-28), in which
33 greater genetic response is considered to indicate greater sensitivity, rather than the reverse. In
34 *Arabidopsis* (9-32/8-10) greater transcriptional response is stated to indicate only that upstream
35 defenses (leaf boundary layer, stomatal response, canopy structure, cuticle morphology,
36 metabolic??) are weaker in the WS than Col-0 genotype.

37
38 **To what extent do the discussions and integration of evidence across scales (e.g., species,**
39 **communities and ecosystems) correctly represent and clearly communicate the state of the**
40 **science?**

41
42 The chapter does a thorough job of integrating effects across scales. However, in many cases the
43 division of the discussion among the various sections dilutes the arguments. The authors may
44 want to consider consolidating the discussion into fewer, but more vertically integrated, sections,
45 with less repetition.

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Reproductive effects and yield

The knowledge gap in yield suppression (9-11/19) is exactly the same one that remains in reproductive effects (in those species in which economic yield is a reproductive part). The text at 2-53/24-27 does not actually address whether these are direct or indirect effects on reproduction; and it may not be important for purposes of this chapter to resolve this. Stresses of all types alter reproductive behavior in annual, perennial, determinate, and indeterminate species. If the reproductive effects are caused by source-sink perturbations caused by ozone impacts on vegetative tissues, then they are not really distinct reproductive effects. The data at 9-50/7 indicate effects on vegetative productivity and indirectly on reproductive development, and only then on yield. The Black et al. papers (9-19/18-22) are not definitive in this regard, demonstrating compensatory responses, but not necessarily direct effects on reproductive structures. In these studies, ozone effects on the exposed stalk (9-50/11-18) might be direct or might reflect reduced local photosynthesis and source strength. Effects on the second, unexposed stalk may reflect a source-sink disruption, or phytohormone signaling of sink load, rather than a stress specific signal. It is not clear (9-55/22), that reproductive organs are particularly sensitive. Effects on pollen tube growth are more definitive evidence of direct reproductive effects.

Carbon and water

The stomatal and gas exchange discussions in Chapter 2 could be consolidated (2-52/1-9, 2-54/26-37). Water cycling represents scaling of stomatal conductance and section 2.7.3.2 could be combined with the earlier discussion of stomata and gas exchange. The watershed data strongly support the earlier arguments about loss of stomatal control, and contrast directly with the typically observed stomatal closure caused by ozone. These arguments would have greater impact if made in one place.

Similarly in Chapter 9, various sections (9-40-41; 9-75/16-39) might be combined with the discussion of gas exchange, water use efficiency, stomatal control, etc. The scale of observation is less important here than the integrated ozone impact on leaf area, leaf conductance, and photosynthetic capacity. These interact in complex ways that are not captured in the discussion. At 9-75/34, an increase in stem hydraulic conductance is possible, but unlikely, and no mechanism is suggested. Unchanged hydraulic conductance referenced to reduced leaf area, and a possible increase in the water potential gradient due to increased solar exposure, turbulence, and stomatal conductance of the remaining leaves may be more accurate. The invocation of water use efficiency at 9-75/29, is probably appropriate due to the changes in stomatal and photosynthetic properties detailed above, but may require greater explanation.

The reference to McLaughlin et al. 2007 (9-45/31) would inform the arguments regarding stomatal control, though the measurements were indirect (sap flow and stem diameter) and the ozone effect was derived from a multiple regression. Changes were likely driven by altered stomatal regulation, and did correlate with independent stream flow data. Loss of stomatal control is also suggested by Gregg et al. as a cause of reduced growth in rural versus urban trees. The Gregg et al. data (9-22/25; 9-23/36) demonstrate an ozone response through comparison of OTC and rural/urban exposure gradient data (9-41/23; 9-45/31), but do not demonstrate parallel physiological responses in the OTC and gradient studies, contrary to the text (9-23/37). In the

1 field, stomatal conductance was measured on young leaves, while only in the OTCs were
2 responsive older leaves measured. In any case, the Gregg et al. data are more difficult to interpret
3 than their frequent reference in the text implies. The rural trees (with putative loss of stomatal
4 control), exhibited greater rates of photosynthesis, but lower biomass, than urban trees, and the
5 ozone impact was much greater than expected from previous experiments.

6
7 The controversy over whether direct ozone impacts on photosynthesis affect stomatal
8 conductance or vice versa, continues, and is important. This could be clarified (2-52/1-9). The
9 mode of action of ozone impacts on photosynthesis (2-54/27-28) is not well known, and only
10 effects (not mechanisms) are documented in section 9.4. In general modest stomatal closure will
11 only reduce photosynthetic rate significantly (by reducing intercellular CO₂) in C₃ plants, yet
12 ozone reduces photosynthesis in C₄ plants, too. The arguments at 9-45/26 do not demonstrate
13 direct effects on stomatal guard cells. Wang et al. specifically state that both stomatal and non-
14 stomatal impacts were involved. Kitao et al. show mainly stomatal effects, but state that in shade
15 leaves, both are involved. A stomatal limitation of photosynthesis may be demonstrated by
16 showing reduced intercellular CO₂, but only if photosynthesis is unchanged, which is unlikely in
17 a C₃ plant with declining intercellular CO₂. Photosynthesis and stomatal conductance can decline
18 together, with no change in intercellular CO₂. It is often hard to tell from these measurements
19 which effect is primary. The definitive test is derived from a photosynthesis vs. intercellular CO₂
20 response curve.

21
22 The data of Paoletti and Grulke 2010 (9-46/2) show that stomatal properties may predispose snap
23 beans to ozone sensitivity. However, the tolerant snap bean altered its stomatal response kinetics
24 in response to ozone to become more sluggish than the sensitive line, which weakens the
25 argument for the importance of this parameter. This paper does not deal with cutleaf coneflower,
26 as implied in the text. The coneflower experiments (Grulke et al., 2007 (9-46/2)) do not
27 demonstrate protective stomatal properties, since the plants were already exposed to ozone prior
28 to measurement. The stomatal differences may have been symptoms rather than mechanisms of
29 ozone sensitivity in the co-occurring but genetically contrasting individuals. The conventional
30 wisdom is cited (9-83/9-10) that fast growing, high stomatal conductance species are most
31 sensitive, but this contrasts with a previous conclusion (9-49/18), that slow growing species
32 exhibited greater ozone sensitivity (of the allometric coefficient).

33
34 It is clear that ozone reduces translocation of sugar and growth of distant sinks such as roots. At
35 9-49/12-26, this is obscured by leading with reference to the conflicting literature. The variability
36 is real, but should be placed in context by reference to the summaries provided by Andersen
37 2003, Grantz et al. 2006, and Wittig et al. 2009.

38
39 Elevated CO₂ has been shown experimentally to offset ozone effects, and vice versa. The text (9-
40 13/15) implies that only model evidence suggests this. A possible additional reference could be
41 cited (9-41/25-33), Volin et al., 1998, *New Phytologist* 138: 315 – 325.

42 43 *Dose modeling*

44 The use of exposure at 9-102, where flux is really under discussion, contrasts with the careful
45 distinction made at 9-92/19-20 between flux and exposure. In the modeling scenario (9-92/19-

32), temperature, humidity and soil water are required to model, not measure, stomatal conductance. Thus there is no requirement to measure intercellular ozone concentration. In any case, Laisk et al., 1989 (*Plant Physiol.* 90: 1163-1167) demonstrated that this concentration is near zero. A major limitation to modeling ozone dose is the relationship between stomatal conductance and poorly characterized environmental parameters. The major limitation to modeling impact from dose is poorly characterized temporal and spatial variability in sensitivity to ozone. Both depend on diurnal characterization of ozone concentrations. At high elevation and rural sites the diurnal profile of ozone concentration is relatively flat or may peak at unexpected hours. This leads to alternate modes of stomatal uptake, associated with nocturnal opening and with predawn opening (a putative blue light response). This could be further detailed here.

Semi-direct effects of ozone on reproduction (9-95/1-25) might also inform the relationship between fluxes and impacts and the flux (Level II) approaches (9-98/7). Phenology, time of day, and seasonality are key and currently poorly characterized determinants of impact. The peak in stomatal conductance in mid-morning is usually associated with lower VPD than in the afternoon in high VPD environments, or with soil drought. Otherwise conductance may be bell shaped over the day. The Panek 2004 study was in a summer-drought, western coniferous forest. The Grulke et al. 2002 study indicates the importance of microhabitat. However, the next sentence, “The decoupling of conductance and higher ambient ozone concentration... mesic... xeric..” refers to the early arguments for a flux approach, but does not seem to follow from the references and reasoning presented here.

It is clear that stomata provide the principal pathway for ozone to enter and impact plants. There are better references for this (9-109/22), Fuentes et al. 1992, *Agricultural and Forest Meteorology*, 62, 1-18; Massman and Grantz, 1995; Leuning et al. 1979, *Atmospheric Environment*, 13, 1155-1163; Reich 1987, *Tree Physiology*, 3, 63-91; Wesely et al. 1978, *Boundary-Layer Meteorology*, 15, 361-373; Wesely et al. 1982, *Atmospheric Environment*, 16: 815-820, might be considered.

The discussion at 9-110/10-17 is confusing and not wholly correct. Arguments regarding a consistent measurement height are confused with arguments regarding the ozone concentration to which stomata are exposed. There is an ozone gradient in trees and also in crop plants from this reference height to the ground (including through the understory vegetation in a forest). Different leaves are in contact with different ozone concentrations. The question (line 14) regarding uncoupling of stomatal conductance and high ozone periods is not relevant here. The text requires careful revision.

Has the ISA adequately characterized the available information on the relationship between O₃ exposure and effects on individual plants and ecosystems?

In Chapter 1, much is made of the concept of “adverse” responses. Yet, in many locations in the ISA there are references to “alterations” without stating in what direction, or even if they might be deleterious. The summaries in Chapter 2 and section 9.2 rarely identify the direction of change, and as a result do not adequately summarize the subsequent discussion. The discussion of SOD and POD in sensitive and tolerant tobacco genotypes (9-39/30 – 33), states only that

1 measurements were made, with no consideration of whether changes in any direction were
2 observed. An interesting exception which should be emphasized for its novelty (9-30/19-20), is
3 the demonstration that both up and down regulation of SIPK (salicylic acid induced protein
4 kinase) increases tobacco sensitivity to ozone (i.e. a deleterious alteration no matter which way it
5 changes).

6
7 *Signalling pathways and antioxidants*

8 The ISA appropriately concludes (2-50/9) that ozone is perceived in many ways by plants and
9 cells. Ozone and its reaction products interact with ROS metabolism at several potential places.
10 However, the further conclusion (2-50/5-6; 9-24/9) that ozone is “sensed” by specific “apoplastic
11 receptor proteins” which “still remain(s) elusive” is unwarranted at this time. While the initial
12 site of attack by ozone remains unknown, it appears certain to be in the apoplast, which can be
13 stated with greater certainty (9-37/6). It appears that there is no “sensor” in any conventional
14 sense. The concept of Foyer and Noctor (2005) that oxidative stress is a misnomer and that
15 ozone is just part of the normal oxidative metabolism of plants, is quantitatively false. Plants in
16 high ozone environments do not perform well, indicating that this is outside the normal range of
17 signaling metabolism. The concept was a metaphor for understanding (much as suggested by
18 Sandermann earlier) that ozone plays into existing signaling pathways that evolved as biotic
19 defense mechanisms. The oxidative burst is widely recognized to be component of plant defense
20 against pathogens, calling for greater certainty than “thought to be” (9-38/1-8). Consequences of
21 the signaling pathways seem to lead to the most damage, rather than the raw oxidative potential
22 of ozone. The ISA appropriately reverts to a paradigm associated with oxidative stress and
23 interaction with these pathways at 9-29/27-31. The concept of an ozone sensor is premature and
24 potentially wrong.

25
26 2-50/34, the role of JA (jasmonates) is more complex than suggested. JA does not just
27 antagonize ET and SA, it has impacts on abscission, directly on growth and allocation, and other
28 effects that are not well understood. A reference for the role of ABA in antagonizing JA (9-7/2)
29 would be helpful here (possibly Ludwikow and Sadowski, 2008, currently referenced at 9-34).

30
31 Changes in gene expression, particularly at single loci, do not necessarily indicate much about
32 response at the plant scale. Proteome results support some genetic changes but not others (9-
33 6/30-32). For example (9-5/12-15) it is not clear that these changes scale to responses at plant or
34 community level, due to compensatory changes and to genotypic changes that have little
35 phenotypic expression, due to gene redundancy or other mechanisms (9-25/11-13).

36
37 There is no experimental evidence (9-40/8-12) that plants cannot maintain elevated antioxidant
38 levels. Theoretical energy costs may argue against it, but there is little evidence that maintaining
39 carbon in these pools is limiting. It may be that other, more stable, protective systems arise over
40 time. The strength of the oxidized glutathione transport system across the plasma membrane is a
41 key component of the regeneration of reduced glutathione. Therefore the fraction present in the
42 apoplast and its redox status are only partially responsible for the strength of the ascorbate
43 defense system. The functional limitation of the ascorbate pool is not sufficiently described (9-
44 38/24-25) to allow a conclusion whether, or not, other antioxidants may be involved.

1 **Subject areas that should be added, expanded upon, shortened or removed**

2
3 The consideration of ozone impacts on stomatal conductance and its ramifications at various
4 scales could be condensed and consolidated, for brevity and clarity.

5
6 While it is clear that Ca^{++} and MAPKs and many other components are involved in ozone
7 responses (9-30/3-16), it is not clear that the entire signaling framework must be described in this
8 chapter. It may be sufficient to note how ozone enters these existing pathways and the havoc that
9 these pre-programmed responses can cause, quite apart from the oxidizing potential of ozone,
10 itself. This establishes plausibility, without getting tangled up in interacting pathways that remain
11 very poorly characterized.

12
13 The coverage of effects on mammals due to changes in vegetation is rather brief. There may be
14 digestibility studies, if not actual feeding studies, related to dairy or beef production. There are
15 ongoing feeding studies on rabbits, but these are not yet published. Similarly, the coverage of
16 effects on insect herbivory is rather brief. An older paper of relevance here (9-87/12-23), is
17 Summers et al., 1994, J. Agric. Entomol. 11: 181-187, showing increased aphid growth at
18 elevated ozone.

19
20 **Specific comments:**

21
22 Chapter 2 could use a brief Executive Summary, or the chapter itself could be condensed into
23 such a summary. The redundancy (minus the references) with later chapters is substantial.

24
25 At 2-51/23-27, and in section 9.4.5.2, it is important to differentiate root from shoot respiration.
26 The mechanisms and consequences are likely to differ.

27
28 2-53/14, perhaps “pasture” would be a better word than “hayfields”.

29
30 Stomatal conductance is not a rate (9-17/8). Transpiration is a flux with a rate.

