Comments to the Clean Air Scientific Advisory Committee Ozone Panel on the Document:
Second External Review Draft Integrated
Science Assessment for Ozone and Related Photochemical Oxidants
(EPA/600-R-10/076B) (Released September 30, 2011)

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Summary

The "Second External Review Draft Integrated Science Assessment for Ozone and Related Photochemical Oxidants" incorporates modest revisions to the First Draft which the CASAC Ozone Panel reviewed and commented on earlier. The Ozone Panel, both collectively and individually, offered substantial comments for improving the Integrated Science Assessment. However, in many areas the EPA failed to adequately consider excellent advice provided by the Ozone Panel. At the time the Ozone Panel reviewed the First Draft Integrated Science Assessment (May 20, 2011 and July 6, 2011 with a letter to the EPA Administrator dated August 10, 2011), the Agency was still advancing the "reconsideration" Ozone NAAQS. The "reconsideration" proposal was subsequently withdrawn on the advice of the Office of Management and Budget and President Obama's decision to not approve it.

Many members of the current Ozone Panel supported revision of the Primary Ozone NAAQS in the range of 70 to 60 ppb (highest 8-hour average with no change in the form). This places a special responsibility on the Panel Members to review the Integrated Science Assessment in an impartial manner without giving deference to their previously stated views on the policy outcome of the Ozone NAAQS review process. I urge the Panel to critically review the Second Draft paying special attention to the extent the Agency has, or has not, responded to the guidance offered in the Panel's letter of August 10, 2011, including the numerous excellent comments of individual Panel Members. I urge the Panel to avoid focusing excessively on developing "consensus" statements on the four elements of the NAAQS; (a) indicator, (b) averaging time, (c) concentration and (d) form. I make this point since I am concerned that some Panel Members have given undue attention to the level of the NAAQS and not adequately considered how the level for a given indicator (Ozone) must be considered in association with the averaging time and form.

Introduction

I am pleased to offer these comments to the CASAC Ozone Panel on the Second Draft (September 2011) of the "Integrated Science Assessment for Ozone and Related Photochemical Oxidants," hereafter referred to as the ISA (EPA/ISA, 2011). As detailed in the "Integrated Review Plan for the Ozone National Ambient Air Quality Standards," (EPA/IRP, 2011) hereafter referred to as IRP, the ISA plays a central role in the multi-phased process for reviewing the National Ambient Air Quality Standard (NAAQS) for Ozone. The ISA is intended to provide "a

concise review, synthesis, and evaluation of the most policy relevant science, including key science judgments that are important to the design and scope of exposure and risk assessments, as well as other aspects of the NAAQS review." The ISA is intended "to reflect the current state of knowledge" that "forms the scientific foundation for the NAAQS review and is intended to provide information useful in forming judgments about air quality indicator(s), form(s), averaging time(s) and level(s) for the NAAQS." The IRP notes that the ISA places emphasis on "information that has become available since the last air quality criteria review in order to reflect the current state of knowledge."

The comments I am providing are my own professional views on the adequacy of the ISA relative to the broad statement of intent for the ISA summarized above. These brief comments are intended to complement and summarize the comments I submitted to the EPA Ozone Docket on December 30, 2011 (McClellan, 2011a). Those comments are attached and include 3 papers that I believe will be of interest to the Panel. The papers are:

1. McClellan, R.O. "Role of Science and Judgment in Setting National Ambient Air Quality Standards: How Low is Low Enough?" *Air Quality Atmosphere Health*, published on-line June 1, 2011b. It is available on-line at http://springerlink.com/content/1873-9318/?k=McClellan or you may contact Dr. McClellan for a copy of the paper.

2. Rhomberg, L.R. et al., "Linear Low-Dose Extrapolation for Noncancer Health Effects is the Exception, Not the Rule," Crit. Rev. Toxicol. 41(1): 1-19, 2011. Available on-line at http://informahealthcare.com/doi/full/10.3109/10408444.2010.536524 or you may contact Dr. McClellan for a copy of the paper.

3. Carter, W.P.L. and Seinfeld, J.H. (2011). Winter Ozone Formation and VOC Incremental Reactivities in the Upper Green River Basin of Wyoming. Atmospheric Environment J. (in press). (You may contact Dr. McClellan for a copy of the paper).

Comments on NAAQS Review Process

Before offering comments on the ISA, I would like to offer some over-arching comments on the NAAQS Review Process as summarized in Figure 1.1 of the IRP.

It is apparent from the IRP and past experience, both the EPA staff (and its numerous contractors and consultants) and CASAC have central roles in the Review Process. The Agency Staff prepares the (a) Integrated Review Plan, (b) Integrated Science Assessment, (c) Risk/Exposure Assessment, (d) Policy Assessment, (e) draft proposal notice and (f) draft final notice of the rule. The latter two elements are intended to reflect both the science and scientific

judgments that are the basis of the rule and inform the policy judgments made by the EPA Administrator on the four elements of the NAAQS.

