UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

DATE

EPA-CASAC-14-XXX

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Health Risk and Exposure Assessment for Ozone (Second External Review Draft – February, 2014)*

Dear Administrator McCarthy:

The Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel met on March 24 - 27, 2014, to peer review the EPA's *Health Risk and Exposure Assessment for Ozone, Second External Review Draft* (*February, 2014*), hereafter referred to as the Second Draft HREA. The charge questions from the agency, the CASAC's consensus responses to the agency's charge questions and the individual review comments from the CASAC Ozone Review Panel are enclosed.

The CASAC commends the EPA for substantial revision to the First Draft HREA based on its prior advice (November 2012), and notes tremendous improvement in the Second Draft HREA. Overall, the document is well written, well founded based upon comprehensive analyses, and adequate for its intended purpose of providing strong support for the Second Draft Policy Assessment. The CASAC supports the new methodology and new data used in the revised assessment, as well as the selection of endpoints.

For air quality characterization, the quadratic rollback approach has been replaced by a scientifically more valid Higher-order Decoupled Direct Method (HDDM). HDDM uses the Community Multi-scale Air Quality (CMAQ) photochemical model to simulate the changes in ozone concentrations under the conditions of "just meeting" the existing ozone standard or a different alternative standard, based on reductions in U.S. anthropogenic emission of oxides of nitrogen and volatile organic compounds. Sources of background ozone are incorporated in the modeling; therefore, separate specification of U.S. background ozone concentrations is unnecessary. Another major improvement is the use of a new Downscaler methodology that combines modeled and monitored ozone concentrations to provide concentration estimates in unmonitored areas while improving the accuracy of estimates in the monitored areas. These

estimates are used for evaluation of the national burden of mortality risk.

For characterization of human exposure to ozone, exposures were modeled for selected at-risk groups residing in 15 urban study areas in the United States. The CASAC found that the methods are generally well-presented and are technically sound, particularly with regard to the description of data inputs, the modeling process, and the results. However, the robustness of the urban case study exposure results should be considered with respect to possible geographic differences in activity patterns that would not be explained by age, sex, and ambient temperature. As appropriate, the EPA should refine the urban case studies or provide clear priorities for future work to improve the Consolidated Human Activity Database (CHAD) to enable future quantification of differences among geographic areas.

For characterization of health risks based on controlled human exposure studies, the McDonnell-Stewart-Smith (MSS) model was used to estimate forced expiratory volume in one-second (FEV1) responses for individuals associated with short-term exposures to ozone, in addition to the exposure-response function approach used in the previous assessment. The lung function risk assessment evaluated risks of lung function decrements due to ozone exposure for selected groups in 15 cities. The CASAC finds that the updated and expanded lung function risk assessment is technically sound and represents a significant improvement in the approach to this component of ozone risk characterization. The CASAC finds the MSS model to be scientifically and biologically defensible. The incorporation of time-dependent inhaled ozone dose and detoxification dynamics represent a substantial improvement over the mean population response analyses at a fixed level of exertion that were done in the previous risk assessments. The CASAC also appreciates the addition of more recent time-activity pattern data to CHAD, which addresses a concern raised previously by the CASAC that more current activity pattern information be used to reflect changing activity patterns among the US population.

For characterization of health risks based on epidemiological studies, the CASAC supports the agency's decisions to: (a) estimate risk based on total risk; (b) use core-based statistical areas (CBSA) rather than central urban areas; (c) substitute the Bell et al. (2004) concentration-response (C-R) functions for short-term exposure related mortality with the Smith et al. (2009) C-R functions; and (d) base exposure on peak exposure metrics.