31
32 9-13/28, insert “transpirational” to modify “water” at end of line, as this was the only aspect of
33 ecosystem water loss that (apparently) did increase. In Figure 9-1, “water production” could be
34 replaced with a more appropriate descriptor, perhaps runoff, stream flow, or watershed yield.

35
36 Fig. 9-34, the line labeled “control” is defined as “ROS control measurements”, which is unclear.

37
38 The alleged methodological problems of Perry et al. 2007 should be consolidated at first
39 mention, and deleted from the subsequent two locations.

40
41 The protocol at 9-35/37 was “eXogenous” rather than eNDogenous application of MeJA.

42
43 At 9-49/32, seed quality should probably be a 5th category, distinct from yield.

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1 9-55/32, it is incorrect to characterize 79.9 ppb as ambient in the study of Grantz and Shrestha
2 (2006). The study imposed a diurnal profile similar to a maximal daily exposure, but did so on a
3 daily basis. This treatment is considerably in excess of ambient exposure.
4

5 9-58/37, typographical error, probably should read "...84% of the variability in the relative feed
6 value..."
7

8 9-64/25-26, it is unclear what is meant by "ozone enhances negative effects of ozone".
9

10 9-84/25, over-representation of vegetation (128%) is not intuitively obvious, greater explanation
11 would be helpful.
12

13 9-89/9-11, it is unclear how an over-temperature represents a hypothermic response. This needs
14 to be clarified, or a typographical error corrected.
15

16 The Grulke et al. 2007 references should be a or b, since there are two such references.
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1 **Dr. Jack Harkema**

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3 Chapter 5: Dosimetry and Mode of Action

4

5 Q. Is the review of basic dosimetric principles of O₃ uptake presented accurately and in sufficient
6 detail?

7 A. Yes.

8

9 Q. What are the views of the Panel on the approach taken in Chapter 5 to characterize modes of
10 action for O₃-related effects?

11 A. I think this is a good approach/addition. I think some brief text describing how Figure 5-6 was
12 derived would be helpful (e.g., why some things were included and others not)? Figure 5-6 does
13 not include *GAPs in Knowledge* as identified in 5.2.11 (e.g., MOA for systemic effects?)

14

15 See comments below.

16

17 General Comments:

18

19 In general, the overall format for this chapter is appropriate and the text is clearly written. The
20 author(s) have thoroughly reviewed the recent literature and have included the most pertinent
21 recent studies. The chapter, however, could be improved by:

22

- 23 • More emphasis on recent studies (2006-2010)
- 24 • More concise description of past studies with more summarization of overall conclusions
25 from the previous ISA
- 26 • Specific descriptions of the important results of key studies before 2006 could be placed
27 in an appendix and referenced in the shortened main text
- 28 • Description of the GAPs in knowledge should be expanded and other areas identified
29 (e.g., effects of ozone:1) on other extrapulmonary organs such as the liver, gut, and
30 gonads; 2) in the context of multipollutant exposures; 3) effects of ozone on facets of the
31 metabolic syndrome including obesity, diabetes, and hypertension)
- 32 • Inclusion of the effects of ozone on other important preexisting conditions such as
33 obesity and facets of the metabolic system could be highlighted (e.g., studies by Shore
34 SA et al.)
- 35 • More co-referencing of other ISA chapters
- 36 • Addition of past and recent results for other photochemical oxidants where appropriate

36

37 Specific comments/questions:

38

39 Author(s) need to be careful in their wording of ozone's promotion of allergic airway disease
40 (avoiding the term "causing asthma" when it is not appropriate).

41

42 Does ozone really interact directly with cell membranes of some cells in vivo (e.g.,
43 macrophages) as alluded to in some parts of the text? Or is the interaction predominantly
44 secondary reactive by products? References should be provided.

45

1 **Dr. Daniel Jacob**

2
3 **1. Chapter 3 of ISA, Atmospheric Chemistry and Ambient Concentrations (Charge**
4 **Question 4)**

5 I found chapter 3 of the ISA to be overall very well informed and up to its task. Specific
6 comments are below. The most important comments relate to determination of the PRB and
7 trends in background ozone. These are indicated by asterisks.

8
9 3-6, line 20: stratospheric intrusions are not a significant source of NO_x.

10
11 3-6, lines 20-34: Smith and Mueller (ACP 2010) should be cited for a recent perspective on
12 natural NO_x emissions in the US.

13
14 3-6, lines 20-34: it should be acknowledged that natural NO_x emissions are most important in
15 summer when ozone is of most concern.

16
17 3-7, line 33: 26% must be a typo, it's inconsistent with figure 3-2.

18
19 3-8, lines 1-12: Kopacz et al. (ACP 2010) should be cited for the apparent bias in NEI05 CO
20 emissions having a large seasonality, possibly reflecting cold start emissions in winter.

21
22 3-8, line 14: I'm surprised that natural CO emissions could be that high. Or does it include
23 oxidation of biogenic VOCs?

24
25 3-8, line 33: CFCs would be VOCs by this definition. The proper definition of VOCs is precisely
26 what the acronym says it is – gaseous organic molecules.

27
28 3-14, lines 1-2: Wise and Comrie (AE 2005) actually show a strong positive correlation of ozone
29 with temperature in the SW US.

30
31 3-14, lines 25-29: the description of low-NO_x and high-NO_x regimes is not precise. At very low
32 NO_x (cf. zero NO_x), VOC oxidation is in fact a sink for radicals (through peroxide formation).
33 "Free radicals" is presumably meant to describe HO_x, but NO_x species are also radicals. Ozone
34 production is limited by the supply of HO_x radicals in both the low-NO_x and high-NO_x regimes.

35
36 3-15, line 22: OPE depends on many other factors including solar radiation, VOCs, and ozone:
37 cf. Hirsch et al., JGR 1996.

38
39 3-16, lines 1-10: should cite satellite work on using HCHO/NO₂ column ratios from GOME and
40 OMI to diagnose NO_x-limited and NO_x-saturated regimes. See Martin et al., GRL 2004 and
41 Duncan et al., AE 2010.

42
43 *3-25, section 3.4: either in this section or in section 3.2 there should be some discussion of three
44 major chemical uncertainties that could affect model PRB simulations: halogen chemistry (not
45 just in urban areas but in background), isoprene chemistry, and the chemical evolution of fire

1 plumes. It should be noted that current models simulating the pre-industrial and early 20th
2 century atmosphere greatly overestimate the observed concentrations at the turn of the century.
3

4 *3-27, lines 12 and 37: it is essential to discourage the notion that PRB could be measured. On
5 line 12, “PRB conditions” should be changed to “PRB-relevant conditions”. On line 37, TH
6 cannot be applied to “PRB conditions” if only because of US anthropogenic contribution to the
7 northern mid-latitudes background ozone. On the flip side, it is important to recognize the
8 importance of measurements at background sites to test model PRB values. These measurements
9 present challenges to the PRB models in terms of reproducing high observed values and
10 correlations. In particular, Parrish et al. ACP 2010 should be cited for suggesting that surface
11 ozone in the Sacramento Valley could have an unexpectedly large background concentration
12 based on correlations with ozonesonde data at Trinidad Head.
13

14 *3-27, line 12 and beyond: The importance of measurements at background sites for testing PRB
15 models must be stressed, at the same time one must also stress that these sites are in general not
16 representative of the US. Ozone concentrations measured at Trinidad Head are representative
17 of...Trinidad Head.
18

19 *3-29, line 3, and elsewhere: use the + sign when indicating a positive trend.
20

21 3-36, line 9: I don’t understand, “too high by only 5 and 3 ppb”.
22

23 *3-37, lines 20-27: these statistics illustrate that models have a difficult time capturing the high
24 extremes of the ozone distribution and this would have implications for PRB estimates, for
25 example with regard to stratospheric intrusions at mountain sites or fire plumes. Some different
26 strategy or screening would be needed for such exceptional events.
27

28 3-50, lines 11-30: the limitations of satellite observations with regard to vertical resolution
29 should be stated.
30

31 *3-93, lines 1 and beyond: the increasing trends of ozone over the US west coast need to be
32 mentioned here (they were mentioned earlier in the chapter in the PRB context). I have heard
33 talks from EPA scientists about rising ozone in national parks in the west, although I don’t know
34 of a peer-reviewed publication. if these trends are robust they should definitely be mentioned.
35 Such rising trends would be of particular concern in meeting a tighter NAAQS.
36

37 **2. Chapter 10 of ISA, The Role of Tropospheric Ozone in Climate Change and UV-B** 38 **Effects (charge question 11)** 39

40 This chapter is definitely useful in view of recent interest in chemistry-climate interactions and in
41 combining air quality and climate goals for environmental policy. Overall I found it to be very
42 well informed. I think that it should give more play to methane as the only ozone precursor for
43 which control would effectively reduce climate forcing. It should also give more play to the
44 recent RCP scenarios of IPCC AR5, since these scenarios will provide the core of future
45 assessments of climate forcing for emissions relevant to air quality and they present a very

1 different picture than the older SRES scenarios. Below are specific comments. Important
2 comments are flagged by asterisks.

3
4 *10-3, line 24: the IPCC SRES scenarios are now considered obsolete. I understand that they
5 should be described in this chapter as the literature is based on them. But more attention should
6 be given to the RCP scenarios, and they should be mentioned in this paragraph.

7
8 10-5, Figure 10-1: feedback from climate change should apply to the emissions of ozone
9 precursors.

10
11 10-8, lines 18-19: is there any evidence of increasing ozone in the SH? Is there any evidence of
12 increasing tropical biomass burning?

13
14 10-8, line 37: for bromine effects on ozone cite Yang et al., JGR 2005. The Parrella paper
15 doesn't exist.

16
17 10-8: Ordonez et al. GRL 2007 should be cited for a natural explanation of decadal ozone trends
18 at northern mid-latitudes.

19
20 10-11, lines 14-18: it may be better to cite the IPCC values for emission-based RF as a
21 community consensus.

22
23 10-12, line 30: but there's no SW radiation over the Arctic in winter. Isn't it a general feature of
24 greenhouse warming to be most intense at high latitudes in winter?

25
26 *10-13, section 10.2.6: I think that the concept of emission-based RF should receive more play
27 because it is so relevant to ozone. It makes the point in particular that only methane controls
28 provide climate benefit. I suggest including (or at least commenting on) Figure 2.22 of IPCC
29 AR4, which shows that present-day methane emissions are more important than CO₂ emissions
30 in driving climate change over a 20-year time horizon, in part because of methane as a precursor
31 of ozone.

32
33 *10-14, lines 21-34: I think that it would be useful to include a figure of 21st-century RCP
34 projections of global emissions for AQ-relevant species. Also it would be worth mentioning that
35 the RCP scenarios provide continuity with the previous SRES scenarios in terms of overall
36 radiative forcing: RCP8.5 ≈ A2, RCP6 ≈ A1B, RCP4.5 ≈ B1. However, the projections of
37 emissions for AQ-relevant species are very different.

38
39 10-16, line 15: isoprene does not systematically decrease ozone under NO_x-limited conditions.

40 41 **3. Air Quality Considerations in the REA document (chapter 2 and chapter 3)**

42 This chapter of the REA document provides the atmospheric basis for the exposure analyses. I
43 am concerned about the use of 2008-2010 ambient data for the exposure analyses because 2009-
44 2010 are considered to be low-ozone years for reasons having to do with meteorology and
45 possibly the economy. 2006-2008 would be much more representative. In addition, the available

1 PRB calculations from GEOS-Chem are for 2006-2008, and temporal coincidence is very
2 important for sites where the PRB can make a large contribution to total ozone concentrations as
3 in the intermountain West. If EPA decides to keep 2008-2010 as basis for its exposure analyses
4 then GEOS-Chem PRB calculations will be needed for that period. However, a better option is to
5 use 2006-2008.
6

7 Also, the EPA needs a strategy for correcting GEOS-Chem biases in PRB estimates. I think that
8 it is useful to distinguish between two types of biases:

- 9 • Regional biases, such as in the Southeast US in summer where the model background is
10 too high. A simple correction (and probably good enough) would be to use regionally
11 representative sites (such as CASTNet) and attribute GEOS-Chem biases relative to
12 observations proportionately to PRB and to North American sources. More sophisticated
13 corrections are possible by comparing model and observed frequency distributions of
14 ozone at these sites but they may not be any more accurate.
- 15 • High-ozone events in the observations that may be related to PRB and that the model
16 doesn't capture. From my inspection and understanding, I think that these happen only at
17 mountain sites in the West and are associated with stratospheric intrusions or wildfire
18 influences not captured (or excessively diluted) by the model. From my analysis of model
19 vs. observation statistics (and this will be reported in the Zhang et al. [2011] paper
20 describing the GEOS-Chem PRB calculation), the model can properly capture the overall
21 frequency of events > 70 ppb but fails above 75 ppb. Individual inspection of these events
22 in the observations may be necessary to screen for PRB influence.

23 A few other specific comments:
24

25 2-5, line 4: proper reference is Wang et al., AE2009, instead of Bey et al.
26

27 2-6, lines 26-28: according to the IPCC AR5 RCP scenarios methane is not projected to further
28 increase in the future. These scenarios may turn out to be wrong, but one cannot just assume that
29 methane will continue to increase.
30

31 3-17, lines 23-30: I'm surprised that not more attention is paid to near-roadway exposure. The
32 report states that ozone would be lower because of titration by NO to NO₂, which an uneducated
33 reader might assume would reduce exposure, but in fact ppb for ppb NO₂ is no better than ozone.
34
35

1 **Dr. Steven Kleeberger**

2
3 **Chapter 8 Populations susceptible to ozone-related health effects**

4
5 *Are the characteristics included within the broad susceptibility categories appropriate and*
6 *consistent with the definitions used?*

7
8 Initially, the authors of the chapter clarified the meaning of ‘susceptibility’ for the
9 purposes of the ISA to eliminate confusion that has arisen in previous ISA documents for other
10 NAAQS pollutants. That is, susceptible populations include susceptible, vulnerable, and at risk
11 sub-populations. This was very helpful moving forward.

12
13 The authors then did a very good job capturing what are considered to be the most
14 important known categories of factors that may contribute to enhanced susceptibility to ozone-
15 induced adverse outcomes. The 13 major categories for discussion included pre-existing
16 disease/conditions (8.1), lifestage (8.2), sex (8.3), genetics (8.4), diet (8.5), body mass index
17 (8.6), socioeconomic status (8.7), air conditioning use (8.8), involvement in outdoor activities
18 (8.9), race/ethnicity (8.10), physical conditioning (8.11), smoking (8.12), and hyperthyroidism
19 (8.13). Broadly, the 13 categories could be considered intrinsic (8.1-8.6, 8.10, 8.13) and
20 extrinsic (8.7-8.9, 8.11, 8.12) susceptibility factors. Some of the categories could be collapsed to
21 be more inclusive, e.g. involvement in outdoor activities and physical conditioning; pre-existing
22 disease/conditions and hyperthyroidism and smoking. However, with the given structure, the
23 authors were consistent with the broad meaning of susceptibility and how the various factors
24 may influence responses to ozone exposure.