Science and Personal Preferences

In my opinion, the EPA staff (and their contractors and consultants) are not neutral, impartial participants in the review process. Each staff member brings to the process both their scientific, legal, or other professional expertise and their personal ideologies and preferences related to the final rule. For some of these individuals success will be defined by issuance of a more stringent NAAQS. I am concerned that for all of these documents the authorship of specific components is anonymous, i.e. the Agency speaking. The proposed and final rule is written in the voice of the EPA Administrator to conform to the specific requirements of the Clean Air Act. In my opinion, I think the authors should be identified for specific chapters in the documents that have the strongest science base, such as the ISA and Exposure/Risk Assessments. The present ISA identifies 76 individuals (Executive Directors, Scientific Staff, Technical Staff Support, Authors, and Contributors) as having a key role in its preparation and 41 individuals involved in its review. Most of the 28 authors and 41 reviewers were EPA staff. The desirability of having the authors (of individual chapters) identified has been noted in the past including comments made by CASAC Panel members.

The importance of identified authorship relates in part to recognition that the ISA is not merely a review and synthesis of the science, it is an "evaluation of the most policy relevant science, including key science judgments ---" as noted in the IRP. The Public has a right to know who is making the key science judgments documented in the ISA. Because the ISA does reflect judgments it is important that these specific judgments and how they were arrived at be clearly documented in the ISA.

The individual members of CASAC and the CASAC Panel are likewise not neutral, impartial participants in the Review Process. In making this comment, I am not questioning the scientific credentials of any current or past member of CASAC or CASAC Panels. These individuals typically have extraordinary scientific credentials and are drawn almost exclusively from academic, government or non-profit institutions.

In the case of some CASAC Panel members, the situation is complicated by their role in reviewing ISA that contains science they have conducted and reported in the literature. These individuals have a vested interest in seeing their findings used. As with Agency Employees, a

successful outcome for a particular NAAQS review may be viewed by some CASAC Panel Members as a more stringent NAAQS. In some cases, CASAC Panel members have previously expressed opinions on the need for more stringent standards. For example, 11 of the 23 members of this current CASAC Ozone Panel were part of the previous CASAC Ozone Panels that expressed the need for a more stringent standard, specifically a standard at the level of 60-70 ppb. Other members of the current panel have signed a letter that was sent to the Administrator again recommending a more stringent standard set at the level of 60-70 ppb. Such views are clearly not only interpretations of science but represent their personal preferences as to a particular policy outcome, a more stringent Ozone NAAQS.

Consensus Masquerading as Science

In recent years, CASAC and the EPA have increasingly focused on having consensus views expressed on the science that informs policy judgments on the setting of the NAAQS. In my opinion, the essence of science is not about achieving consensus, it is about clearly relating the richness of scientific information including areas of general agreement and areas of uncertainty as a basis for developing and testing of hypotheses and using science to inform public policy decisions. Consensus is a sociological phenomenon well-suited to religious, fraternal and political entities. Excessive reliance on consensus by science-based groups such as CASAC threatens to move science into the political arena and obscures the boundaries between science and policy preferences.

The credibility of the CASAC process is enhanced when each CASAC Panel member clearly documents in written comments their views on the science being considered in the review process.

The written comments attached to the CASAC August 10, 2011 letter were excellent. I look forward to seeing this high standard continued as the review process continues. In my opinion, CASAC in recent years has excessively depended on small writing groups, working outside of public view, to develop draft consensus statements for incorporation into the CASAC letters to the Administrator. This approach, as well as excessive use of teleconferences, reduces the public transparency of the NAAQS review process. The credibility of CASAC and its opinions is enhanced when all CASAC deliberations are conducted in public meetings with teleconferences used very sparingly.

Distinguishing Between Science and Judgment

At every step in the NAAQS Review Process it is important to make clear the interface between science and judgments. This is important for the documents prepared by the EPA staff and, equally as important, for the CASAC deliberations that are ultimately formalized in advisory letters to the EPA Administrator. My views on these matters are not restricted to CASAC Comments on the Policy Assessment and Proposed and Final Rules. The need for distinguishing between science and judgment certainly extends to the ISA and Exposure/Risk Documents since as the IRP notes, these documents do involve scientific judgments. These science judgments and how they were reached should be clearly documented.

Comments on Integrated Science Assessment

In my comments to the Ozone Docket, I noted a number of areas where the ISA could be improved. I was pleased to note that the CASAC Panel raised many of these same issues in its review (collectively and individually) of the First Draft of the ISA. The major areas of concern covered in my comments to the Ozone Docket are:

(1) Need for clarity in making decisions on "causality" classifications.

(2) Inadequate analysis of concentration-response relationships.

(3) Inadequate consideration of co-pollutants and other variables.

(4) Failure to clearly relate ozone metrics.

(5) Inadequate consideration of multiple factors in extrapolating findings in laboratory animals to humans.

(6) Inadequate consideration of concentration-response relationships for multiple mechanistic endpoints.

(7) Over-emphasis on observations on populations outside of the USA.

(8) Critical need for updating chapter in atmospheric chemistry with better recognition of the complex role of VOCs, NOx and solar ultra-violet radiation. The current chapter is inadequate, especially as regards the current understanding of ozone formation and degradation in the western USA (see the recent paper by Carter and Seinfeld) which is included as Appendix D in my "Comments on the Document: Second External Review Draft Integrated Science Assessment for Ozone and Related Photohemicals Oxidants" (McClellan, December 30, 2011) which are attached.