Based on analysis of 12 selected urban areas representative of the U.S. population, the EPA has appropriately estimated that the annual mean number of premature deaths avoidable for short-term exposure to ozone ranges (based on differences in meteorology) from 140 to 270 at a level of 70 ppb; 650 to 990 for a level of 65 ppb; and 790 to 1170 for a level of 60 ppb, compared to just meeting the current standard. Similarly, the preventable annual mean number of premature deaths from long-term exposure to ozone is estimated to range from 330 to 440 for a level of 70 ppb, 910 to 1160 for a level of 65 ppb, and 1220 to 1500 for a level of 60 ppb, all compared to just meeting the current standard. The relative reduction in mean annual premature mortality ranges from 2.1 to 3.6 percent and 4.0 to 5.1 percent for short- and long-term exposure, respectively, at a level of 70 ppb compared to just meeting the current standard. The relative reduction increases to ranges of 9.3 to 13.3 percent and 10.9 to 13.4 percent for short- and long-term exposures, respectively, at a level of 65 ppb, and to 11.2 to 15.7 percent and 14.6 to 17.3 percent, respectively, at a level of 60 ppb. The CASAC is confident that there are meaningful reductions in mean, absolute, and relative

premature mortality associated with ozone levels lower than the current standard and that these mean estimates, and the associated quantified uncertainties, are useful for policy analysis.

The basis for estimating long-term mortality (respiratory) risks relies on a single study, and the HREA should acknowledge the uncertainty and confidence in modeling results from the use of a single study, albeit a good one. In response to a public comment that a threshold model would provide better fit for the concentration-response curve, the EPA is proposing to conduct a threshold sensitivity analysis and will provide the results in the final HREA. The CASAC concurs with this plan.

The HREA also estimates the national scale mortality risk burden attributable to recent short-term and long-term exposures to ambient ozone, based on application of risk estimates from epidemiology studies. The CASAC recommends the rationale for the selection of the concentration-response functions used in the analysis be provided in the HREA to clarify the approach.

In conclusion, we believe that the current NAAQS standard for ozone is not protective of human health. The HREA emphasizes the conclusion reached in the ISA that there is a causal relationship between short-term ozone exposure and a broad range of respiratory effects, including lung function decrements, respiratory symptoms, inflammation, hospital admissions, and emergency department visits – all of which are observed below the level of the current ozone NAAQS. This HREA presents ample scientific evidence from human controlled exposure and epidemiology studies that adverse health effects occur with exposures to 72 ppb of ozone. For example, the combination of decrements in FEV1 together with the statistically significant alterations in symptoms in human subjects exposed to 72 ppb ozone meets the American Thoracic Society's definition of an adverse health effect (ATC, 2000).

The CASAC appreciates the opportunity to provide advice on the HREA document and looks forward to receiving the Agency's response.

Sincerely,

Dr. H. Christopher Frey, Chair
Clean Air Scientific Advisory Committee

Enclosures

NOTICE

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

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Clean Air Scientific Advisory Committee
Ozone Review Panel

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CASAC Responses to Charge Questions on the Second Draft Health Risk and Exposure Assessment for Ozone

Chapter 1: Introduction

1. *To what extent does the Panel find the introductory and background material, including that pertaining to previous reviews of the O_3 standards and the current review, to be clearly communicated and appropriately characterized?*

Chapter 1 is brief – six pages long – yet does an excellent job of introducing the entire document. The complex history of the ozone standard is well described, including the controversial decisions and legal challenges that occurred during the past decade. The essential facts are included and links to more detailed documents are given. The summary of the goals and approaches is helpful. The final section, "Organization of Document", is a brief but useful guide. The material on the current approach and the organization of the HREA is clearly communicated and is of the appropriate length.

This chapter and the entire Second Draft HREA is a marked improvement over the First Draft HREA, and over the HREAs from previous years. It shows a very positive evolution in the approach and the presentation. It represents a tremendous amount of work. The effort that has gone into the air quality characterization and the characterization of ozone concentration changes in response to emissions controls as described in Appendix 4 is laudable.

With regard to the status of the current ozone standard, EPA could give a summary of the current status of ozone air quality, such as the number of areas and counties (as well as the population in those areas and counties). Of note is that there are 46 areas including all or parts of 227 counties with a population of 123 million people that are not in attainment of the current standard (source: http://www.epa.gov/airquality/greenbook/hntc.html). The main point of such a summary is that ozone is a significant air quality and public health concern, and that many Americans are exposed to ozone levels higher than the current standard.