25
26
27 *Are there any key susceptibility factors that were not included and need to be added?*

28
29 In the "Lifestage" section, the authors briefly mention *in utero* exposures and effect on
30 lung function and immune response in animal (mouse and rat) models. It should be more
31 strongly emphasized that pre-term neonates represent a particularly susceptible population,
32 subject to injurious effects of air pollutant exposure as the exposures may disrupt normal fetal
33 developmental processes. Epidemiological studies have also reported associations of air
34 pollution exposures (including ozone) with affected reproductive outcomes including intrauterine
35 and infant mortality, preterm birth, low and very low birth weight, intrauterine growth
36 restriction, and birth defects. Perhaps pregnancy should be considered a temporary ‘pre-existing
37 condition’ and adverse outcomes are reproductive/birth parameters.

38
39 The Genetics section was well-written, and adequately considers recent genetic
40 association studies in human epidemiological and chamber investigations. It may be worthwhile
41 stating that, due to small sample sizes, many of the chamber studies are limited to testing only
42 those potential candidate genes that have very high minor allele frequencies in order to obtain
43 appropriate statistical power. Other genes with potential impact on ozone-induced outcomes
44 may be important, such as those identified in some of the mouse models, but power
45 considerations have limited testing these genes in human populations.

1
2 It was a bit surprising that the discussion of toxicological studies did not include more
3 thorough consideration of other potentially important genes besides those mentioned (e.g. *Tnf*,
4 *Nqo1*). A number of recent investigations have implicated additional candidate genes that
5 could/should be considered for future investigations in human populations, including for
6 example *Il10*, *Mmp9*, *Il6*, *Tlr2*, *Marco*, *Hsp1a*, *H2-Aa*, *Ab1*, *Eb1*, *Eb2*, *Ea* (histocompatibility
7 genes), *Lta*, *Nos2*, and TLR4 and TNF signaling genes such as *Myd88*. Perhaps a table should be
8 created that identifies these and other genes that have been implicated to be important in the
9 pathogenesis (or protection against) ozone-induced lung inflammation and injury.

10
11 The inclusion of diet as a susceptibility factor was timely and important. Given that this
12 factor was not considered in previous AQCDs, the authors should have the flexibility to cite
13 older papers to give the factor appropriate context. In addition to vitamins C and E, vitamin A
14 deficiency has also been shown have important consequences on ozone-induced inflammation
15 (see e.g. Paquette, et al, *Am J Physiol* 270:L475-82, 1996). Caloric restriction (protein
16 deficiency) was briefly mentioned, but this area could be better developed by including
17 additional studies such as Kari et al (*Am J Respir Cell Mol Biol* 17:740-747, 1997).

18
19
20 Minor comments:

21
22
23 Table 8-1. ‘Obesity could be included in the table as it is a potentially highly prevalent risk
24 factor.

25
26 Page 8-4, lines 14, 15. Formatting errors.

27
28 Page 8-4, line 34. ...asthmatics to, on average, experiences... should be ...asthmatics, on
29 average, experience...

30
31 Page 8-4, line 38. ‘Only study’ should be ‘Only one study’.

32
33 Page 8-7, line 3. Formatting error.

34
35 Page 8-7, line 4. ...and atherosclerosis were noted... should be ...and atherosclerosis was
36 noted...

37
38 Page 8-9, line 11. Epitheliar should be epithelial.

39
40 Page 8-11, line 16. ...85 year of age... should be ...85 years of age...

41
42 Page 8-15, line 6. ‘individuals with both GSTM1 genotypes’ is a bit confusing since individuals
43 can have only one genotype. Sentence should be re-written to state individuals with either
44 genotype.

Deliberative Draft Letter to be discussed on July 6, 2011 Teleconference of the CASAC Ozone Review Panel. Do not cite or quote. This draft has not been approved by the chartered CASAC nor does it represent EPA policy. Updated 6-17-11.

1 Page 8-15, line 35. It is not clear why Nrf2 was stated as a possible susceptibility factor. No
2 references were cited, and this transcription factor has not been well characterized for
3 responsivity to ozone.

4

5 Page 8-16, line 1. Inf-1 and Inf-2 should be identified as quantitative trait loci, not genes.

6

7

8

1 **Dr. Fred J. Miller**

2
3 **Chapter 5: Dosimetry and Mode of Action**

4
5 The dosimetry and modes of action of O₃ are discussed in Chapter 5. The primary focus of the
6 dosimetry discussion is to highlight factors that might lead to differences in dose between
7 individuals and between species. Some potential modes of action that may underlie a number of
8 health outcomes and that may contribute to the biological plausibility of health effects of short-
9 and long-term exposures are described in detail.

10
11 Is the review of basic dosimetric principles of O₃ uptake presented accurately and in sufficient
12 detail?

13 There is actually very little presented about the dosimetric principles of O₃ uptake aside from a
14 discussion of what biomolecules O₃ react with in the ELF and in the tissue. There is no
15 discussion of the physical and chemical factors involved in gas transport and mechanisms that
16 result in the penetration into and removal of O₃ in various regions of the respiratory tract. The
17 roles of convection, bulk flow, laminar versus turbulent flow, effective axial diffusion, radial
18 diffusion, solubility, and Henry's-Law are among the topics that should have been discussed if
19 the principles determining O₃ uptake were to be accurately and sufficiently presented. There is
20 limited discussion of species differences in nasal structure and lung morphometry and the
21 composition of the ELF together with the cellular composition in the major respiratory tract
22 regions (extrathoracic, tracheobronchial, and alveolar). This information affects the strength of
23 species homology and also illustrates what needs to be taken into account in interspecies
24 dosimetric extrapolations.

25
26 Most of the dosimetry material centers on factors influencing uptake such as depth and route of
27 breathing, the importance of interindividual variability in O₃ uptake, regional experimental
28 uptake data in humans, and factors that influence attempts to correlate measures of internal dose
29 with response in human experimental studies. If this is what the Agency means by dosimetric
30 principles, then the chapter comes closer to meeting its objectives.

31
32 What are the views of the Panel on the approach taken in Chapter 5 to characterize modes of
33 action for O₃-related effects?

34 The MOA material is a combination of effects descriptions mixed in with studies that are more
35 mechanistically oriented. Very little information from animal studies is brought into the MOA
36 discussion. For example, Section 5.2.3. on Activation of Neural Reflexes goes on for 4 pages
37 describing human study results and then in Section 5.2.3.1 on New Cellular and Molecular
38 Insights, animal studies are first brought into the discussion. If some pre 2006 animal studies
39 were cited along the way that support the human findings, the cases for the MOAs would be
40 stronger. The same can be said for other sections.

41
42 The figure on page 5-62 depicting the key events and pathways for the effects of ozone on the
43 respiratory tract would be more useful if it was placed at the beginning of the MOA discussion as
44 part of an introduction. Perhaps the section numbers could be included with the boxes; that way
45 if a reader is interested in a particular aspect of one of the MOAs, they could go directly to the

1 material. And the figure could be retained at the end of the chapter as part of the overall
2 summary. In addition, the MOA Overall Summary is weak, as it does not convey the strength
3 and the importance of the findings discussed in the MOA subsections.
4

5 Other points relevant to the MOA presentation and material are included below in my general
6 and specific comments.
7

8 **Preliminary General Comments**

- 9 • While the chapter combines material on the dosimetry and mode of action (MOA) of O₃,
10 there is no particular reason why they should be combined. The chapter organization
11 comes through as if the pairing of the two was an after thought. As the ISA meeting last
12 week, Dr. Jim Ultman provided an example of how the chapter might be organized to
13 better tell the story of exposure-dose-response and how MOA fits into the story.
- 14 • The dosimetry chapter discusses various human study results and basically concludes,
15 “this study shows that O₃ does that”. Almost every one of these revelations is a
16 confirmation of what mathematical O₃ dosimetry models predicted 10 to 20 years earlier.
17 More inclusion of references to the modeling papers would strengthen the presentation of
18 the human dosimetry findings as was done in the material on “Pulmonary Ozone Uptake
19 and Dose”.
- 20 • Whatever happened to the Agency criteria that to be included in the Criteria Document
21 (and now the ISA document) studies needed to be at or below 1 ppm O₃? Or if higher
22 levels were included, at least the investigators went down in exposure concentration. I
23 find it ridiculous to cite papers at 3 parts ppm O₃ for several hours and talk about how
24 they contribute to our understanding of mechanisms or modes of action. Such high
25 exposures have no relevance to the real world and invoke “fictitious findings” (for
26 example, the Williams et al. (2007) study exposing mice to 3 ppm O₃ for 3 hour would
27 have “blown away” the lungs of the mice and allowed O₃ to directly react with the blood
28 – what relevance can one possibly assert to mode of action of O₃ at environmental
29 exposure levels?).
- 30 • In a number of sections, the text appears to be a stringing together of statements or
31 findings from the original authors as sentence after sentence has a string of references at
32 the end of the sentence. The frequency of references actually interferes with reading the
33 material.
- 34 • In the MOA material, the authors need to be careful about making statement that a study
35 shows one species is more sensitive to O₃ than another. A good example of this can be
36 found on page 5-34 starting at line 20. The text states that Dormans et al. (1999) exposed
37 rats, mice, and guinea pigs to O₃ and found guinea pigs to be the most sensitive with
38 respect to alveolar macrophage elicitation and pulmonary cell density in the centriacinar
39 region. And mice were most sensitive to bronchiolar epithelial hypertrophy ... and the list
40 goes on. Such statements about sensitivity are simply not valid unless there is
41 normalization to the dose received. One species may remove more O₃ than another in the
42 nasopharyngeal region or one species may receive a greater pulmonary dose. The author
43 of this paragraph points out the problem 9 lines later! Why waste text describing
44 something that is not valid?

- 1 • Throughout the MOA material, the O₃ exposure level and duration needs to be included
 2 more often. As an example, on page 5-53 starting on line 21, the study by Arito et al.
 3 (1990) is cited as showing O₃ can induce several cardiovascular effects in animals
 4 exposed to O₃. One might have an initial reaction of “So What?” Only by going to HERO
 5 do you find out that very low exposures of 0.1 to 0.2 ppm O₃ were used for 5 days in rats.
 6 These results clearly have relevance to humans and clearly offer insight into a MOA for
 7 O₃.
- 8 • In multiple places, the text asserts that Pryor et al. (1992) show that O₃ can not penetrate
 9 an ELF layer more than 0.1 microns in thickness, and, thus, effects of O₃ on epithelial
 10 cells must be due to secondary reaction products. This assertion is more appropriate for
 11 the mucous layer than it is for the surfactant layer. But even for the mucous layer, the
 12 beating of the ciliated cells ensure that the layer is not stagnant and increases the chance
 13 that some O₃ may be able to react directly with epithelial cells. In the alveolar region, 98
 14 % of the alveolar epithelium is covered by an ultrathin (< 0.02 μm) surfactant layer (see
 15 Miller, Toxicol Lett 82/83:277–285, 1995). The surfactant layer pools in the corners of
 16 the alveoli during part of the breathing cycle leaving only a monolayer film of surfactant
 17 over the cells, thereby allowing the cells to be in almost direct contact with O₃ in the gas
 18 phase. Moreover, the surfactant layer normally only approaches a thickness of 0.1 to 0.2
 19 μm over Type II cells and in crevices, and, Type II cells cover only about 5 % of the
 20 alveolar surface area. Thus, there is ample opportunity for O₃ to react directly with both
 21 cell types in addition to forming reaction products with constituents of the surfactant
 22 layer.
 23

24 **Specific Comments**
 25

Page, line	Comment
5-2, 25	The statement that the mucous coating becomes patchy in the distal conducting airways is highly debatable. The method used to fix the lung specimens greatly influences the results. The most accurate method to preserve the lining lay involves both blood and gas-phase fixative methods. To my knowledge, Mercer’s study was the only one meeting these criteria, and he showed that the layer was continuous even in the terminal bronchioles.
5-2, 27	The sentence beginning with “The progressive thinning ...” needs to be reworded. The authors are trying to refer to the radial distance from the center of the air phase to the ELF, but the way the sentence is currently worded implies they are talking about the axial distance into the lungs.
5-3, 1	Suggest inserting the word “mediating” before “...O ₃ toxicity in the airways.”
5-6, 33	Is the reaction rate constant for GSH stated correctly? If it is, can it be converted to the same units as shown for UA and AH?
5-7, 38	The part of this sentence “... and to prevent penetration of O ₃ deeper ... is not correct. Effective axial diffusion ensures O ₃ penetration deeper into the lungs while the radial gradient locally affects tissue toxicity.
5-9, 15	As the senior author of the paper referenced here, I object strongly to

	calling our O ₃ dosimetry model limited because the URT was not included. We normalized dose to a per microgram of ozone entering the trachea. One only needs to specify the concentration at the beginning of the trachea in order to use our model for lower respiratory tract absorption of O ₃ . The fraction of O ₃ removed in the extrathoracic (ET) region in human experiments is given in Table 5-2 for various human studies and later on the chapter cites Hatch as determining about 50% of the inhaled O ₃ being taken up in the ET region of rodents. So if resting humans breathe 116 µg/m ³ (i.e., 60 ppb) and one uses the fractional nasal removal value of Gerrity et al. (1988) of 0.36, then 74 µg/m ³ arrive at the start of the trachea. So for the dose patterns we show for humans, multiple the values by 74 and you have the predicted dose to the tissue in the various LRT generations.
5-9, 18	The discussion here does not include Wiester et al. (1987) where only 40% in the total respiratory tract was measured over a concentration range from 0.3 to 1 ppm O ₃ . Has this study been discredited? If not, then it should be included to reflect that there is not complete agreement in the published literature about how much O ₃ is removed in the head in animals. The Wiester et al. ((1987) study also would affect the statement on page 5-20 starting at line 18 where pulmonary uptake is discussed.
5-11, 16	A caveat needs to be added here. The sentence “increased f _B will shift ... respiratory airspaces” is only correct if tidal volume increases.
5-12, 7	This correct statement is why exercise imparts effects of O ₃ exposure sooner. It should be captured in the chapter summary.
5-14, 6	Clarify what is meant by lower airways. FEV ₁ does not reflect only a lower airway effect.
5-14, 24	If this really is present thinking (i.e., ... linearity of the dose relative to ventilation relationship has not been carefully studied.), it is incorrect as shown by Miller et al. (1985). Comparing the heaviest exercise simulation to the one for normal respiration showed a 10-fold increase in total mass uptake. The increase was distributed unevenly in that the tissue and mucous layer of the tracheobronchial region had mass increase by about a factor of 1.4, while the surfactant layer and alveolar tissue had uptake increase by factors of 5.2 and 13.6, respectively.
5-14, 26	The Sawyer et al. (2007) study was on nasal uptake. HERO did not have the full paper. How was the lower airway uptake determined?
5-15, 6	The model described by Taylor et al. (2007) only had one bifurcation. A significant amount of text is devoted to this paper. However, some caution is appropriate because the pattern of airflow downstream is impacted by the flow 2 bifurcations upstream as also shown by Schroter and Sudlow.
5-15, 33	Is it supposed to be “< 0.05”?
5-16, 19	The authors state that to date studies have failed to show that the large differences in biological response between subjects can be explained by differences in uptake. This reviewer has commented previously on why this has likely been the case in view of the Overton et al. (1996) paper on the role of TB expansion and volume on O ₃ uptake. The following is taking