As the CASAC Ozone Panel completes its review of the Second Draft, and evaluates the need for yet another draft, special attention should be given to the adequacy of the science assessment for informing the rest of the review and, ultimately, policy judgments on all four elements of the NAAQS; (a) indicator, (b) averaging time, (c) concentration and (d) form. It appears a foregone conclusion that the indicator will be ozone and the averaging time for the Primary Standard will be the daily highest 8-hour average. In my view, there is a need for the Panel to more clearly consider how the science being evaluated informs the relationship between averaging time, concentration and form. As noted in the comments of Professor Armistead Russell on the First Draft, this issue needs more attention and, especially, as relates to consideration of Policy Relevant Background. I endorse his comments. However, in my opinion the discussion should address a range of 60 to 80 ppb, not just the 60 to 75 ppb range he noted. In my opinion, this issue was not adequately addressed when the Primary NAAQS daily highest 8-hour average) was revised from 84 ppb (with standard rounding convention) to 75 ppb.

The last issue I will note relates to the lack of contextual information within the document for the policy judgment decisions, informed by science, that the EPA Administrator must make as to "how low is low enough" when the four elements of the Primary NAAQS are considered together. These critical decisions will certainly be aided by an ISA that more clearly relating the quantitative impact of confounders such as co-pollutants. I would concur with the suggestion of one Panelist that such data for various endpoints should be displayed in tabular form along with the estimated concentration-response coefficients for ozone. Moreover, the document would be improved if it included scientific information on the occurrence of key endpoints in States and Communities across the USA and other known risk factors that are important in influencing the occurrence of the health outcomes being considered. It is important to recognize that review of the Ozone NAAQS and any potential revision made be carried out within a context of a multitude of factors that affect public health.

In my opinion, the deficiencies in the Second Draft ISA are sufficiently serious that I urge the CASAC Ozone Panel to recommend the development of a Third Draft Integrated Science Assessment. The present draft, even with modest revisions, will not provide a scientifically credible basis for informing the rest of the Ozone NAAQS review process.

References

Carter, W.P.L. and Seinfeld, J.H. (2011). Winter Ozone Formation and VOC Incremental Reactivities in the Upper Green River Basin of Wyoming. Atmospheric Environment J. (in press).

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McClellan, R.O. (2011b). Role of Science and Judgment in Setting National Ambient Air Quality Standards: How Low is Low Enough? Air Qual Atmos Health, published on-line June 1, 2011.

Rhomberg, L.R., Goodman, J.E., Haber, L.T., Dourson, M., Andersen, M.E., Klaunig, J.E., Meek, B., Price, P.S., McClellan, R.O. and Cohen, S.M. (2011). Linear Low-dose Extrapolation for Noncancer Health Effects is the Exception, Not the Rule. Crit. Rev. Toxicol. 41(1): 1-19.

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Summary

The "Second External Review Draft Integrated Science Assessment for Ozone and Related Photochemical Oxidants" is generally improved in scientific quality and completeness compared to previous Criteria Documents for Ozone. The document is encyclopedic in length (1442 pages) and in many areas does not provide a clear exposition of the science and scientific judgments needed to inform the ultimate policy judgments to be made by the EPA Administrator in reviewing the indicator, averaging time, level and form of the Ozone National Ambient Air Quality Standard (NAAQS) and considering any changes. An ISA that is scientifically credible and an associated credible review by the CASAC Ozone Panel will be difficult to achieve. A major difficulty relates to potential impartiality of the EPA staff and other individuals who authored the ISA and may be motivated by a personal desire to produce a document that will ultimately support a more stringent Ozone NAAQS than that introduced in March 2008. That impartiality extends to a substantial portion of the CASAC Ozone Panel members who are already on record as supporting a reduction of level of the primary NAAQS (highest 8-hour averaging time) to 70 ppb or lower while retaining the current form.

The document has a strong "causality" focus and to a more limited extent addresses the critical issue of the nature of the concentration-response relationship for key health endpoints. In my opinion, the concentration-response relationships are not given adequate attention. In particular, the document gives excessive credence to linear relationships extending to low ambient concentrations. Inadequate attention is given to the existence of practical thresholds as documented by an absence of statistical significant health responses in a number of large cities, especially in the Western USA.

The manner in which the document is written leads the casual reader to conclude that current ambient ozone concentrations, which have been substantially reduced over the last four decades, represent a serious health threat despite the very low estimated excess risks that have been observed. The document does not address the attributable risk of ambient ozone as one of the many factors responsible for key health endpoints. The document has a singular focus on Ozone with limited comparative analyses that would illustrate the role of other air pollutants and numerous other risk factors. In short, the document provides very limited context for evaluating the role of ambient ozone exposures as a public health risk. Such information will ultimately be

crucial to the Administrator's policy judgments in considering whether any changes in the current Ozone NAAQS are warranted.

Introduction

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The comments I am providing are my own professional views on the adequacy of the ISA relative to the broad statement of intent for the ISA summarized above. A copy of my biography is attached as Appendix A so the reader may be aware of my expertise and experience related to the material presented in the ISA. My views are heavily influenced by my service on EPA's original Science Advisory Board (SAB) Executive Committee formed soon after the Agency was created and service on numerous SAB Committees and Panels. That service included participation in the Clean Air Scientific Advisory Committee (CASAC) and related activities beginning soon after the Clean Air Act (CAA) was amended in 1970. That included service as Chair of CASAC and membership on numerous CASAC Panels reviewing specific criteria pollutant NAAQS. My last CASAC Panel participation was on the Particulate Matter (PM) Panel whose service concluded with issuance of the 2007 revision to the PM NAAQS. I offered comments to the EPA Ozone Docket and CASAC during the review process that concluded with the March 2008 revision of the Ozone NAAQS and termination of the "reconsideration" of 2008 Ozone NAAQS by President Obama on the advice of Cass Sunstein, Administrator of the Office

of Information and Regulatory Affairs (letter dated September 2, 2011). My views on those matters are summarized in a paper "Role of Science and Judgment in Setting National Ambient Air Quality Standards: How Low is Low Enough?" *Air Quality Atmosphere Health*, published on-line June 1, 2011. Related to copy right issues, it is not possible to attach the original paper. It is available on-line at: http://springerlink.com/content/1873-9318/?k=McClellan or contact Dr. McClellan for a copy of the paper (see Appendix B).