Chapter 2: Conceptual Model

2. *To what extent does the Panel find that the discussions accurately and clearly reflect the air quality, health effects, exposure and risk considerations relevant for quantitative exposure and risk assessment, building from information contained in the final ISA? What are the views of the Panel on the additional flowchart provided for the overall assessment and the additional information regarding specific elements of the exposure and risk assessments?*

Chapter 2 as rewritten is clearer and more effective than in the First Draft HREA. The chapter clearly shows how the conceptual model builds on information from the final Integrated Science Assessment (ISA) for Ozone. The authors did an excellent job of accurately and clearly discussing the key elements of air quality and health effects that collectively form the risk characterization. The key findings from the ISA are brought forward into this chapter to support the formulation of the conceptual model used in the HREA.

This chapter provides an useful overview of the complex HREA process. The flowchart in Figure 2-1 (page 2-2) is helpful in understanding how the various parallel components of both the exposure assessment model (Air Pollution Exposure Model - APEX) and risk assessment (Benefits Mapping and Analysis Program - BenMAP) support the overall risk characterization. Including the relevant HREA chapters for each component in this flowchart is very useful. Each component of the HREA process is clearly summarized in a well-structured manner; these summaries provide a contextual understanding of the more detailed discussions in later chapters. Figure 2-2 (page 2-11) is a clear summary of the causal determinations of both long-term and short-term ozone health effects. A brief definition of the strength of evidence categories of suggestive, likely, and causal is needed. Page 2-21, lines 24-29 provide a helpful discussion of "attributable risk" and of how estimates of total risk remaining after meeting the existing standard form the "reference value" for evaluation of risk reductions from meeting potential lower standards.

One topic that seems to be missing is a discussion of ozone background in various forms and how that influences the interpretation of the available data. For example, the Higher-order Decoupled Direct Method (HDDM) approach used for assessment of air quality scenarios does not require an explicit exogenous background calculation, but implicitly takes background into account based on contributions of boundary conditions and non-anthropogenic precursors. Furthermore, background is not used in the risk calculations. These methodological approaches should be explained as part of a discussion of how background is addressed indirectly in air quality analyses and as to why background is not needed for the risk estimation process.

The end of Section 2.2.1 should be modified to note that ozone formation may be NO_x-limited during summer/high ozone conditions. In contrast, during much of the year, ozone formation in cities can be radical-limited due to the lack of sunlight.

Chapter 3: Scope

3. *To what extent does the Panel find the scope of the health risk and exposure assessment is clearly communicated? To what extent does the panel find the additional flowcharts for each analytical component to be useful additions?*

This chapter is very well written and clearly communicates the scope of the HREA. Elements of the HREA are discussed in a logical order, and the "Conceptual Diagram" flowcharts help with understanding the key components of each phase (such as characterization of air quality, exposure assessment, the controlled human exposures, and others).

Figure 3-3 is useful in terms of connecting ~~linking~~ exposure to uptake of ozone in the lungs. It delineates the multiple factors that affect the links between exposure levels in the ambient environment and the exposure of lungs. As a consequence there are ~~However, the bottom oval is incomplete in that it focuses only on~~ changes in the one-second forced expiratory volume (FEV1). The CASAC believes that these ~~For example,~~ modest changes in FEV1 ~~by themselves~~ are usually associated with ~~may be of less significance than related~~ inflammatory changes, such as more neutrophils in the bronchoalveolar lavage fluid. Such changes may be linked to the pathogenesis of

chronic lung disease. ~~Therefore, focusing only on FEV1 decrement may lead to failure to adequately consider the consequences of chronic ozone exposures.~~ There is also great~~er~~ interest in how ozone ~~and other air pollutants~~ might affect lung growth in children as well as increased long-term declines in pulmonary function ~~with~~ in adult~~s aging~~.