	<p>directly from that paper “Variability in PAR dose, as a function of TB volume already described, has significant implications for human studies, particularly those conducted at low exposure levels where measured changes are expected to be minimal. Individual responses to a given O₃ level are highly reproducible (McDonnell et al., 1985). McDonnell and coworkers (1993) found that there is significant interindividual variability in changes in FEV₁ that correlational analyses ascribe to exposure level and to the age of the subject. Alternatively, though, a portion of the variability observed may simply reflect the variability in TB volume that was likely present among the subjects. Since anatomical dead space, which includes TB volume, can be measured, future clinical studies involving reactive gases would be more powerful if dead space is controlled or adjusted for in selecting subjects, thereby allowing exposure-response curves to be translated into dose-response curves. Exercise tends to reduce variability among subjects in PAR dose. Thus, controlling for dead space may also become more important in clinical studies using extended exposure periods (6-8 h/day) with levels of exercise considerably lower than those used in 2-h exposure studies in the past.”</p>
5-16, 32	<p>Of course rodents have few terminal bronchioles – they have smaller lungs. However, the terminal bronchioles are not the site of major O₃ absorption – it is the bronchiolar-alveolar duct junction. The morphometry studies of Crapo and Cheng definitively show this.</p>
5-16	<p>The species homology section falls short of including enough material that shows how homologous species are for the effects of ozone on the respiratory tract. Additional figures could be added that would help drive this point home. For example, a figure with 2 panels showing monkey tissue dose of 18-Ozone measured by Hatch and colleagues in one panel and the predicted tissue dose pattern in humans from Miller et al. (1985) in the other would show the reader homology between these species.</p>
5-17, 3	<p>Species differences but not the site may affect the amount. It is the respiratory bronchioles in primates and humans and the bronchiolar-alveolar duct junction in rodents.</p>
5-17, 6	<p>How does a lower body temperature affect the amount of O₃ dose to the lungs? The amount of temperature drop is not enough to affect the air phase diffusion coefficient for O₃.</p>
5-20, 16	<p>The space devoted to this paper is too much. The model structure is far from being realistic.</p>
5-21, 20	<p>The text states “Although the O₃ molecule is consumed and may not reach the apical plasma membrane of airways and alveolar epithelium,” is an overstatement as far as the alveolar region is concerned. During breathing, the 98 % of the alveolar epithelium that is covered by an already ultrathin (< 0.02 μm) surfactant layer pools in the corners of the alveoli, thereby allowing some cells to be in almost direct contact with O₃ in the gas phase. Moreover, the surfactant layer normally only approaches a thickness of 0.1 to 0.2 μm over Type II cells and in crevices, and, Type II</p>

	cells cover only about 5 % of the alveolar surface area.
5-22, 8	The statement that O ₃ does not diffuse very far into the mucous layer is overall a correct one. However, since the cilia are bathed in the aqueous layer and beat at 1200 beats per minute, the layer is far from stagnate and may allow some O ₃ to come into direct contact with epithelial cells in the TB region.
5-27, 17	The authors state that an important consideration is the non-uniformity of the injury response to O ₃ . Both Mercer and colleagues and Pinkerton and coworkers have shown that this is due to the variability in tracheobronchial path length and the volume of all the acini attached to a given terminal bronchiole. This is why pathologists describe non-uniform injury when slides are cut randomly through lung tissue, particularly at low exposure levels.
5-28, 1	The statements here about where maximal effects occur are exactly in accord with dosimetry modeling predictions. This is an example of why the general comment was made to cite the modeling papers more at various points in the MOA discussion.
5-30, 18	This excellent paper by Schelegle et al. (2007) should be expanded upon in the discussion. There are a number of good points shown in their publication.
5-32, 11	Why all the listing of references up to 30 years old? This comes across as the MOA only bears insight after all of this time.
5-48, 3	This is an accurate and powerful statement that should be highlighted in the chapter Overall Summary (Section 5.2.10).
5-53, 21	Here is an example of the need to include the O ₃ exposure levels and durations. The Arito study involved 5 days of exposure of rats to only 0.1 to 0.2 ppm O ₃ that found the cardiovascular effects described here.
5-56, 14	Are the authors not aware of the 2011 publication by Kim et al.? The whole paragraph on this page goes on about GSTM1 involvement but does not mention the negative finding of no relationship to PMN percentage to O ₃ exposure at 60 ppb reported by Kim and colleagues. This recent publication showed that GSTM1 has no role in modifying the effects of neutrophilic inflammation at environmentally relevant exposure levels.
5-58, 13	Here is another example of where the O ₃ exposure level and duration would have been useful. The cited study involved 0.42 ppm for 1.5 hours. So increased body mass index (BMI) is not likely a risk factor at environmentally relevant exposure levels given the small but significant effect seen for females by Bennett et al. (2007).
5-61	The MOA Overall Summary section is very weak and does not reflect the strength of the findings discussed in the subsections. The current section comes across as “the authors ran out of gas”.

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Chapter 8: Populations Susceptible to Ozone-related Health Effects

Chapter 8 is a discussion of potential susceptibility factors.

1
2 Are the characteristics included within the broad susceptibility categories appropriate and
3 consistent with the definitions used?

4 The characteristics included are consistent with the definition of susceptibility presented on the
5 first page of the chapter. Providing EPA's definition of susceptibility was critical for evaluating
6 the material included in the chapter. As a statistician and familiar with the concept of tolerance
7 distributions, I personally do not like the Agency's definition of susceptibility; tolerance
8 distributions are founded on the recognition of innate biological differences that make some
9 individuals respond at a given dose while other persons do not. And as the dose is increased the
10 tolerance distribution becomes narrower.

11
12 Are there any key susceptibility factors that were not included and need to be added?

13 Exercise is only indirectly treated as part of the sections on children and on outdoor activities. At
14 ambient exposure levels, exercise is the single most important driver of the amount of ozone
15 inhaled and the likelihood of causing effects in individuals of any age or disease condition. As
16 such, more discussion of the role of exercise and exercise levels should be included in Chapter 8.
17 This should extend to covering how minute ventilation levels greater than about 35 L/min in
18 adults leads to oronasal breathing and an increase in LRT absorption due to bypassing much of
19 the filtering efficiency of the nose.

20
21 **Preliminary General Comments**

- 22 • The chapter would be made stronger if evidence from animal toxicology studies were
23 included that provide support for the susceptibility characteristics under discussion. A
24 good example is Section 8.1.1 Influenza/Infections. The section is only a short paragraph
25 about findings in epidemiology studies. However, there are a number of animal studies
26 showing the ability of ozone to increase the incidence and/or mortality from respiratory
27 infections, even to exposures as low as 0.08 ppm O₃. Inclusion of such material would
28 strengthen the case for O₃ being able to cause similar effects in humans.
- 29 • The chapter summary identifies older age groups as being one of the most susceptible
30 populations to O₃ exposure. However, the studies discussed in Section 8.2.2 (Older
31 Adults) do not give the reader this impression. For each type of effect discussed, both
32 positive and negative studies are typically available. This section also provides an
33 example of how the results from clinical and animal studies can provide biological
34 plausibility for some endpoints (see the discussion starting at line 33 on page 8-11). The
35 evidence may be stronger for some endpoints than for others, and this should be the
36 bottom line carried forward to the chapter summary.
- 37 • The rambling style of the presentation of studies in various sections makes the material
38 difficult for the reader to take away the bottom line about the importance of some of the
39 susceptibility characteristics being discussed.

40
41 **Specific Comments**

42

Page, line	Comment
8-4, 9	Why would one even discuss an epidemiology result based on an N of 4?
8-8, 1	Lung development (i.e., airway branching, addition of alveoli) is completed

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	between ages 6 and 8. This is different from lung growth, which continues until ages 18-20.
8-14, 18	As noted in the Dosimetry and Mode of Action chapter, why isn't the Kim et al. (2011) study discussed? Their study shows GSTM1 does not play a role in O ₃ responses at environmentally relevant exposure levels.
8-18	Section 8.7 on Socioeconomic Status should make clear to the reader that SES is an indicator variable reflecting such things as access to health care, quality of housing, and pollution gradient.
8-23, 3	Smokers are most likely less responsive to O ₃ due to increased mucous production and because most of the endpoints studied do not reflect alveolar level insults.

1
2

1 **Dr. Howard S. Neufeld**

2
3 **Chapter 2**

4 I believe this chapter adequately sums up the evidence and conclusions presented in later
5 chapters. It is well written, although it is somewhat lengthy for a summary chapter. My main
6 recommendation would be to provide the reader with a two page (max) executive summary,
7 complete with tables of known causality.

8
9 Of particular usefulness are the concluding statements at the end of each section which
10 summarize the findings and provide the reader with the state of causality for that process. I
11 found very little factually with which to take issue. There are a few places where some clarity of
12 wording might improve the document, but these would be relatively minor changes. In general,
13 this is a good integration and summary of the remaining chapters in the ISA.

14
15 The policy relevant background section (2.1.3) is particularly well written, and the definition of
16 PRB, for those not familiar with this parameter, is excellent and easy to understand.

17
18 Section 2.1.5.4, on Hourly Variations, states that for most locations, diel maxima of ozone occur
19 in mid-afternoon and minima at night. This seems to ignore high elevation ecosystems, where
20 just the opposite can and does occur. Data from the Smokies and other high elevation locations
21 around the world often show flat profiles over time, and sometimes the maxima can occur at
22 night instead of during the day. Because so many sensitive plants may be located at high
23 elevations, I think a distinct discussion of high elevation ozone patterns warrants more discussion
24 and elaboration. It is also not clear to me whether diel patterns at high elevations have remained
25 unchanged over the past 20 years like that for low elevation sites.

26
27 I can't comment to any great extent on the sections concerning human responses to ozone, as that
28 is outside my areas of expertise, but even so, they appear to be well constructed, and to take into
29 consideration most, if not all, sources of variation and effects with respect to ozone exposure.
30 My only comment is that by section 2.4, I think the document should make it more clear whether
31 the responses being discussed were obtained using acutely high exposures (unrealistic with
32 respect to known ambient levels) or were obtained using near ambient exposures.

33
34 The tables (2.1, 2.2, and 2.4) provide the reader with quick summaries of the ISA conclusions,
35 and are very useful. It might be nice to reiterate the category definitions beneath each table so
36 readers are reminded of the degree of certainty with which EPA considers ozone as a cause for
37 each item mentioned.

38
39 In Section 2.5.1, potentially susceptible populations, I wonder whether any studies have been
40 done on class/economic distinctions with respect to ozone exposure. In this vein, I'm thinking
41 about whether certain classes of people are disadvantaged by income or race, which causes them
42 to live in areas that predispose them to higher pollutant exposures. For example, wealthy people
43 living on the coast of California would be exposed to lower ozone than those further inland or in
44 the central valley. I didn't see any mention of this in the ISA, but certainly, the EPA has studied
45 similar issues with regard to environmental justice and the placing of nuclear and toxic waste

1 sites. However, because ozone is often a regional phenomenon, it may not be easy to distinguish
2 differences in exposure due to these issues over much of the rest of the country.

3
4 In section 2.5.2, the last sentence seems awkwardly constructed. The first phrase states that
5 single day ozone exposures underestimate the public health impact. The second phrase starts off
6 with the disclaimer “*but*” and then states that multi-day effects are limited to the first few days.
7 The way it is constructed almost makes it seem as if the latter part is not as important as the first.
8 I would substitute “*while*” for “*but*” which would give equal weight to both clauses.

9
10 I have to admit that I thought Figure 2.1 was less than helpful. It’s too confusing with the colors
11 and multi-faceted studies. Is there any way to simplify this? Figure 2.2, in contrast, is much
12 better constructed, but you need to define HA/ED visits. Since everything else is spelled out in
13 the figure, just spell these acronyms out too. In fact, there is no need for any acronyms in this
14 figure at all.

15
16 With respect to welfare effects, I also have a problem with Figure 2.3. I believe the figures are
17 too simplified. The leaf panel is simply too cluttered, and all the arrows make it confusing to
18 figure out what is going on. Some pathways are covered over by the water vapor arrow. There
19 is no mention of reactive oxygen species inside the leaf, nor any distinction between apoplastic
20 and symplastic reactions, even though the text extensively discusses these things. Also, C4
21 plants, which constitute a significant fraction of our crop plants, do not have this leaf anatomy,
22 and that difference could have significant influences on why most C4 plants appear less sensitive
23 to ozone than C3 plants (if that indeed is true). The ecosystem panel uses the term “*water*
24 *production*” but in the key to the side uses the phrase “*water cycling*”. Cycling is the more
25 proper term. Ecosystems don’t “*produce*” water; rather, they use and cycle it. A better
26 indication of trophic cascades could be included. As of now, the insects and animals are just
27 standing off to the side as if separate from everything else. In conclusion, I think this figure
28 could be redrawn to higher standards.

29
30 Section 2.7.1 closes with a discussion of ozone-induced changes in stomatal functioning. I don’t
31 think sluggish stomata always mean that they do not close after exposure to ozone. Rather, when
32 ozone injury is apparent (such as when foliar symptoms are seen), there is a reduction in stomatal
33 conductance which may or may not be accompanied by sluggishness. That is, sluggishness
34 doesn’t necessarily occur when stomata are as open as in plants not exposed to ozone. Also,
35 sluggishness refers to an inability to either close or open, not just close, as stated in the
36 document. Finally, aberrant stomatal functioning often occurs in the absence of any visible
37 injury, suggesting that some other factor must be at work to cause this effect (and it may not
38 always be due to higher internal CO₂). I think the inclusion of a short discussion of potential
39 causal factors (besides increased internal CO₂) would be welcome.