Comments on NAAQS Review Process

Before offering comments on the ISA, I would like to offer some over-arching comments on the NAAQS Review Process as summarized in Figure 1.1 of the IRP.

It is apparent from the IRP and past experience, both the EPA staff (and its numerous contractors and consultants) and CASAC have central roles in the Review Process. The Agency Staff prepares the (a) Integrated Review Plan, (b) Integrated Science Assessment, (c) Risk/Exposure Assessment, (d) Policy Assessment, (e) draft proposal notice and (f) draft final notice of the rule. The latter two elements are intended to reflect both the science that informs the policy judgments reflected in the rule and the policy judgments made by the EPA Administrator.

Science and Personal Preferences

In my opinion, the EPA staff (and their contractors and consultants) are not neutral, impartial participants in the process. Each staff member brings to the process both their scientific, legal, or other professional expertise and their personal ideologies and preferences related to the final rule. For some of these individuals success will be defined by issuance of a more stringent NAAQS. I am concerned that for all of these documents the authorship of specific components is anonymous, i.e. the Agency speaking. The proposed and final rule is written in the voice of the EPA Administrator to conform to the specific requirements of the CAA. In my opinion, I think the authors should be identified for specific chapters in the documents that have the strongest science base, such as the ISA and Exposure/Risk Assessments. The present ISA identifies 76 individuals (Executive Directors, Scientific Staff, Technical Staff Support, Authors, and Contributors) as having a key role in its preparation and 41 individuals involved in its review. Most of the 28 authors and 41 reviewers were EPA staff. The desirability of having the authors (of individual chapters) identified has been noted in the past including comments made by CASAC.

The importance of identified authorship relates in part to recognition that the ISA is not merely a review and synthesis of the science, it is an "evaluation of the most policy relevant science, including key science judgments ---" as noted in the IRP. The Public has a right to know who is making the key science judgments documented in the ISA.

Because the ISA does reflect judgments it is important that these specific judgments and how they were arrived at be clearly documented in the ISA. I will comment more on that issue later.

The individual members of CASAC and the CASAC Panel are likewise not neutral, impartial participants in the Review Process. In making this comment, I am not questioning the scientific credentials of any current or past member of CASAC or CASAC Panels. These individuals typically have extraordinary scientific credentials and are drawn almost exclusively from academic, government or non-profit institutions. Rarely are any individuals from the private sector invited to participate. As in the case of EPA employees and consultants, a central issue relates to the judgments involved in interpreting the science, and especially in reviewing its role in informing policy judgments on the four elements of each NAAQS (indicator, averaging time, level, and form) that must ultimately be made by the EPA Administrator.

In the case of CASAC and CASAC Panel members, the situation is further complicated by the role of many of these individuals in reviewing the ISA science the CASAC Panel Members themselves have conducted and reported in the literature. These individuals have a vested interest in seeing their findings used and, moreover, they have an interest in the prospects of future funding for additional scientific research. As with Agency Employees, a successful outcome for a particular NAAQS review may be viewed by some CASAC Panel Members as a more stringent NAAQS. In some cases, CASAC Panel members have previously expressed opinions on the need for more stringent standards. For example, 11 of the 23 members of this current CASAC Ozone Panel were part of the previous CASAC Ozone Panels that unanimously expressed the need for a more stringent standard, specifically a standard at the level of 60-70 ppb. Other members of the current panel have signed a letter that was sent to the Administrator again recommending a more stringent standard set at the level of 60-70 ppb. Such views are clearly not only interpretations of science but represent their personal preferences as to a particular policy outcome, a more stringent Ozone NAAQS. In the case of the current CASAC Ozone Panel, these views were expressed, even before the current review process was initiated.

The EPA Science Advisory Board staff presumably reviewed the background of each Panel Member and certified that they had no conflict of interest relative to service on the Panel. I wonder if the SAB Officer would have approved participation by an individual who advocated a less stringent standard for Ozone.

In my opinion, the public credibility of the NAAQS review by the CASAC Ozone Panel would be substantially strengthened if at the beginning, and at key junctures, in the process for each NAAQS review, each CASAC Panel Member were required to relate in a public session a "declaration of interest" and make a statement of impartiality on the issue at hand. This statement could include any previous oral or written statements by the Panel members on the indicator, averaging time, level and form of the Standard. It would also be appropriate for the Panel members to note they can address scientific issues in an impartial manner. I have purposefully used the phrase – "declaration of interest" rather than "conflict of interest." In my opinion, "conflicts of interest" are in the eye of the beholder, they are not exclusively interpreted by the individual Panel Member or the Agency official providing oversight for Conflicts of Interest decisions.