Table 3-1 is incomplete and the lack of information should be discussed. Such discussion should at least include acknowledgment of missing or insufficient information and, where possible, explanation or rationale as to why such information is not available. For example, one would question why categories of respiratory hospitalizations, respiratory emergency department visits, or respiratory symptoms were measured in so few of the selected cities. Respiratory hospitalizations were measured in Detroit, Los Angeles, and New York, but not in the other nine selected urban areas.

~~Chapter 3 clearly shows that the current NAAQS for ozone is not protective of human health and needs to be revised. The HREA emphasizes the conclusion reached in the ISA that there is a causal relationship between short-term ozone exposure and a broad range of respiratory effects, including lung function decrements, respiratory symptoms, inflammation, hospital admissions, and emergency department visits – all of which are observed below the level of the current ozone NAAQS. This chapter presents ample scientific evidence from human controlled exposure studies and epidemiology studies that adverse health effects occur with exposure to 70 ppb of ozone. For example, the combination of decrements in FEV1 together with the statistically significant alterations in symptoms in human subjects exposed to 70 ppb ozone meets the American Thoracic Society's definition of an adverse health effect (ATC, 2000).~~

Chapter 4: Air Quality Considerations

4. *What are the views of the Panel on the appropriateness of the methods used to characterize O_3 air quality for the exposure and risk assessment? What are the views of the Panel on the HDDM-based adjustment methodology used to adjust O_3 concentrations to just meet the existing O_3 standard and alternative standards?*

This chapter incorporates present scientific understanding and modeling resources for the purpose of estimating the ozone concentration distributions, in different urban areas under the conditions of "just meeting" the existing ozone standard or a different alternative standard. The replacement of the quadratic rollback procedure by the HDDM procedure is important and supported by the CASAC. The HDDM procedure does not require separate estimation of background ozone, as sources of background ozone are incorporated in the modeling. In addition, a new Downscaler technique is being used, that combines modeled and monitored ozone concentrations. This provides concentration estimates in unmonitored areas while improving the accuracy of estimates in the monitored areas. The Downscaler estimates are used for the estimation of national burden of mortality risk. The EPA also provides extensive Appendices of supporting information for the chapter. Presentations in the chapter are generally clear. Figures 4-3 and 4-6 are great methodology flowcharts that enhance clarity. Overall, this is a very substantial improvement over the first draft.

In the HDDM procedure, there are issues in applying the modeled sensitivity coefficients to adjust for the expected real world impact of emission reductions on ozone. Due to the limited periods (8 months in 2007) for which model simulations are available, the HREA looked for empirical relationship within the model output to link the sensitivity coefficients to ozone concentrations for each grid containing an ozone monitor, each hour of the day, and each season of the year. These relations were then applied to estimate the real-world sensitivity coefficients under similar conditions using the monitored ozone concentrations. Even though there are no theoretical foundations to support the generality of these relationships, the approach is innovative and is suitable for the intended applications. More research will be needed in the future to explore how best to estimate the real-world sensitivity coefficients using information from model simulations and monitored ozone concentrations.

NO_x emission reductions are used almost exclusively to estimate the ozone distributions of areas attaining certain levels of the standard. The HREA should more clearly put these estimates in context with respect to their intended purpose. The purpose of these emission reduction scenarios is not to evaluate the feasibility of emission control or compliance with alternative standards. Rather, the purpose is to develop internally consistent estimates of spatial and temporal variability in ozone associated with specified alternative levels of possible standards. Furthermore, these ozone air quality scenarios, although reasonable with respect to internal consistency, ~~do~~ ~~do~~ may not represent ~~optimal~~ ~~optimal~~ actual control strategies for individual urban areas. ~~Therefore, these estimated spatial and temporal distributions of ozone are appropriate for the intended purpose of evaluating air quality at levels consistent with possible alternative standards, but do not imply a preferred approach for possible future compliance with possible alternative standards.~~ While it is quite sensible to choose NOx-emission reductions as the least complex approach to achieve the intended purpose, ~~Nonetheless,~~ it would be helpful if the HREA provided some analyses or examples, and included a discussion ~~to indicate that the focus on NO_x emission reductions for the purpose of these scenarios is reasonable~~ on the potential impacts of NOx-only emission reductions, and perhaps other pathways like VOC-only and VOC-NOx emission reductions, on the ozone distributions and their corresponding health risk implications. ~~For example, VOC-only reduction may be less desirable in most urban locations, and NO_x-only reduction may provide an upper bound for ozone exposure for areas attaining a given ozone standard.~~