40
41 I agree with most of the rest of this part of Chapter 2. There is a new paper, just accepted to
42 Environmental Monitoring and Management (Smith, G., 2011, in press), which summarizes 16
43 years of FIA monitoring of ozone bioindicators. As Smith states, extreme soil moisture deficits
44 decrease foliar injury on bioindicators, but in some dry years, soil moisture appears to have less
45 effect on controlling injury levels. Soil moisture appears to protect plants against foliar injury no

1 matter what the level of ozone exposure. Finally, when soil moisture balance is positive, high
2 ozone generally causes more injury. Most importantly, the best correlations with injury were
3 with the N100 (number of peak hours at or above 100 ppb) and not with a cumulative index,
4 showing again that peak ozone is critically important in determining plant response.

5
6 Should Shenandoah National Park be included in the list of parks with bioindicator plants and
7 foliar injury (page 2-54, line 19)?

8
9 With respect to section 2.7.2.2, I simply ask if yield losses with respect to ozone could be
10 reduced by farmers either knowingly or unknowingly selecting for ozone tolerant strains of their
11 crops after experiencing losses from ozone in previous years. That would alter the
12 exposure/response relationships over time.

13
14 Also, in this same section, line 22, there is the statement that “*most research on the mechanism*
15 *of O₃ damage has used acute exposure studies.*” Is this still accurate today? I would have
16 accepted this statement 15 years ago, but in my opinion, recent studies have moved to more
17 realistic or near ambient exposures.

18
19 I think the jury is still out with regard to sluggish stomata. Section 2.7.3.2 seems confident that
20 reduced conductance is the main result of ozone exposure, while admitting that sluggishness
21 does occur. I think some compromise needs to be included here. If the weight of evidence is
22 that ozone lowers conductance, and only that conclusion is incorporated into models, then the
23 impacts of sluggishness (failure to close or open properly) are lost, and the results of studies like
24 McLaughlin et al. (2007), which found that sluggishness might be responsible for reducing
25 ecosystem-wide water availability, would not be accounted for.

26
27 The last word in this same section should be changed from “*production*” to “*use*” or “*cycling*”.

28
29 Section 2.7.4.2 discusses night time stomatal conductances. No mention is made of some early
30 studies, such as the one by Peter Tobiessen in 1982 (Oecologia) which showed that some early
31 successional tree species might open their stomata pre-dawn (and to levels approaching day time
32 conductances) or the more recent studies by Lisa Donovan. If this is really happening, then it
33 needs to be addressed. Studies by Lisa Donovan on night-time conductances, and similar
34 parallel studies using eddy covariance, need to be included in the literature review in Chapter 9.
35 Many of these early successional tree species occur at high elevations, where ozone is high at
36 night and in the early morning, and they could take up appreciable amounts of ozone at those
37 times, assuming there is adequate mixing and deposition to the canopy, as discussed elsewhere in
38 the ISA.

39
40 Finally, in the section on tropospheric ozone and UV-B (2.8.2), I did not see any mention made
41 of UV-B-induced catalysis of elemental mercury in lakes and re-volatilization into the
42 atmosphere. In areas subject to acid deposition, where DOC is reduced, and the lakes are made
43 ultra-clear, light penetrates further down the water column. If UV-B light is present, it can
44 convert methyl Hg photolytically into a volatile form of elemental Hg that then escapes into the

1 atmosphere. If ozone alters UV-B radiation, then it could inadvertently affect Hg volatilization
2 and transport within and among ecosystems (See Schindler, D.W., 1998. Science).

3
4 Lastly, the summary table at the end is well done, and provides the reader with an expectation of
5 what to expect in the rest of the ISA.

6 **Comments on Chapter 9**

7 Much of the beginning of this chapter is word for word, the same as that in Chapter 2. I would
8 shorten this chapter by going directly into the specific sections, and leave out all the redundant
9 material. Also, I thought that the sections on stomata were too dispersed and redundant. It
10 seems that some re-organization of topics might make the material flow better.

11
12 In 9.2.2, page 9-6, line 3, it is stated that responses to ozone can be quite rapid, which results
13 from the plant's ability to sense ozone or its breakdown products, which then result in gene
14 activation or down regulation. However, some of these responses could occur prior to any gene
15 activation. In fact, gene activated responses would generally be slower, given the time required
16 for transcription and translation. Might these extremely rapid responses (such as membrane
17 leakiness) simply be physical responses to ozone or ROS, and not the product of gene activity?
18 This would make the situation similar to how auxin responses are propagated in plants – there is
19 a rapid (10-15 mins) physical reaction (acidification of the apoplast for example) followed by a
20 slower (several hours), prolonged response due to gene activation.

21
22 On page 9-7, there is a statement that plants “*need to keep antioxidant metabolites in a reduced*
23 *state*” and that this “*requires a significant shift in C metabolism...*”. While this sounds logical, is
24 there really any hard evidence showing this from an experimental point of view? I don't recall
25 any papers that have actually tested this idea. Yes, respiration rates do tend to go up, but is there
26 evidence that is because plants are attempting maintain their antioxidant defenses, or is it simply
27 a result of foliar injury itself, but with no beneficial results in terms of prolonging leaf life span
28 or function?

29
30 Regarding the action of ascorbate, pictured in Figure 9.4, there is no mention of the mini-review
31 on the chemistry of ozone-ascorbate interactions by Heinrich Sandermann, which appeared in
32 *Biochemical and Biophysical Research Communication* 366:271-274 (2008). In this review,
33 Sandermann points out that reaction of apoplasmic ascorbate (or ascorbate in the respiratory lining
34 of the lungs and airways) results in the production of a zwitterion that decomposes into peroxy-
35 L-threonic acid and oxalic acid when it reacts with ozone. If it reacts with one of the ROS
36 produced upon ozone exposure (singlet oxygen) it produces peroxy-ketone. Singlet oxygen can
37 be produced when ascorbate reacts with ozone. Peroxy ketones can react with water to yield
38 hydrogen peroxide. These secondary toxicants may affect human/animal and plant responses to
39 ozone in ways not yet fully appreciated.

40
41 Section 9.4.3.2 ends with a discussion of gene upregulation and downregulation by ozone. It
42 would be interesting to postulate what differences might exist that cause sensitive plants to react
43 to ozone more readily than tolerant plants, if such knowledge exists. That is, what is the
44 molecular basis for differential gene regulation by plants that vary in sensitivity to ozone?
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For Figure 9.5, there are no labels or units on the Y axis of panel A.

With regard to Section 9.4.4.2, I saw no mention made of Burkey et al. (2006) or Souza et al. (2006) with respect to apoplastic antioxidant levels and degrees of resistance to ozone in native wildflowers, in particular, tall milkweed. These papers showed a clear association of higher apoplastic ascorbate in the reduced state, and reduced foliar injury in the field from ozone for tall milkweed, but not for coneflowers or crownbeard. Although correlative only, it is suggestive of the fact that individual plants of tall milkweed show fewer foliar symptoms from ozone because they have higher apoplastic ascorbate than those plants with reduced amounts which have more foliar injury. Furthermore, tolerant tall milkweed plants maintained elevated apoplastic ascorbate throughout the season compared to sensitive individuals, which slightly contradicts the statement at the end of section 9.4.4.2 that plants cannot maintain elevated antioxidant levels for extended periods of time. Perhaps such patterns are species and environmentally contextual.

In Section 9.4.6, there is the statement, on page 9-46, that ozone-sensitive coneflowers “*have a set of traits, such as a sluggish stomatal response to changes in light intensity, which predispose them to being more sensitive to O₃ exposure...*”. In actuality, there is little evidence for any differences in stomatal conductance prior to the appearance of foliar injury between sensitive and tolerant coneflowers (personal knowledge on my part, paper in preparation). Such differences in the magnitude and responsiveness to environmental variables only show up once sensitive plants show visible foliar injury. So it is not accurate to state that there are “*predisposing*” factors. At this point we simply do not know why one individual is sensitive and an adjacent one is not.

Also, in this same section, there is no extended discussion of Nancy Grulke or Elena Paoletti’s work on stomatal sluggishness.

In Section 9.5.3.2, page 9-59, line 6, Volk et al. are cited with respect to effects of ozone potentially causing shifts in high elevation community species composition. Yet, this study was repudiated later by Stampfli and Fuhrer (2010) and this latter study is cited later in the ISA in section 9.6.5.2, on page 9-84. Perhaps Section 9.5.3.2 and Section 9.6.5.2 should be made consistent with each other. A recent paper (Volk et al. 2011, *Global Change Biology* 17:366-376) shows an influence of N deposition on soil C storage in these high elevation meadows, but no effect of ozone and should be included in the ISA.

Section 9.5.4.4 documents the reported interactions between ozone and N deposition. There is a lack of investigations on the interaction between N deposition and ozone responses, which highlights a major research deficiency in our understanding of how ozone responses by plants can be modified by other forms of pollution.

There are no reports in the ISA of the responses of nonvascular plants (e.g., mosses), lichens or lower vascular plants and their responses to ozone. A quick Web of Science search of papers published since 2006 brought up five papers on lichens and ozone and one for mosses, but none for ferns. Inclusion of a statement that our knowledge of the impacts of ozone on these types of plants has not been a research priority in recent years, and a retrospective summary of past

1 conclusions for these types of organisms might be helpful here. Mosses cover a vast amount of
2 the earth's surface, and if they are negatively impacted by ozone, this could have an effect on the
3 C balance, and hence global climate.

4
5 Most of the ecosystem level studies cited used 2X ambient ozone levels to elicit effects. How
6 relevant are those results then, with respect to current and expected levels of ozone?

7
8 In Section 9.6.3, line 6, page 9-74, the text reads "...leads to greater stomatal apertures." This
9 is not entirely accurate. It can lead to sluggish stomata which fail to close; but only rarely do
10 they open more.

11
12 Section 9.6.6.1 on species-level responses would benefit by having a concluding sentence that
13 summarized the situation. Such a sentence would simply state "*that that there is no consensus*
14 *on how insects respond to feeding on ozone exposed plants.*"

15
16 Section 9.7.3.1 would benefit by inclusion of the Smith paper (see earlier mention) on foliar
17 injury and its relation to peak and cumulative amounts of ozone over 16 field seasons. It too
18 found that peak ozone concentrations (at or above 100 ppb) seemed highly correlated with the
19 degree of foliar injury found in the field; more so than any cumulative index.

20
21 Section 9.7.3.2. makes no mention of Tobiessen's early work on nocturnal conductances in early
22 successional trees (Tobiessen, P. 1982. Dark opening of stomata in successional trees. *Oecologia*
23 52:356-359) and might be improved by its inclusion. Nor does it reference Lisa Donovan's
24 extensive and recent work on this subject.

25
26 In Section 9.7.4.1, Chappelka et al. (WASP 116: 255-260, 1999) documented greater injury in
27 mid-canopy black cherry leaves, rather than those at the exterior and most exposed part of the
28 forest canopy. This probably resulted from an interaction between canopy location and ozone
29 concentration, where fully exposed leaves were more water-stressed and had lower stomatal
30 conductances, while those in mid-canopy had slightly lower ozone, but higher stomatal
31 conductances. Such patterns should be re-emphasized here, even if reviewed in an earlier
32 document.

33
34 Gregg's data in Section 9.8.3.3 is eye-opening to say the least. If this represents what is
35 happening in the field, then certain genotypes of trees have already, or will soon be, eliminated
36 by ozone from the landscape (maybe this has already happened in some poplar clones and in
37 white pine – see Berrang and Karnosky's early work on this). That means a decrease in genetic
38 diversity, which can happen without any noticeable change in appearance of the forest or other
39 plant community, since resistance genotypes would appear visually similar to the sensitive ones
40 that are selected against.

41
42 One final comment on something in **Chapter 3**, page 3-7, line 15. Here, it is stated that
43 coniferous forests are the largest source of VOCs nationwide. In the southeastern states, vast
44 swaths of land have been converted from hardwood forests to production pine plantations. I

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1 wonder if anyone has calculated whether this has caused an increase in the VOC emissions in
2 this part of the country compared to what was present when it was mostly hardwood forests?
3

4 The rest of this chapter is a good summary of the current state of knowledge of how natural and
5 agricultural ecosystems respond to ozone.
6

7 **Comments on Chapter 10**

8 I thought this was a well written summary of both the direct and indirect effects of tropospheric
9 ozone on UV-B radiation impacts. I appreciated how this chapter discussed the climate forcing
10 due to ozone relative to that of CO₂ and CH₄, as well as the way it distinguished between long-
11 term and short-term greenhouse gases.
12

13 With respect to calculating recent ozone trends, E. Henry Lee et al. (2003, History of
14 tropospheric ozone for the San Bernardino Mountains of Southern California, Atmos. Env.
15 37:2705-2747) had a paper out recently comparing trends in California back to the time when
16 ethylene monitors were used and showed that they could reconstruct the ozone trends for that
17 period, but I didn't see it cited in the ISA.
18

19 I thought this chapter fairly evaluated the research to date while also pointing out the paucity of
20 studies of how increasing tropospheric ozone will affect UV-B impacts. It also got the point
21 across that most conclusions regarding these effects are tentative, and, where more is known, that
22 the magnitude of effects is likely to be small to moderate at most. I agree with the last
23 conclusion on page 10-28 that "*the effects of changes in surface-level O₃ concentrations on UV-
24 induced health outcomes cannot yet be critically assessed within reasonable uncertainty.*"
25

26 **Typos Needing Correcting**

27 **I only read Chapters 1, 2, 3, 9 and 10 for typos**

28 Note: for *ALL* figures with legends, they all contain a box after the first sentence or so, which
29 often overlaps with other text.
30

31 **Chapter 1**

32 1-6, line 34 - Change "if" to "of"
33

34 **Chapter 2**

35 2-4, line 25 – Should it be "hPa" or "kPa"??

36 2-9, line 13 – Change "This" to "These". Data are always plural.

37 Line 32 – there is an overlap of the greater than and the left parenthesis

38 2-23, line 12 – insert "of" before "antioxidant"

39 2-36, Table 2-3 – In the short-term section of lung function, second column, the less than and
40 parenthesis signs are on top of each other.

41 2-49, line 8 – insert "that" before "have been"

42 2-58, line 30 – insert "the" before "Carpathian"
43

44 **Chapter 3**

45 3-10, line 16 – the symbols after acyl peroxide radicals are messed up.

1 For many of the figures, using dark blue for the correlation boxes, with black fonts makes the
2 numbers impossible to read.

3

4 **Chapter 9**

5 9-41, line 7, “Acer” should be italicized.

6 9-48, line 35 – insert “production” after “fine root”

7 9-51, line 20, “Smokey” is misspelled. There is no “e”, e.g., Smoky. Also, “Mountain” should
8 be

9 plural, as in “Mountains” – Great Smoky Mountains National Park

10 Table 9-2 – all the scientific names in the table should be italicized.

11 9-53, line 5 – “Asclepias exaltata” should all be italicized.