Consensus Masquerading as Science

In recent years, CASAC and the EPA have increasingly focused on obtaining and expressing consensus views on the science that informs policy judgments on the review and setting of the NAAQS. In my opinion, the essence of science is not about achieving consensus, it is about clearly relating the richness of scientific information including areas of general agreement and areas of uncertainty as a basis for developing and testing of hypotheses and using science to inform public policy decisions. Consensus is a sociological phenomenon well-suited to religious, fraternal and political entities. Excessive reliance on consensus by science-based groups such as CASAC moves science into the political arena and obscures the boundaries between science and collective policy preferences.

In my opinion, the CASAC process would be substantially enhanced if each CASAC Panel member were to clearly document in written comments their views on the science being considered in the review process. I have been astonished to find that some CASAC Panel Members do not regularly provide written comments, however, they sign on to consensus statements. These written comments should be developed, at least in draft form, prior to CASAC meetings and made available to serve as the basis for discussions at the CASAC meetings. They

can also be used in the development of written summary comments from CASAC to the EPA Administrator. In my opinion, CASAC in recent years has excessively depended on small writing groups, working outside of public view, to develop draft consensus statements for incorporation into the CASAC letters to the Administrator. This approach, as well as excessive use of teleconferences, reduces the public transparency of the NAAQS review process. The credibility of CASAC and its opinions would be enhanced if all CASAC deliberations were conducted in public meetings and teleconferences used very sparingly.

Distinguishing Between Science and Judgment

At every step in the NAAQS Review Process it is important to make clear the interface between science and judgments. This is important for the documents prepared by the EPA staff and, equally as important, for the CASAC deliberations that are ultimately formalized in advisory letters to the EPA Administrator. My views on these matters are not restricted to CASAC Comments on the Policy Assessment and Proposed and Final Rules. The need for distinguishing between science and judgment certainly extends to the ISA and Exposure/Risk Documents since as the IRP notes, these documents do involve scientific judgments. These science judgments and how they were reached should be clearly documented.

Comments on Integrated Science Assessment

In the following sections I offer general comments on the ISA.

Causality and Hazard

In recent years, the EPA's Criteria Documents (CD), including ISA's as a specific kind of CD, have made major use of the concept of causality. This concept, with multiple roots, is most frequently traced to the 1964 Surgeon Generals Advisory Committee on Smoking and Health. The concept has proved to be extraordinarily useful. However, "causality" like all conceptual approaches in science and public policy must be used with care. In its simplest form "cause" is defined as a "significant, effectual relationship between an agent and an associated disorder or disease in the host" (HEW, 1964). The word "cause" in this setting is analogous to the term, "hazard" used in risk assessment, i.e. the agent under some conditions of exposure may cause an increase in a particular disorder or disease. Neither "cause" nor "hazard" includes consideration of quantitative relationships between exposure to the agent and the resulting increase in a particular disease.

In my opinion, the ISA places excess emphasis on creating a laundry list of health outcomes identified as caused by exposure to ozone. The process used to classify "causality" appears to be driven more by increasing the list of health outcomes rather than by scientific rigor. In my opinion, lack of clarity in the "causality" classification process results in some health outcomes having their hazard over-stated. The ISA describes its consideration of evidence in broad terms. It states: "Moving from association to causation involves the elimination of alternative explanations for the association. The ISA focuses on evaluation of the findings from the body of evidence, drawing upon the results of all studies determined to meet the criteria described previously. Causality determinations are based on the evaluation and synthesis of evidence from across scientific disciplines. The relative importance of different types or evidence varies by pollutant or assessment, as does the availability of different types of evidence for causality determination. Three general types of studies inform consideration of human health effects: controlled human exposure, epidemiologic and toxicological studies."

In my opinion, the ISA in many areas fails to meet the high standards implied by the previous quote from the ISA. In general, there is an over-statement of evidence to support causality and failure to adequately provide a detailed evaluation of "alternative explanations for the association" as promised. Moreover, while use of the concept of causality emphasizes the need to move beyond consideration of statistical associations, the ISA gives excessive emphasis to statistical associations. Indeed, even when statistical significance is not found by the original authors, the ISA tends to bend over backwards to explain away the lack of statistical significance and strengthen the case for causality.

Inadequate Analysis of Concentration-Response Relationships

The strong focus on causality, albeit without adequate analytical rigor, is accompanied by inadequate evaluation of concentration-response relationships in the ISA. The focus appears to be almost exclusively on the strength of the statistical association with broad statements such as a linear association was observed or a linear relationship could not be excluded. I urge that the ISA be revised to clearly relate that for the health responses of greatest concern, the excess morbidity or mortality is quite small even in the older epidemiological studies with the highest ambient ozone concentrations.

The authors of the ISA seem to be so focused on supporting linear concentration-response relationships that they fail to consider alternative approaches. For example, the

analyses of Bell et al. (2004) and Smith et al. (2009) of the relationship between short-term (24 hr, highest 8-hour average, or highest 1-hour average) ozone and daily mortality both show that there is an absence of a statistically significant association for most U.S. cities. For example, my home city of Albuquerque is one of those not showing health responses associated with ambient ozone. I submit that these data and analyses for Albuquerque and many other cities clearly show that a threshold exists at the level of previous highest 8-hour concentrations above the old NAAQS of 0.08 ppm.

The substantial inter-city and inter-region differences in the presence or absence of statistically significant effects and the concentration-response relationships needs to be more clearly articulated in the ISA.