The HREA describes a procedure to extend the use of sensitivity coefficients to the nonlinear regime in cases where a high-percent emission reduction is necessary. However, a description of this important procedure is not presented until Section 4.5, where uncertainty is discussed. It would be useful to highlight or briefly describe this procedure in the Methods section, perhaps after "Step 4" on p. 4-16.

It is the CASAC's understanding that a nationwide percent emission reduction is assumed in determining the sensitivity coefficients. It would be helpful to clarify that this assumption is not explicitly imposed when a given percent emission reduction is exercised in an urban area to attain a given ozone standard.

The discussion, presented in the last paragraph of p. 4-18 through the top paragraph of p. 4-19, on the limitations of the HDDM procedure applied to Los Angeles and New York for meeting the lower alternative standard levels is not very clear. In particular, the statement that "the mean

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estimate does not capture the variability in modeled responses on similar days" needs further clarification. It is fairly well described on p. 25 of Appendix 4D.

~~It would be helpful to identify t~~The percentiles corresponding to the top and bottom horizontal lines of the box-and-whisker plots in the chapter and the appendices must be identified.

It would be useful to provide a Summary/Key Observations section consistent with other chapters.

5. *To what extent does the Panel find that the discussion of uncertainty related to the air quality inputs to the exposure and risk assessment appropriately covers important sources of uncertainty?*

Section 4.5 contains a useful discussion of uncertainties associated with the use of the HDDM procedure to estimate the ozone concentration distributions. There are important sources of uncertainty whose magnitude and biases cannot be readily determined presently and that should be further described and discussed. They include the general validity of the linear regression approach linking the sensitivity coefficients to ozone concentration, and the steps and implicit assumptions used to apply the CMAQ model-based regression relationship to the real world.

In the discussion on the use of linear regressions to estimate the sensitivity coefficients in the high-ozone regimes for an area to meet a given standard level, the HREA indicates an underestimation of the benefits of reducing high ozone concentrations and the disbenefits of increasing low ozone (p. 4-39, lines 33-36, and again on p. 4-47). Does this mean an underestimation of *the variability of* the benefits and of the disbenefits? If not, then this would be referring to bias, which obviously exists to some extent but was discussed only in the 3-step high-NO_x reduction approach. Such biases are considered to be small, can be in either direction, and thus do not significantly undermine estimates or the robustness of relevant findings. Biases introduced because of limiting the range of the sensitivity coefficients in the regressions are discussed on p. 18 of Appendix 4D but not in Section 4.5, and appear not to be connected to the statement in question. The connection between these should be made clearer.

Table 4-6 contains a very comprehensive list of sources of uncertainty together with the associated estimated sizes and rationale. The uncertainty in CMAQ modeling (Item C of Table 4-6) should probably be "medium" rather than "low-medium" based on extensive model evaluations to date. So would be the uncertainty for CMAQ-derived sensitivities (Item D). The uncertainty associated with the application of HDDM sensitivities to ambient data and to un-modeled time periods (Items E and F, respectively) is more difficult to determine because the regression relationships used are empirical and there are still ambiguities in how best to translate these relationships to the real world. A designation of "low-medium" may be an indication of over-confident. It may be more appropriate to designate it as "medium."