12 9-56, line 37 – take out “a” before “the individual”

13 9-58, line 22 – There is some confusion in units on this line. The sentence states that yields are
14 reduced “*by -0.38 to -1.63% ppb/v across the five years.*” Should that be are reduced “*by*
15 *0.38 to 1.63% per ppbv/yr*”? That is, take out the negative signs, and correct the ozone
16 unit, and insert yr in the denominator.

17 On this same page, but line 28, “dependant” is misspelled. Should be “dependent”.

18 9-59, line 4 – change the second “was” at the end of the line to “were”

19 9-63, line 12 – both Rhizobium and Frankia should be italicized.

20 9-64, line 25 – I think a word is missing here. The sentence says that O₃ may enhance O₃
21 effects. I think the first O₃ should be “drought”, right?

22 9-66, line 7 – Change “on” to “in” before photosynthesis.

23 9-70, line 11 – “function” should be plural, “functions”

24 9-71, line 25 – insert “in” before “O₃ concentration”

25 9-72, line 2 – insert “the” before “northeastern”

26 Line 38 – Change “that” to “than”

27 9-81, line 5 – insert “the” after “Since 2003”

28 9-83, line 6 – subscript the “4” in “CH₄”

29 9-86, line 27 – take out the comma after “O₃” and put in a space

30 Line 32 – change “have” to “has”. This verb refers back to “performance” on the
31 previous line, which is singular.

32 9-129, line 3 – change “confirms” to “confirm” – should be in the plural form since this verb
33 refers back to cottonwood “data”, and data is a plural word.

34 9-131, line 8 – insert “%” after “17.9”

35

36 Note that for **ALL** references in this (and probably other chapters) that contain scientific names,
37 none of them are italicized, and they should be.

38

39 **Chapter 10** – I did not find any typos in this chapter.

40

41

42

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44

45

1 **Dr. Ted Russell**

2
3 Review of the Integrated Science Assessment for Ozone and related Photochemical Oxidants
4 (First External Review Draft)

5
6 Overall, I thought that the ISA is in pretty good shape for a first draft. It is still a bit long in
7 places (see below), but that may be unavoidable. My main issue is that I think more attention
8 needs to have more information on both the health studies and the air quality analyses at
9 relatively low levels (40-60 ppb) and the potential role of confounding when ozone is around
10 those levels. After all, ozone is around those levels more often than it is above those levels.

11
12 In general, I think Chapter 3 does most of its job pretty well, and some parts may be a bit long. I
13 was glad to see that a significant fraction was moved to an Appendix. For the most part, the
14 chemistry and transport are relatively well known, and the last ISA did a good job on its
15 description and analysis of observational data. I think there are a couple of potential areas that
16 need to be more fully addressed:

- 17
18 1. Relationship between various ozone metrics at lower levels. The likely driving question
19 associated with this review process is where in the range of 60-75 ppb, 8-hr average
20 should a new standard be set. In part, this will rely on various epidemiologic studies.
21 Various studies have used different ozone metrics, e.g., 24-, Max 8-, and Max 1-hr
22 averages, and it is important to be able to relate those metrics to each other. Some of
23 those studies provide more than one metric and that is good. However, for those that
24 don't, it is important to be able to relate one to another, with particular interest in what is
25 happening in the 60-75 ppb range. Thus, a good way to convert would be useful.
26 However, the relationship varies between city and between concentration range, so a
27 single value to convert is not likely appropriate. (If it is, great, and show this.) Thus, it
28 might be useful if EPA looks at how this conversion should be done and provide such in
29 the ISA. I might recommend a graph of the 8-hr max compares to 24-hr average for a
30 number of cities and the country as a whole.
- 31 2. PRB. The PRB discussion is pretty good, though abbreviated in that it was not apparent
32 what the conclusion is (likely because this is a 1st draft and that updated PRB analysis
33 will be done). Further, and while I do not know how it is best to address this subject, is
34 that this could be a very key issue since the results show that the PRB levels in parts of
35 the country could be similar to the levels of a proposed standard, thus suggesting the
36 potential need for changing the form of the standard. I suspect that info from the recent
37 PRB workshop will be utilized, assuming that the publication is completed and accepted.
38 To me, the fundamental question is how to mix an observed quantity with a modeled
39 quantity, particularly a modeled quantity that has apparent bias in some locations.
40 Further, it is not apparent that a bias-less product will be developed (if so, great). Thus, a
41 question is how one can modify the PRB to remove bias, or how to use the simulated
42 ozone that is due to North American emissions, along with observations. At present, I
43 think that the former is easier and less open to criticism. EPA should set out a strategy to
44 identify the reason for the observed biases. I think this can be done using the adjoint
45 capabilities in the model. The knowledge gained from such an exercise can provide

1 some confidence in using an adjusted PRB product. In regards to how knowledge of the
2 PRB might influence the determination of the form of the standard (or averaging time), it
3 would be good to provide additional information on PRB ozone distributions for key
4 urban locations, along with values akin to the design value based on 4th highest, 10th
5 highest (etc.), 8-hr ozone. The details could be in the Appendices, but summarized in the
6 main report.

7
8 Chapter 9 can be shortened, and streamlined to directly address what are the appropriate
9 indicators. This ISA, as well as the documents developed in the last review, provide strong
10 support for the linkage between ozone and ecosystem damage, and CASAC concurred. What
11 needs to be taken head on is which metric(s) is best and why.

12
13 Chapter 10 does a good job of addressing how ozone can potentially impact radiative forcing and
14 hence global change. A couple of things are needed to complete some of the thoughts that go
15 along with this in terms of standard setting. First, it would be good to also integrate the
16 information from the PRB analysis and modeling in to this chapter, e.g., taking on the question
17 of what the impact of the ozone from NA emissions. A second issue is how the warming can
18 impact health. Be very careful to note the uncertainties associated with assessing how health
19 impacts might be linked to future climate changes. I might refer to the Weaver manuscript
20 (BAMS) that discussed the results from many groups.

21 Some general comments that should be addressed throughout:

- 22
23 1. Given that this document is to be used for policy determination, the staff should be very
24 careful to only use studies that have relied upon data and models that are now or have
25 been readily available and/or have been independently evaluated and verified. If the staff
26 feels that specific references that do not fall in to that category are absolutely necessary,
27 they should identify this problem and justify the use of that study within the document.
28 This should be an underlying principle for such documents and assessments (and it might
29 extend beyond documents that are used for policy setting).
30
31 2. Make very sure that the figures and tables have the appropriate units and metrics
32 specified in detail (e.g., “3-yr average of the 4th highest 8-hr maximum daily ozone” as
33 opposed to “ozone”).
34
35 3. It would be good if every chapter had an “overall summary” and “gaps in knowledge”
36 similar to Chapter 5.
37
38 4. Ozone (and other pollutant) results from models applied to historical cases should be
39 referred to as “modeled” or “simulated” as opposed to predicted
40

41 Some specific comments:

- 42
43 • 1-2-26: “mobile”
44 • 1-4-3. I might rephrase “Photochemical pollution (or smog) is a mixture of pollutants,
45 many of which are oxidants formed from reactions that take place in the presence of

- 1 sunlight. Historically, ozone has been used as an indicator of photochemical smog, in
2 part because it is one of the most abundant photochemical pollutants and it has been
3 demonstrated to have health effects.”
- 4 • 1-7-12: You should make explicit the current status of the standard and what it means
5 that the Administrator has decided to reconsider in terms of actions taken to meeting an
6 0.075 standard.
 - 7 • Chapter 2: the amount of text on the plant impacts is a bit out of balance. .
 - 8 • 3-2-5: compounds, as well as particulate matter.
 - 9 • 3-3-7: ... in the eastern US, concentrations of ozone
 - 10 • 3-3-28 remove small scale unless you are ready to define it (and it is unnecessary here).
 - 11 • 3-4-8 “square kilometers” is not a distance, and a few thousand square km is not that big
12 of an area.
 - 13 • 3-4-15 Make sure you are consistent about the importance of stratospheric exchange
14 throughout the document.
 - 15 • 3-6-14: I do not think compensated is correctly used here.
 - 16 • 3-6-34: What is a small amount? 0.05%, 0.5% 5%?
 - 17 • 3-7-8: Are you saying that wildfires are anthropogenic and contribute 1/6 of the
18 anthropogenic VOCs?
 - 19 • 3-7-28: It is important to note that controls mute the response of CO formation to fuel-
20 oxygen.
 - 21 • 3-8-33: I think VOC was defined earlier.
 - 22 • 3-9-11 “they” is ambiguous.
 - 23 • 3-9-25: Make sure NO_x is defined.
 - 24 • 3-11-12 “... O₃ and other compounds.”
 - 25 • 3-17-6: We don’t just use finite difference techniques, and there is no reason to be this
26 specific anyway. (also found on 3-19-7)
 - 27 • 3-17-23: “... about 100 hPa,”
 - 28 • 3-18-4 “Historically, CMAQ has been...”
 - 29 • 3-20-40/24: This paragraph raises problems that need to be more quantifiably
30 demonstrated to be an issue in the general application of models in practice. Provide
31 citations and relate to magnitude of other problems.
 - 32 • 3-21-11: Is the MCM considered a benchmark? I would suggest that being shown to
33 reproduce the controlled laboratory studies is more of a benchmark.
 - 34 • 3-21-38: Provide citations as to the importance of coupling and also what is meant by
35 heavily polluted (Beijing or LA?) Be quantitative. From reading this chapter one might
36 get the idea we should not use CMAQ because it does not include enough vertical
37 resolution, does not resolve the nocturnal jet, the chemical mechanism is flawed and not
38 as good as the MCM, and does not generally incorporate coupling. Are you ready to say
39 this?
 - 40 • 3-23-7: Actually many components are tested individually when possible.
 - 41 • 3-25-24/26: Again, this part is speculative and citations are necessary. Should we not
42 use CMAQ?
 - 43 • 3-33-29:L Should you add low spatial resolution such that elevated sites are not fully
44 captured.

- 1 • 3-33-35: Show this graphically.
- 2 • 3-37-6 It is not that the air is too high, it is that the simulated ozone concentrations are
- 3 too high.
- 4 • 3-55-33: A mixing ratio is not, technically, a concentration. You might state this, but
- 5 then say the general practice is to call ppm/ppb concentration.
- 6 • Fig. 3-18: It would be of interest to identify the two outliers.
- 7 • Tables 3-6& 3-7: I don't see the Max column.
- 8 • Table 3-9: SEARCH monitors year-round.
- 9 • Figures 3-30/35: Possibly a couple more in Appendix. 3-83-20: The AM monitoring site
- 10 seems to be the real outlier to be discussed.
- 11 • 4-14-17/25 The choice of articles cited is rather (extraordinarily) strange. Choose the
- 12 classical and most influential ones.
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1 **Dr. Helen Suh**

2
3 **Response to Charge Question 3:** Chapter 2 presents the integrative summary and conclusions
4 from the O₃ ISA with detailed discussion of evidence in subsequent chapters. Is this a useful and
5 effective summary presentation? How does the Panel view the appropriateness of the causal
6 determinations?

7 **General Comments**

8 Chapter 2 is an effective and useful presentation of the health and welfare findings for ozone.

9 The Chapter clearly and cogently summarizes and integrates findings, successfully relating new

10 findings to those from the earlier 2006 AQCD and highlighting whether and how the new

11 findings support or contrast these earlier findings. The inclusion of welfare, climate change, and

12 UF-B effects in this summary chapter was welcomed. In general, the Agency's determinations

13 of causality were appropriate, with the exceptions of the causal determinations of "suggestive"

14 for the effects of short- and long-term ozone exposure on cardiovascular effects. The causal

15 determinations of "suggestive" for the effects of short- and long-term ozone exposure on

16 cardiovascular effects should be better justified or possibly revisited. Although findings from

17 toxicological studies provide some evidence of short- and long-term ozone impacts on

18 cardiovascular effects, very few epidemiological studies examining ozone-mediated

19 cardiovascular effects have been conducted, with their findings inconsistent (as summarized in

20 Section 6.3.2.9 and Section 7.3.3) and possibly confounded by PM_{2.5} or sulfates. Further,

21 substantial questions remain regarding the biological mechanisms by which ozone may impact

22 cardiovascular health. It is not clear from the criteria described in Table 1-3 whether together the

23 body of evidence is sufficient for a causal determination of "suggestive".

24 To serve as a more effective integrative summary, the Chapter would benefit from a

25 reorganization or more distinct delineation of the sections, with the primary goal to reduce

26 repetition of health findings. Section 2.6 (Integration of Ozone Health Effects) repeats much of

27 the health evidence presented in Sections 2.3.2 (Possible Pathways/Modes of Action) and 2.4

28 (Health Effects). Of the sections, I found Section 2.6 to be the best, as it was a cogent and

29 concise summary of our understanding of ozone health effects that integrated findings from the

30 different disciplines. Section 2.6 was enhanced further by its effective use of tables and figures

31 and by its noting of the ozone levels at which relationships or effects were observed. If the

32 Chapter were to be reorganized, it is possible that Section 2.4 and Section 2.3.2 could be

33 replaced by Section 2.6, with the summary tables of causality determinations (Tables 2-1 and 2-

34 2) kept at the beginning of Section 2.6. Absent of a reorganization, the purpose of the sections

35 should be more narrowly defined to minimize their overlap.

36 **Specific Comments**

37 • *Study Citations:* Study citations should be included for the best of the relevant studies and for
38 major statements (for example, the sentence beginning "recent studies in humans and animal
39 models..." on Page 2-20, line 6-7). Such citations would help connect the summary to later
40 discussions and would provide more scientific context.