Co-Pollutants and Other Variables

Key epidemiological studies cited in the ISA did consider multiple risk factors in analyzing for the presence or absence of ozone related health effects. This is laudable. Unfortunately, the magnitude of the association with these other risk factors is rarely revealed in the ISA. A typical statement is that they were accounted for in the analyses and the statistical association for Ozone and remained robust. Unfortunately, in some cases these analyses are not reported in most cases by the authors of the original papers. The authors apparently had "tunnel vision" toward evaluating the ozone response. When the results of analyses for other risk factors, including other air pollutants, are available they should be presented and discussed in the ISA. These results provide context for evaluating and interpreting the ozone results.

Failure to Clearly Relate Ozone Metrics

The various metrics used to describe ambient ozone concentrations (highest 1-hour average, highest 8-hour average, daily average, seasonal average, etc.) are of critical importance in interpreting ozone concentration-response outcomes. This ISA does a better job of relating the ozone metric for specific studies and analyses than previous CDs. Nonetheless, there is still room for improvement. In my opinion, for any study cited in the ISA, the ozone metric used should be clearly identified. In many cases such immediate notations are absent. The reader is left with the impression that the goal of the ISA is to document again and again that exposure to Ozone is hazardous, i.e. a causal relationship for a health endpoint exists. That kind of "tunnel vision" orientation results in a document that falls short of providing a comprehensive evaluation of the science needed to inform policy judgments on the indicator, averaging time, level and

form of the NAAQS. Ultimately, the EPA Administrator must make policy judgments as to how low is low enough, a decision that science should inform. However, that decision cannot be made based on science alone.

Extrapolation of Findings in Laboratory Animal Studies to Humans

The ISA in some areas does an excellent job of relating the challenges associated with extrapolation of the findings of studies in laboratory animals to humans, an example is the dosimetry section. Other sections fall short and fail to adequately relate the Ozone exposure metric, the use of a single exposure level, the presence or absence of positive controls and in many cases, the very high Ozone concentrations studied. There is a tendency to devote similar attention to very poor studies and the most robust studies. For example, in my opinion, the best chronic bioassay in mice and rats of ozone exposure was conducted with joint sponsorship by the Health Effects Institute and the National Toxicology Program (NTP). This study is critical (NTP, 1994 and Boorman, 1994) in the ISA. However, it is inadequately described, evaluated and interpreted. Is that the case because this multiple exposure level study did not reveal significant ozone exposure related health effects? The large scale, multi-investigative study needs to be more carefully considered in the ISA.

A key issue related to the extrapolation of findings of alleged systemic effects of ozone from laboratory animals, and especially mice and rats, to humans is the marked differences in regional deposition within the respiratory tract among mammalian species. As discussed in the dosimetry chapter, mice and rats have substantially greater fractional deposition of ozone in the nasopharyngal region relative to tracheobronchial and pulmonary deposition than is observed in humans. These differences are related to the dimensions of the nasal airways in the rodents and are amplified by the fact that these rodents are obligate nasal breathers. It is quit possible that systemic effects attributed to ozone exposure of rodents are of limited relevance to humans.

Concentration-Response Relationships for Multiple Endpoints

The ISA gives the most attention to concentration-response relationship for the epidemiological studies. The ISA is seriously deficient in failing to consider concentration-response relationships for mechanistic endpoints. Most of these studies were conducted in laboratory animals and in a few cases involved controlled human exposures to ozone. In the vast majority of these studies, only a single relatively high exposure concentration of Ozone was used.

While the ozone conditions are usually described, limited attention has been given to the relevance of the mechanistic findings to realistic human exposures. There seems to be an automatic assumption that because mechanistic data have been developed, it must be relevant to understanding ambient ozone exposures. I submit that most, if not all, of the mechanistic endpoints evaluated are likely to have concentration-response relationships that differ from what may be observed as diseases in humans. It is important to not automatically assume a linear concentration-response function extends to current ambient ozone concentration profiles in the USA.

The issue of linear versus non-linear concentration response relationships for both cancer and non-cancer endpoints is a matter of continuing scientific debate. My views on the matter are related in the paper entitled "Linear Low-Dose Extrapolation for Noncancer Health Effects is the Exception, Not the Rule," Crit. Rev. Toxicol., 2011. Related to copyright issues, it is not possible to attach the original paper. It is available on-line at: http://informahealthcare.com/doi/full/10.3109/10408444.2010.536524 or contact Dr. McClellan for a copy of the paper (see Appendix C). The Rhomberg et al. paper was developed in part to an earlier paper by White et al. (2009).

Relevance of Observations from Populations Outside the USA

The ISA cites numerous epidemiological studies performed on non-U.S. populations. These studies are not adequately discussed with regard to extrapolation to U.S. populations and conditions. The pollutant profile in many of these countries is certainly different than found in the USA and must be considered in interpreting the epidemiological studies even when multi-pollutant models are used. I am not convinced that any of these studies provide unique scientific insights that should be considered in setting the U.S. NAAQS. I think that abundant analyses are available suggesting caution in making inter-city and inter-region extrapolations with the USA, especially on a quantitative basis. That caution deserves to be amplified when extrapolating results form multiple countries and continents to the U.S.

Ambient Ozone

Chapter 3 is a generally well-written chapter on Atmospheric Chemistry and Ambient Ozone. However, it is out-of-date by several years, especially as regards Ozone in the western U.S. I am concerned that continued reference to the "ozone season," "warm season," "cold season," etc. represents an outdated view of ambient ozone. As related below, the essential

ingredients for ozone formation are VOCs, NO_x and solar ultraviolet (UV) radiation. Greater care should be taken in ascribing ambient ozone formation to warm or cold seasons or an Ozone season when what is actually driving ambient ozone are three factors – VOCs, NO_x and UV flux.