~~On p. 4-47, the statement regarding the underestimation of benefits of reducing high ozone and disbenefits of increasing low ozone needs to be clarified. See the second paragraph of the response to this charge question for more detailed discussions.~~

Chapter 5: Characterization of Human Exposure to Ozone

Chapter 5 is well written and comprehensive, representing a significant improvement over the First Draft HREA. In particular, the addition of the targeted analyses and uncertainty discussion is welcome and well done. The chapter would benefit from the addition of a paragraph in its front section describing the overall exposure assessment approach and its relation to the exposure and risk assessment for the controlled human and epidemiological studies. This description would help to support Figure 5-1, which is particularly helpful in framing the exposure assessment process.

6. *To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded population-based exposure analysis to be technically sound, appropriately balanced, and clearly communicated?*

The methods are generally well presented and are technically sound, particularly with regard to descriptions of data inputs, the modeling process, and the results. The discussion of model outputs, however, is difficult to follow, and the figures are poorly annotated and formatted. Hence, the HREA should more clearly present figures with sufficient descriptive information so that the figures are legible and self-explanatory, coupled with adequate explanations in the main body of the text.

The exposure assessment modeling is based on activity diary data that can be stratified with respect to age, sex, day-of-week, and ambient temperature. However, activity patterns may also differ by geographic region. Therefore, the robustness of the urban case study exposure results should be considered with respect to possible geographic differences in activity patterns that would not be explained by age, sex, and ambient temperature. For example, the targeted sensitivity analyses should be expanded to examine whether time spent outdoors varies by geographic location. As appropriate, the EPA should refine the urban case studies or provide clear priorities for future work to improve the Consolidated Human Activity Database (CHAD) to enable future quantification of differences between geographic areas. ~~In addition, the chapter would benefit from better description of how the APEX analysis relates to epidemiological concentration-response functions and regulations that rely on ambient levels.~~

7. *Chapter 5 includes several evaluations of key APEX inputs and model outputs, including for example analysis of time-activity data and comparison of actual personal exposures with modeled exposures. What are the views of the Panel on the appropriateness and usefulness of these evaluations and the conclusions drawn from these evaluations?*

The CASAC strongly supports the inclusion of the targeted analyses. These analyses are well designed and interpreted and further demonstrate the validity of the exposure analysis and to identify sources of uncertainty in exposure estimates. The CASAC notes the lack of agreement of modeled exposure estimates and measured exposures from Wayne County, MI~~.~~ and believes that the ~~R~~reasons for ~~the lack of agreement~~this discrepancy should be identified, and ~~the~~its implications ~~of this lack of agreement for~~for subsequent analyses ~~should be~~ discussed.

8. *Chapter 5 includes several scenario-based exposure simulations that focus on specific populations or behaviors. What are the views of the Panel on the design, results, and interpretation of these additional scenario-based exposure simulations?*

The additional scenario-based exposure simulations were useful, well described, and an important addition to the analysis. A concise summary should be added to the end of this section to highlight key findings and to discuss their implications to exposure estimates.

9. *To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the exposure estimates?*

The discussion of uncertainty and variability is comprehensive, appropriately listing the major sources of uncertainty and their potential impacts on the APEX exposure estimates. The section, however, would benefit from a discussion of overall uncertainty. Such a discussion should focus on uncertainty in model results based on the joint propagation of uncertainty in model ~~. Such a discussion should focus on uncertainty in model results based on the joint propagation of uncertainty in model inputs and parameters, taking model uncertainty into account. Most~~ inputs and parameters, taking model uncertainty into account. Most input and parameter uncertainty sources are characterized as low or low-to-moderate, which may give the false impression that overall uncertainty of the model results will also be low or low-to-moderate. ~~However, this impression may be false, given~~EPA should clarify that overall model uncertainty may be larger than that for the individual uncertainty sources and should quantify as best as possible the overall model uncertainty. One way to quantify the overall model uncertainty is to cite results from the comparison of measured and simulated ~~the apparent systematic biases in model results compared to measured daily~~daily mean ozone exposure in the Wayne County, MI validation study, which show disagreement between modeled and measured ozone exposures. Possible factors that may contribute to the observed disagreement in the Wayne County study should be discussed.~~.~~ In addition, the uncertainty for adjusting the air quality using HDDM should be designated as "medium" rather than as low-to-moderate.