41 • *Exposure Error:*

42 ○ Page 2-13, lines 36-39; Page 2-16 lines 13-15: The document states that "Taken together,
43 results from previous and recently published studies indicate that while...O₃

44 concentrations measured at central-site monitors are representative of day-to-day changes
45 in average personal O₃ exposures. This conclusion does not follow the preceding phrase

- 1 nor is well supported by the scientific literature. The agency should either revisit its
2 conclusion or provide a better basis for its conclusion.
- 3 ○ Page 2-15, lines 21-25: The phrase beginning “although this may be less of an issue for
4 ozone ...” appears to contradict findings of intra-urban, traffic-related variability in ozone
5 levels. Since many epidemiological studies are based on MSAs, with populations living
6 in both urban and suburban environments, it is not clear that this is less of an issue for
7 ozone as compared to other pollutants. Further, evidence from Atlanta study may not be
8 directly applicable, given that an alternative explanation could be that ozone is not related
9 to changes in HRV in this study.
- 10 ○ Page 2-15, lines 27-29: Even though ozone may exhibit low spatial variability in
11 comparison to CO and NO_x, ozone may still vary enough spatially to impact
12 epidemiological studies and exposure error. Further, issues related to confounding in
13 epidemiological studies have to do more with PM_{2.5}, for which spatial variability is less
14 than that for ozone.
- 15 ● *Diagram:* Page 2-17, Section 2.3.2: This section would benefit from a flow diagram or other
16 figure, such Figure 2-2, describing the possible pathways and modes of action by which ozone
17 causes damage. The addition of such a diagram again speaks to the need for possible
18 consolidation of section 2.3.2 with section 2.6.
- 19 ● *Organization:*
- 20 ○ Page 2-24, lines 4-12: This section includes discussion of ozone-related impacts on
21 respiratory mortality, which is misplaced and may confuse the reader with regard to the
22 causal determination that follows, which does not include mortality.
- 23 ○ Page 2-25, lines 8-14: This section includes discussion of ozone-related impacts on
24 cardiovascular mortality, which is seemingly misplaced. Since ozone-mediated
25 cardiovascular mortality impacts were considered in the causal determination for O₃ and
26 cardiovascular effects, it is possible that this section of the chapter should be reorganized
27 to improve its flow.
- 28 ○ Page 2-28, Section 2.4.2.1: This section should be reorganized to make a clearer case
29 supporting the Agency’s causal determination. For example, lines 7-13 should be
30 incorporated into the paragraph beginning on line 19, as they discuss the same effects. In
31 addition, the evidence from rodents and primates was not introduced in this section, but
32 referred to here.
- 33 ○ Page 2-29, lines 23-27: The sentence beginning “Although questions exist...” refers to
34 possible modes of action, which should have been first introduced in Section 2.3.2.
- 35 ○ Page 2-29, Section 2.4.2.3: Section 7.4.10 is essentially the same section. It, however,
36 summarizes and supports the causal determination of the impact of ozone on reproductive
37 and developmental effects more effectively in almost the same amount of space.
- 38 ● *Potential for Confounding:* Page 2-25, Section 2.4.1.2: his section should discuss the
39 potential for confounding of ozone-mediated cardiovascular effects by other pollutants and
40 acknowledge the general lack of studies investigating this issue.
- 41 ● *Susceptible Populations:* Page 2-25, lines 6-8: This sentence about susceptible populations is
42 conjecture and should be rephrased.
- 43 ● *Cardiovascular Effects:* Page 2-25, lines 17-19: The literature examining the relation
44 between ozone and HRV is mixed. A phrase or sentence to this effect should be added.

Deliberative Draft Letter to be discussed on July 6, 2011 Teleconference of the CASAC Ozone Review Panel. Do not cite or quote. This draft has not been approved by the chartered CASAC nor does it represent EPA policy. Updated 6-17-11.

- 1 • *Mortality*: Page 2-26, lines 15-18: This section should clearly state whether research post-
- 2 2006 more fully established the underlying mechanisms by which ozone contributes to
- 3 mortality. If so, what are these mechanisms?
- 4 • *Welfare Impacts*: Section 2.7 would benefit from the addition of information about the ozone
- 5 levels at which the adverse impacts were observed.
- 6 *Climate Change*: A summary causal determination table is missing.

1 **Dr. James Ultman**

2
3 **Chapter 5. Dosimetry and Mode of Action(rev. 5/19/2011)**

4
5 This chapter does a good job of integrating new literature on O₃ dosimetry and mode-of-action
6 and its integration with the literature available in the 2006 ACQD. In general, sufficient detail is
7 presented to serve as a background for the health risk assessment. However, the first part of the
8 chapter on dosimetry is essentially disconnected from the second part of the chapter on mode-of-
9 action. An implied by link is O₃ reaction with ELF substrates that simultaneously augments the
10 uptake O₃ and the production of toxic byproducts that can reach epithelium. Perhaps an overall
11 chapter introduction should explain why the two topics are presented in the same chapter. How
12 about a figure showing the continuum between O₃ exposure concentration → inhaled dose → net
13 dose → tissue dose → mode-of-action → health effect?

14
15 I think there needs to be one place in section 5.1.3 (Possibly, the paragraph beginning on line 9
16 on page 5-8) where all the dosimetry terms used in the chapter are carefully defined and
17 compared. The terms you might include are: flux, absorbed fraction, absorption efficiency,
18 inhaled dose, net dose and tissue dose.

19
20 The material on O₃-ELF reactions as presented in sections 5.1.2 and 5.2.2 are overly redundant.
21 I recommend that the former section focus on issues that are primarily directly connected to
22 dosimetric aspects (*e.g.*, the structure of kinetic rate equations, rate constant values of different
23 substrates, and diffusion-reaction models that estimate O₃ penetration into ELF). The latter
24 section should be more concerned with issues that influence mode-of-action (*e.g.*, mechanisms of
25 the O₃-ELF substrate reactions and the toxicology of the possible reaction products).

26
27 There is a lack of clarity regarding the effect of breathing pattern changes on O₃ uptake. For
28 example, figure 5-3 indicates that O₃ uptake efficiency among different subjects decreased with
29 increasing breathing frequency. The figure caption fails to point out that the subjects were
30 coached to maintain the same minute volume. Thus, the decrease in frequency was also
31 accompanied by an increase in tidal volume.

32
33 Also, given the potential importance of exercise on physiological responses to O₃, I suggest that
34 the subsection on “Physical Activity” (page 5-14) more fully discuss the specific breath patterns
35 (*e.g.*, frequency and tidal volume) associated with different exercise levels. For example, a
36 change from low to moderate exercise level is accompanied primarily by a change in tidal
37 volume whereas an increase in frequency becomes more important when exercise increases from
38 moderate to heavy levels. Based on past dosimetry measurements and dosimetry models, how
39 do these different breathing patterns at different exercise levels expected to affect ozone uptake
40 and uptake distribution?

41
42 *Page:Line, Table or Figure*

Specific Comments and Suggestions

43
44 5-4:3 Perez-Gil work was published after 2006.

- 1 5-7:8 to11 It is unlikely that O₃ molecules are reacting in the gas phase since the
2 substrates are not volatile. Perhaps, the concept to stress is the large surface to volume ratio of
3 microdrops that may promote an interfacial reaction that is not evident from previous studies that
4 used bulk liquid phase bioreactors.
5
- 6 5-9:1 Change “lung” to “lung epithelium”
7
- 8 5-10:20 to 22 Replace sentence “Uptake...concentration” with “Uptake efficiency is
9 changed by a number of variables including O₃ exposure concentration, exposure time and
10 breathing pattern. For breaths of similar waveforms, respiratory patterns are uniquely described
11 by frequency (f_B) and tidal volume(V_T), by minute volume(MV=f_V×V_T) and f_B, or by MV and
12 V_T. Respiratory flow that is directly related to MV is less frequently used.:
13
- 14 5-10:25 The statement about Overton’s simulations that “fraction uptake increased
15 with V_T” does not indicate whether f_B, MV or neither were held constant.
16
- 17 5-10:25&26 Subjects in the Ultman study targeted a fixed MV so that increases in V_T
18 were accompanied by decreases in f_B. I think that breathing in Gerrity’s study was
19 unconstrained.
20
- 21 5-10:28 Change “...the lung.” to “the lung at a particular MV.”
22
- 23 5-10:28 & 29 The sentence “While...f_B.” is no longer needed if previous suggested
24 changes are made.
25
- 26 5-10:30-32 Change the sentence “Nasal...(Fig. 5-3).” to “Nasal O₃ uptake is inversely
27 proportional to flow rate (Santiago) so that an increase in MV will increase O₃ delivery to the
28 lower airways. At a fixed MV, increasing V_T (corresponding to decreasing f_B) drives O₃ deeper
29 into the lungs and increases total respiratory uptake efficiency (Fig. 5.3).
30
- 31 5-10:32-33 State whether V_T or MV (or neither) was kept constant in Overton’s
32 simulations.
33
- 34 5-11: fig 5-3 Change graph and caption labels uniformly to either “uptake fraction” or
35 uptake efficiency.”
36
- 37 5-11: 11 to 12 The portion of the sentence “This...inlet air...” is not accurate. Ozone
38 uptake fraction (or efficiency) is normalized by the amount of O₃ in inhaled air. Thus, when
39 diffusion and reaction rates are proportional to O₃ concentration, O₃ uptake fraction is
40 independent of inhaled O₃ concentration. On the contrary, O₃ uptake is an unnormalized
41 quantity that will be proportional to inhaled O₃ concentration when diffusion and reaction rates
42 are linear (Actually, Santiago did find a slight negative dependence of uptake efficiency on inlet
43 O₃ concentration. Still, one can conclude from her results that the transport processes are
44 essentially linear with respect to O₃).
45

- 1 5-11: 16&17 The beginning of the sentence “Increased f_B will shift the O_3 uptake....”
2 should read “Decreased f_B at a fixed penetration volume will shift O_3 uptake...
3
4 5-12:14 &15 The sentence “Similarly...efficient” doesn’t make sense to me since
5 fractional O_3 uptake by the respiratory tract is essentially equivalent to O_3 uptake efficiency.
6 You might want to remove this statement.
7
8 5-13:6 This sentence makes more sense if “ O_3 uptake by the respiratory tract” is
9 replaced by “ O_3 induced responses such as FEV_1 .
10
11 5-15:32 Define MCA, CSA2 and CSA3.
12
13 5-16:5 Change “...in smokers...” to “...in smokers during continuous O_3
14 exposure.”
15
16 5-16:13 Change sentence “Fractional absorption will decrease with increasing f_B
17 and decreasing V_T when MV is held constant.”
18
19 5-17:13 Change “structure” to “structure and ELF chemistry.”
20
21 5-54:11&18 These sentences are repeated, word for word.
22
23 5-55:4 Change “extrapulmonary effects of O_3 ” to “extrapulmonary effects of
24 relatively high levels of O_3 exposure.
25
26 5-61:4 Define CAPS
27

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

This chapter contains a large amount of information, and the authors are to be commended on both the organization and the clarity of writing. There are only a few possible improvements that I would like to suggest.

First, the exposure-response curve in figure 6.1 that is obtained from McDonnell's publication provides strong support for the response data from laboratory research on humans at low exposure concentrations. Thus, more detail concerning the nature of the model and data utilized to estimate the model parameters should be given in this chapter.

Second, many of the pulmonary function responses in section 6.2 are reported as pre-to-post exposure changes in an endpoint relative to that observed in filtered air; this is referred to as "O₃-induced response." Frequently, pulmonary function of subjects who are exercising and breathing filtered air improves relative to pre-exposure measurements. Thus, O₃-induced response might be significantly larger than the corresponding pre-to-post changes in an endpoint. Because of this, I feel that the chapter needs to contain some specific information comparing pre-to-post responses to O₃ with the corresponding O₃-induced responses that are referenced to filtered air.

Third, I think that many of the graphs comparing epidemiological studies with different endpoints placed above a single abscissa (figures 6-3 to 6-11) are confusing. I think it would be better if studies were grouped above different abscissa's, each having a range of values that is logical for the endpoint in question.

Page:Line, Table or Figure

Specific Comments and Suggestions

6-6:35	Remind reader what is meant by "inhaled dose."
6-6:36	Units on dose rate should be in "ppb per unit time."
6-8:15 to 17.	Does this sentence imply that a threshold exposure concentration is possible?
6-10:10	I don't think that "clinically meaningful" can be equated to an adverse health effect. Can you be more precise in your understanding of this term?
6-13:11	Define SES.
6-19:8	I couldn't find the values 0.76 and 48 in table 6-2.
6-20: Fig. 6-3:	I suggest breaking this down into two graphs with unique units on their abscissa's. The present use of a single abscissa that accommodates two different units does not help me compare the results of the studies with two different endpoints.
6-27: Fig. 6-6	Please give the rationale in the text for the standardization stated in this and several other figure captions.

1 **Dr. Sverre Vedal**

2
3 **Charge Question 2:** *The framework for causal determination and judging the overall weight of*
4 *evidence is presented in Chapter 1. Is this framework appropriately applied for this O3 ISA?*
5 *How might the application of the framework be improved for O3 effects?*

6 1. Causation.

7 Causes do not need to be “significant” (1-14. line 1); the term is also ambiguous. So, this
8 definition in essence relies on the term “effectual” (as in effectual relationship) to define
9 causality. Not a very informative (as in “cause and effect,” therefore a little circular) or useful
10 definition. Couching the definition of causality in counterfactual terms, as alluded to in line 5, is
11 arguably the most informative. This incorporates the notion of “all else being equal” and is most
12 readily operationalized, reflecting what is attempted in both experimental (e.g., control
13 exposures) and observational (e.g., control of confounding) studies.

14 2. Confounding and effect modification.

15 The concepts of confounding and effect modification are more clearly expressed in this
16 ISA. Including a discussion of multiple pollutants in this context (1-16, lines 8-13) is
17 appropriate, but it needs to be made clear that what is being developed here is the notion that
18 ozone effects might be confounded by effects of other pollutants, which is not clear from the
19 discussion.

20 The discussion of effect modification should define it (e.g., differences in the effect of
21 exposure [ozone] by differences in another factor) before launching into a discussion of how it
22 differs from confounding. Also, temperature is presented as a potential effect-modifier, but it
23 might be valuable (and less confusing) to contrast how temperature is also (and more
24 importantly) a potential confounder. Essentially, effect modification refines our understanding
25 of the effect of an exposure while confounding addresses whether an effect is actually present, or
26 what the size of that effect is, if present.

27 The discussion of measurement error (1-17, para 3) should refer to ISA Chapter 4,
28 especially 4.5.1 “Exposure Measurement Error” and 4.6. The discussion here in this context
29 (confounding) is merely confusing. The point should be that measurement error that differs in
30 degree across pollutants complicates interpretation of individual pollutant effect estimates in
31 multi-pollutant regression models – effects of pollutants that are measured with less error can
32 dominate effects of other pollutants, even though their effects may in fact be weaker.

33 3. Causality determination and weighing evidence.

34 The Hill “criteria” are listed in Table 1-2. Coherence also refers to findings across
35 epidemiological study designs, not just between epidemiological, toxicological and other
36 experimental studies. It is noteworthy that presence of exceptions to each of the “criteria,”
37 except temporality, is still consistent with causality (Rothman).

38 The weighing of evidence to come up with a causality grade is reasonable. This worked
39 reasonably well in the context of PM. I like the inclusion of a “not likely to be a causal
40 relationship” category in this version – it maintains symmetry.

41 I’m not sure that studies with concentrations “within an order or two of ambient” (1-22,
42 line 5) concentrations are relevant for causality determination. This would imply that for, say, an
43 ozone concentration of 0.070 ppm, findings from studies of 7.000 ppm would be relevant. I
44 doubt that.

45 4. Effects on human populations.

1 The shape of the exposure-response relationship is influenced by the degree of
2 measurement error, as touched on (1-23, line 8). Specifically, measurement error at lower
3 concentrations can obscure a threshold and make it appear that a linear relationship extends to
4 lower concentrations (Brauer M et al. Exposure misclassification and threshold concentrations
5 in time series analyses of air pollution health effects. *Risk Anal* 2002; 22: 1183-1193). This
6 could potentially be a particularly important issue for pollutants such as ozone that exhibit large
7 degrees of measurement error.