The basic photochemical processes involved in ozone formation are described in a number of sources (e.g. Seinfeld and Pandis, 2nd edition, 2006, Chapter 6). Gas-phase oxidation pathways for the smaller hydrocarbons are quite well understood. Those for larger compounds, including aromatics, are less thoroughly understood. One notable area involves the extent of nitrate formation during the photochemical degradation. The chemistry of isoprene, the dominant biogenic hydrocarbon in the atmosphere, has been the subject of intense investigation over the past few years, leading to a reasonably complete picture of its degradation pathways. The relative level of VOC concentration versus that of NO_x is key in the chemical oxidation pathways as well as in determining the relative change in ozone production resulting from a change in the precursor concentrations. Large-scale field studies over the past decade, such as in Houston (2006) and Los Angeles (2010), have revealed uncertainties in emissions inventories as well as the importance of nitrous acid (HONO) in the ozone formation chemistry.

Besides VOCs and NO_x, the essential ingredient in ozone formation is solar UV radiation. The role of radiation manifests itself most prominently in photolysis of the NO_2 molecule to yield NO and an O atom. The O atom immediately reacts with atmospheric O_2 to produce O_3. The O + O_2 reaction is the only source of ozone in the atmosphere. To a first approximation, the level of O_3 achieved depends directly on the rate of photolysis of NO_2. Temperature influences ozone formation through the rate constants for reactions involved as well as some effect on the branching ratio of reactions. One notable effect of temperature is on the rate of thermal decomposition of nitrate-containing products; at higher temperature such compounds more readily thermally decompose, releasing the sequestered NOx back into the active reaction cycles. The most prominent example is peroxyacetylnitrate (PAN). On the whole, lower temperatures would tend to be associated with decreased ozone formation.

The Integrated Assessment cites observations of elevated winter ozone concentrations in the Jonah-Pinedale gas fields in Wyoming (page 3-16). The study of Schnell et al. (2009) is cited. The prevailing wisdom has been that elevated ozone formation is associated with high temperatures in urban areas. The occurrence of elevated ozone in the remote gas-producing area of Wyoming in the dead of winter with very low temperatures was unexpected. Carter and

Seinfeld (Winter Ozone Formation and VOC Incremental Reactivities in the Upper Green River Basin of Wyoming, Atmospheric Environment, 2011, in press, see Appendix D for availability of paper) have carried out a comprehensive analysis of winter ozone formation in this region with support from Shell Exploration and Production Company and the cooperation of the Wyoming Department of Environmental Quality and other scientists. As deduced in the paper of Schnell et al. (2009), ozone production requires snow-covered ground and a shallow, stable boundary layer. In fact, when the ground is not snow covered, ozone excursions do not occur, regardless of the state of the boundary layer or of the VOC and NO_x concentrations. The snow-covered surface reflects the solar radiation back up into the atmosphere, providing a second chance for the photochemical reactions involved in ozone formation to occur. Hence, the total UV flux in late February and early March with continuous snow cover is greater than found in June in the same area despite the higher incoming UV flux. Winter ozone formation in this region provides a profound example of the essential role played by solar UV radiation in ozone formation.

Two other surprises emerging from the Wyoming winter ozone formation are the considerably different VOC profile as compared with that in a typical summertime urban area and the extreme difference in VOC-to-NO_x ratio from that in urban areas. Carter and Seinfeld assess relative contributions of oxides of nitrogen (NO_x) and individual volatile organic compounds (VOCs), and nitrous acid (HONO) in winter ozone formation episodes in this region. The conditions of two ozone episodes, one in February 2008 and one in March 2011, were represented using a simplified box model with inputs adapted for the temperature and radiation conditions arising from the high surface albedo of the snow that was present. Sensitivity calculations were conducted to assess effects of varying HONO inputs, ambient VOC speciation, and changing treatments of temperature and solar radiation conditions. The locations modeled were found to be quite different in VOC speciation and sensitivities to VOC and NO_x emissions, with one site modeled for the 2008 episode being highly NO_x-sensitive and insensitive to VOCs and HONO, and the other 2008 site and both 2011 sites being very sensitive to changes in VOC and HONO inputs. Incremental reactivity scales calculated for VOC-sensitive conditions predict far lower relative contributions of alkanes to ozone formation than in the traditional urban-based conditions and that the major contributors to ozone formation were the alkenes and the aromatics, despite their relatively small mass contributions.

Policy Relevant Background ozone concentrations are defined as the sum of those background concentrations from natural sources everywhere in the world and from anthropogenic sources outside of continental North America. Because the mean tropospheric lifetime of ozone is about a month, ozone produced anywhere in the Northern Hemisphere can be transported as a blanket around the globe. Measurements of ozone at sites on the coast of California relatively removed from local sources routinely reach 8-h average levels as high as 50 ppb and occasionally reach 60 ppb. With a background level of ozone on the order of 50 ppb extending over the western U.S., it is necessary that year-round ozone formation resulting from local sources be well understood and considered in the setting of the Ozone NAAQS. It is important to recall that the Harvard team estimated that highest 8-hour Ozone concentrations could be achieved by shutting down all anthropogenic sources of Ozone precursors.