8 I am happy to see a discussion of publication bias included in this ISA (1-23) and the
9 reference to Ioannidis, 2008. The observation that publication bias in the case of ozone may not
10 be so important (1-23, line 27) is contradicted by the work of Bell showing substantial difference
11 in ozone effect estimates from meta-analyses of published studies and multi-city study effect
12 estimates.

13 The discussion of susceptibility indicates that the term here will be used in a general sense
14 to include both susceptibility and vulnerability, terms that include both disease risk factors and
15 factors that increase exposure (1-23, line 36) and therefore risk.

16 17 5. Adversity.

18 The discussion of adversity is appropriate to include here. There is no discussion, however,
19 of the types of endpoints that are more problematic in a discussion of adversity, such as markers
20 of inflammation or oxidative stress, for example.

21 Specific.

22
23
24 1-13, line 15. It is not clear that the type of important evidence would vary by pollutant – It
25 would vary if this were based on the availability of evidence for different pollutants, but I would
26 think the important evidence should be pretty much the same, given findings across multiple
27 lines in inquiry.

28
29 1-15, line 35. While this is true, clinical studies also have the potential of overestimating effects
30 when exposures used (concentration or intensity) are seldom experienced in the real world.

31
32 1-16, lines 29-31. Drop this unless you intend to be inclusive, since effect modifiers can be
33 found in many other settings than these in air pollution epi studies.

34
35 1-16, line 33. Some approaches to controlling confounding are very satisfactory. I think what
36 may be intended here is that approaches to controlling co-pollutant confounding are not very
37 satisfactory.

38
39
40

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1 **Charge Question 5.**

2 *Chapter 4 describes human exposures to O3. Is the evidence relating human exposure to ambient*
3 *O3 and errors associated with exposure assessment presented clearly, succinctly, and*
4 *accurately? Do the characterizations of temporal and spatial variability of O3 in urban areas*
5 *provide support for better understanding and interpreting epidemiologic studies discussed later?*
6

7 4-21, lines 1-5. This makes it seem that exposure measurement issues are not so important for
8 ozone, whereas they are probably more acute for ozone than for any other pollutant.
9

1 **Dr. Kathleen Weathers**

2
3 *Question 10: Chapter 9 describes effects of O₃ on vegetation and ecosystems. Are the major*
4 *effects of O₃ exposure on vegetation and ecosystems identified and characterized? To what*
5 *extent do the discussions and integration of evidence across scales (e.g., species, communities*
6 *and ecosystems) correctly represent and clearly communicate the state of the science? Has the*
7 *ISA adequately characterized the available information on the relationship between O₃ exposure*
8 *and effects on individual plants and ecosystems? Are there subject areas that should be added,*
9 *expanded upon, shortened or removed?*

10
11
12 In general, I think that this chapter is quite clear, and clearly presented; it describes in some
13 detail the major effects and pathways that ozone impacts species and ecosystems. It was helpful
14 that the new knowledge-- and to what extent this information supported (or did not) previous
15 ISA conclusions --was identified in the text. It appears, however, that there is little additional,
16 directly relevant (to standard setting) scientific literature that has been published since the last
17 ISA. Nonetheless, the last part of Chapter 9, where the newly-published data and studies were
18 integrated and compared was quite useful.

19
20 While a significant part of the chapter was focused on the results from new tools that reveal
21 physiological mechanisms of damage due to ozone, and there was some redundancy among
22 sections, I did not find it problematic.

23
24 General and specific comments:

25 It would be useful to include a conceptual diagram of how ecosystem processes (the flow of
26 energy, materials and information—e.g., productivity and nutrient cycling) have been shown to
27 be, or are likely to be affected, based on the research presented. To wit, I found Figure 9.1 to be a
28 bit too simple, somewhat misleading and overly descriptive; I think that actual effects on
29 processes at interacting plant, community and ecosystem scales could be demonstrated, even
30 when there is still considerable uncertainty. Many of the processes shown in the “plant” scale,
31 for example, are those that are central to biogeochemistry/ecosystem fluxes of nutrients (e.g.,
32 decomposition). Similarly, many of the processes outlined in Table 9-1 are linked (reduced
33 productivity and C-sequestration, for example). In fact, later in the chapter, Figure 9.7 might be
34 reused and modified to illustrate relative magnitudes of ozone effects (based on the literature).

35
36 “Scale” should be defined when it is used throughout the document—spatial, temporal, or?
37 I found water production to be awkward phrasing. Water redistribution might be a better way to
38 characterize this “ecosystem service” (page 9-3).

39
40 The meta analyses that have been performed since 2006 are quite important to this ISA. They are
41 central to “what’s new” in this document. Some clarification about those results is needed, for
42 example, do the results from the meta analysis (page 9.8) refer to current annual average ambient
43 concentrations?

44
45 9-64: I’m confused about the sentence that starts with “Conversely” on line 25.

1 9-68: The description and definition of ecosystem could be strengthened. What's most important
2 is that ecosystems "have" boundaries—they are defined by the researcher (or whomever is
3 discussing an ecosystem), and are often connected to some physical process (e.g., watershed),
4 but it is an important part of the ecosystem concept.

5
6 I suggest adopting, or at least comparing/examining The Millennium Ecosystem Assessment's
7 definition and description of ecosystem services (9-69).

8
9 See my general comment about use of "scale" throughout the ISA. It would be useful to include
10 the range of spatial scales inferred on 9-69, line 24.

11
12 9-69: I'd get rid of the first line on line 24—it suggests that ecosystem effects are the sum of the
13 (plant) parts, which is unlikely to be true. Storage and transformation of carbon in an ecosystem,
14 for example, often has much to do with microbial function in the soil as it does with plant
15 fixation and respiration.

16 9-70: Again—see my comment about scale (line 2)—there's nothing that suggests that
17 ecosystems have to be large in spatial scale.

18 9-70: "Stand" should be modified, e.g., "forest stand," and, it is not a set spatial scale.

19 9-71: Zelig. MOSES-TRIFFID, etc. should be very briefly described, or at least classified (as in
20 section 9.6.2). In fact, Table 9-5 should include both "spatial" scale in the column header and
21 perhaps another column for the models that give a descriptor of the type of model. Further, a
22 table of models in the ecosystem/landscape section, their classification (in this ISA), and a
23 column that describes the primary mechanism invoked (e.g., 9-75, lines 13 and 14) would be a
24 useful addition.

25 Figure 9-7 could/should indicate that litter quality can be affected (e.g., C:N) in addition to litter
26 inputs (amount) to the soil. It's in the text, and should be in the figure. Further, Table 9-6 might
27 include not just the effect on various metals or nutrients ("response" column), but also the
28 carbon:nutrient or metal effect, if it was reported.

29 9-82, line 1: This section might start with a brief introduction to mineralization, and then note
30 that nutrient cycling is a fundamental ecosystem function. Nitrogen is thought to be the limiting
31 nutrient for most temperate terrestrial ecosystems.

32 9-85: I'm confused that a lysimeter (used to collect soil water) study was used to
33 examine PLFA profiles. Qualify and/or describe.

34 The description of the UNECE critical levels and differences between the UNECE and US in
35 setting standards and planning targets for reductions is a useful and interesting
36 contrast/discussion.

37 The Table legend and column labels in Tables 9-11 and 9-13 should be clearer in regard to the
38 relative numbers (e.g., relative = ratio of elevated to ambient), or convert them to percentages
39 and identify them as such.

40 It would be helpful to add a comparative column in Tables 9-12, 1-13 and 9-14 that contrasts
41 directly the methods/results.

42 And, to further reinforce the results of these comparisons, I suggest adding some measure of
43 "notably close" (page 9-135, line 2) in parentheses in the text.

44 9-125: "Nuisance variables...now there's a euphemism for the research world!"

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- 1 Adding a column that shows the general result of the meta-analyses listed in Table 9-15 would
- 2 be useful as well.
- 3 Overall, I was struck by the fact that there remains a paucity of data and research about the
- 4 impact of ozone in real field situations and/or that is useful to standard setting. The recent
- 5 biomonitoring results and programs notwithstanding; much important monitoring and research is
- 6 yet to be done.

1 **Dr. Peter B. Woodbury**

2
3 **Chapter 9 Comments**

4 **Charge Question:** Are the major effects of O₃ exposure on vegetation and ecosystems identified
5 and characterized?

6 In general terms, yes.

7
8 **Charge Question:** To what extent do the discussions and integration of evidence across scales
9 (e.g., species, communities and ecosystems) correctly represent and clearly communicate the
10 state of the science?

11 In general the discussions do represent the state of the science, a few specific suggestions
12 are presented below.

13
14 **Charge Question:** Has the ISA adequately characterized the available information on the
15 relationship between O₃ exposure and effects on individual plants and ecosystems?

16 In general terms, yes. The comparison of exposure response from the NCLAN and
17 NHEERL studies with recent SoyFACE and Aspen FACE results is particularly useful as it
18 clearly confirms that both approaches provide extremely similar results. The fact that these
19 comparisons are so extremely close is quite important because it provides very strong evidence
20 that we can have confidence in using these exposure response functions to estimate effects across
21 multiple species and varieties and across multiple regions of the county.

22
23 **Charge Question:** Are there subject areas that should be added, expanded upon, shortened or
24 removed?

25 It is difficult to strike the balance of being reasonably comprehensive, but not excessively
26 long. The summary in Chapter 2 helps this issue by providing a brief summary of key results.
27 The summary at the beginning of the chapter was initially confusing to me, but I think it should
28 be retained because it is more thorough than the initial summary in Chapter, and provides key
29 citations.

30
31 **Additional Chapter 9 Comments**

32 Page-Line

33 9-74. Table 9-5 should include “modeled” in the title.

34
35 9-71. Section 9.6.2.2. A more critical discussion and interpretation of model results would be
36 useful. This draft just briefly lists a main conclusion from each of a number of studies. However,
37 the models discussed are very different in scope and complexity. Some models represent all
38 vegetation as a single “big leaf”. Other studies use detailed physiological models of single trees
39 linked to stand-level models to represent competition among individual trees of different species.
40 Not surprisingly, such different models produce different results. A more critical discussion
41 focusing on the strengths and weaknesses of different approaches would be much more useful.

42
43 9-75. A more critical discussion of the differences in effects of ozone on transpiration from
44 different models and from different experiments is warranted, focused on likely effects on
45 streamflow at the catchment scale. Many such studies are discussed, including studies of tree

1 seedlings, mature trees in forests, and various modeling studies. But further critical discussion to
2 clarify reasons for discrepancies among such studies is warranted as this is an important topic
3 and with substantial supporting literature.

4
5 9-77. Better resolution for Figure 9-7 and other figures would make them easier to read.
6 Additionally, the font on some of the smaller text in figures could be increased.

7
8 9-77. In Figure 9-7 and many other figures, an erroneous box appears often overlapping with
9 the first letter of a sentence.

10
11 9-83. A more critical discussion of effects of ozone on forests, including the sacred fir forests
12 in Mexico and forests in the Carpathian Mountains is warranted. The text briefly mentions that
13 there are potentially confounding variables such as drought, but further discussion of the strength
14 or weakness of the evidence for ozone effects is warranted.

15
16 9-90. Line 26-28 regarding pheromones does not fit within the subheading topic.

17
18 9-96. Line 10. There is a typo here and elsewhere for the citation – see “MEMberson”

19
20 9-114. In the legend for Equation 9-2, there is an erroneous box.

21
22 9-122. Line 4. Change “between prediction” to “between these predictions”.

23
24 9-122. Please clarify the 2 scaling methods. For example, on Line 24, are data from the
25 SoyFACE study used in the scaling?

26
27 9-123. Table 9-12. Move column headings to match those in Table 9-11.

28
29 9-127. Table 9-14. Aligning data on decimal point, eliminating the 10ths place, and adding a
30 comma for the thousandths place would improve readability.

31
32 9-131. Would it be possible to compare one of more of the recent meta-analyses to the NCLAN
33 and NHEERL data by using a concentration metric to interpret the NCLAN and NHEERL
34 results? Obviously, this is not as useful as comparing them using a metric such as W126, but
35 would be better than no comparison at all.

36 37 **Chapter 10 Comments**

38 **Charge Question:** What are the views of the Panel on the scientific soundness and usefulness of
39 the discussion in Chapter 10 on the role of O₃ in global climate change and changes in mean
40 global temperatures?

41 In general, this chapter is useful, but this is a complex topic, with many interactions
42 among gases, for example ozone concentrations can affect methane concentrations. Additionally,
43 there may be important effects of ozone at the regional or continental scale in addition to the
44 global scale, as discussed on Page 10-12. Could such regional impacts be additional to the range
45 of impacts on radiative forcing cited from IPCC? If so, this topic warrants further discussion.

1 There could also be effects of climate change on circulation, thus on mixing of
2 stratospheric ozone into the troposphere, although effects on surface-level ozone might not be
3 large.

4 There may be complex feedbacks with vegetation, but there are substantial uncertainties
5 in modeling such feedbacks due to limitations of models and heterogeneous responses of
6 different types of vegetation to various aspects of climate change. For example, the publication
7 by Sitch et al. (2007) may not adequately include the variation in response to ozone among
8 genotypes within a species and among species. As discussed in Chapter 9, numerous
9 experimental and modeling studies support the observation that in mixed-species communities,
10 some species may increase growth in response to increased ozone exposure due to competition
11 with species or genotypes that are more sensitive to ozone. Thus it is too simplistic to assume
12 that ozone will decrease the growth of vegetation communities composed of mixtures of species,
13 growth (and CO₂ uptake) may not change if less sensitive species grow more quickly when
14 released from competition by more ozone-sensitive neighbors.

15 As discussed on Page 10-8, models currently seem to overestimate preindustrial ozone
16 concentrations, indicating a lack of data, inadequate parameterization, or lack of inclusion of key
17 processes in ozone chemistry models. Such uncertainty implies that there is substantial
18 uncertainty about non-anthropogenic ozone concentrations. Discussion of this topic in relation to
19 the policy-relevant background may be warranted.

20 The conclusion that there is a causal relationship between tropospheric ozone and
21 radiative forcing is warranted based on the scientific literature, as is the conclusion that there is
22 likely to be a causal relationship between tropospheric ozone and climate change.

23
24 **Charge Question:** Is there any information regarding the climatic effects of domestically
25 produced O₃ on climate in the U.S. that should have been included?

26 As mentioned above, further discussion of potential regional and continental effects of
27 ozone on radiative forcing and climate may be warranted.

28
29 **Charge Question:** Is there important new information on UV-B effects or other welfare effects
30 such as materials damage that have been overlooked and should be incorporated into this
31 chapter?

32 To my knowledge, the discussion of these topics is adequate.
33
34
35