Declaration of Interest

These comments reflect my personal views and do not necessarily reflect the views of any past or current sponsors of my work. Review of the ISA and preparation of these comments was supported by my own financial resources and support from the American Petroleum Institute (API). Neither API nor any other client of mine was given the opportunity to review and/or comment on this written statement.

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APPENDIX A

BIOGRAPHY

ROGER O. McCLELLAN, DVM, MMS, DSc (Honorary),
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ROGER O. McCLELLAN is currently an advisor to public and private organizations on issues concerned with human health risk analysis and inhalation toxicology focusing on issues of air quality in the ambient environment and work place..

He is President Emeritus of the Chemical Industry Institute of Toxicology, having served as Chief Executive Officer and President of the Institute from September 1988 through July 1999. The Institute has a mission of creating an improved knowledge base for understanding and assessing the adverse effects of exposure to chemicals. During his tenure, the organization achieved international recognition for the development of science undergirding important environmental and occupational health regulations. Prior to his appointment as President of CIIT, Dr. McClellan was Director of the Inhalation Toxicology Research Institute, and President and Chief Executive Officer of the Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico. He began his career with Lovelace in 1966. During his 22 years with the Lovelace organization, he provided leadership for development of one of the world's leading research programs concerned with the toxic effects of airborne materials. The Institute continues operation today as a core element of the Lovelace Respiratory Research Institute. Prior to joining the Lovelace organization, he was a scientist with the Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, DC (1965-1966), and Hanford Laboratories, General Electric Company, Richland, WA (1959-1964). He received his Doctor of Veterinary Medicine degree from Washington State University in 1960 and a Master of Management Science degree from the University of New Mexico in 1980.

Dr. McClellan has served in an advisory role to numerous public and private organizations. He has served on numerous U.S. Environmental Protection Agency advisory committees including past Chairman of the Clean Air Scientific Advisory Committee (CASAC), *Ad Hoc* Committee to Review Criteria Document for Airborne Lead, Environmental Health Committee, Research Strategies Advisory Committee, CASAC Panels for all the Criteria Pollutants, and Member of the Executive Committee, Science Advisory Board, U. S. Environmental Protection Agency. In addition, he was a Member, National Council on Radiation Protection and Measurements; Member, Advisory Council for Center for Risk Management, Resources for the Future; Member, Health Research Committee, Health Effects Institute; and service on numerous National Academy of Sciences/National Research Council

Committees, including Committees on Toxicology (Past Chairman), Risk Assessment for Hazardous Air Pollutants, Health Risks of Exposure to Radon, Research Priorities for Airborne Particulate Matter, as well as the Committee on Environmental Justice of the Institute of Medicine.

Dr. McClellan serves or has served as Adjunct Professor at Duke University, University of North Carolina at Chapel Hill, North Carolina State University, University of New Mexico, University of California-Los Angeles, University of Arkansas, Colorado State University, and Washington State University. In addition, he frequently speaks on risk assessment and air pollution issues at other institutions and meetings in the United States and abroad. He is active in the affairs of a number of professional organizations, including past service as President of the Society of Toxicology and the American Association for Aerosol Research. He serves in an editorial role for a number of journals, including service as Editor of CRC Critical Reviews in Toxicology. He is a Diplomate of the American Board of Toxicology and the American Board of Veterinary Toxicology and a Fellow of the Academy of Toxicological Sciences, the Society for Risk Analysis, the Health Physics Society, and the American Association for Aerosol Research.

Dr. McClellan's contributions have been recognized by receipt of a number of honors, including election in 1990 to membership in the Institute of Medicine of the National Academy of Sciences. He is a Fellow of the American Association for the Advancement of Science. In 1998, he received the International Aerosol Fellow Award from the International Aerosol Research Assembly for his contributions to aerosol science and technology. He received the Society of Toxicology 2005 Merit Award for a distinguished career in toxicology. In 2005, The Ohio State University awarded him an Honorary Doctor of Science degree for his contributions to the science under-girding improved air quality. He has a long-standing interest in environmental and occupational health issues, especially those involving risk assessment and air pollution, and in the management of multidisciplinary research organizations. He is a strong advocate of risk-based decision-making and the need to integrate data from epidemiological, controlled clinical, laboratory animal and cell studies to assess human health risks of exposure to toxic materials and to inform policy makers in developing standards and guidance to protect the health of workers and the public.

APPENDIX B

McClellan, R.O., "Role of science and judgment in setting national ambient air quality standards: how low is low enough?," Air Quality Atmosphere Health Journal, published on-line June 1, 2011 reprint on next page. (Available on-line at: http://springerlink.com/content/1873-9318/?k=McClellan) or contact Dr. McClellan for a copy of the paper.

APPENDIX C

Rhomberg, L.R. et al., manuscript entitled "Linear Low-Dose Extrapolation for Noncancer Health Effects is the Exception, Not the Rule," Critical Reviews in Toxicology 41(1): 1-19, 2011 on next page. (Available on Open Access at: http://informahealthcare.com/doi/full/10.3109/10408444.2010.536524) or contact Dr. McClellan for a copy of the paper.

APPENDIX D

Carter, W.P.L. and Seinfeld, J.H. manuscript entitled "Winter Ozone Formation and VOC Incremental Reactivities in the Upper Green River Basin of Wyoming," Atmospheric Environment Journal, in press, 2011) on next page. (Contact Dr. McClellan for a copy of the paper).