Chapter 6: Characterization of Health Risk Based on Controlled Human Exposure Studies

10. *To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded lung function risk analysis to be technically sound, appropriately balanced, and clearly communicated?*

The updated and expanded lung function risk analysis is technically sound and represents a significant improvement in the approach to this component of the overall ozone risk characterization.

The implementation of the McDonnell-Stewart-Smith (MSS) model in the HREA is clearly described. The comparison of the MSS model results to those obtained with the exposure-response

(E-R) model is of tremendous importance. Typically, the MSS model gives results about a factor of three higher than the exposure-response function model for school-aged children, which is expected because the MSS model includes responses for a wider range of exposure protocols (under different levels of exertion, lengths of exposures, and patterns of exposure concentrations) than the E-R model of previous reviews.

The HREA presents a myriad of risk estimates across the cities, age groups, and outdoor workers that were examined. These estimates provide a strong foundation for the policy assessment and are briefly summarized. For example, the percentage of children aged from 5 to 18 years old in each analyzed urban area experiencing selected FEV1 decrements was estimated for scenarios based on just meeting the current standard and meeting alternative standards, such as 65 ppb. The proportion of children with an FEV1 decrement ≥ 10 % for air quality just meeting the current standard was 11% to 22% across urban areas, compared to a range of 2% to 18% for meeting a 65 ppb level. Of the same child age group, 2% to 6% are estimated to have an FEV1 decrement of ≥15 % at just meeting the current standard, compared to 0% to 4% at meeting a level of 65 ppb.

Under a scenario of just meeting the current standard, 4.3% of outdoor workers aged 19 to 35 are estimated to experience 1 or more FEV1 decrements ≥ 15 %, while 1.2 % of such workers are estimated to experience 6 or more such decrements. For a scenario based on an alternative standard of 65 ppb, these proportions decrease to 2.5 % for 1 or more decrements and 0.74 % for six or more decrements. The reductions in frequency of clinically significant decrements in FEV1 in both children and outdoor workers for the above alternative standard scenarios ~~emphasize~~ underscore the need for the current ozone standard to be lower to be protective of the public's health.

11. *What are the views of the Panel on the implementation of the McDonnell-Stewart-Smith model to specify the exposure-response function linking the change in FEV1 to O_3 exposure?*

The McDonnell-Stewart-Smith (MSS) model and its implementation are clearly described. The main differences between the MSS model for individual responses versus the population model used in this and past assessments are clearly articulated. The MSS model is scientifically and biologically defensible. The use of the threshold version of the model is appropriate. However, there are no major differences in risk estimates between the threshold and non-threshold model. ~~Moreover, despite the need for some assumptions, t~~The incorporation of time-dependent inhaled ozone dose and detoxification dynamics represent a substantial improvement over the mean population response analyses at a fixed level of exertion that were done in previous risk assessments. ~~The extent to which the results are robust to the assumptions should be discussed.~~ The comparison of the MSS model results to those obtained with the exposure-response model is a useful exercise.

The extent to which the results are robust to the model assumptions needs to be discussed. For example, the assumption of children having the same age sensitivity as adults could be strengthened by reference to the work of McDonnell and colleagues (1985) who showed that children and adults had the same pulmonary function responses to ozone exposure when dose was normalized to body surface area but exhibit lesser symptoms. Also, because of insufficient data on

diseased lungs, such as those of asthmatics, the model is currently based on measurements made in healthy individuals. The Agency should be clear that because of this limitation, risk estimates made with the model possibly underestimate the risk to such subpopulations

12. *To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the risk estimates?*

The addition of more recent time activity pattern data, addresses a concern raised previously by the CASAC concerning how activity pattern information should be brought up to date.

~~Discussion of major constituents of uncertainty and variability is well done. The EPA should consider examining inter- and intra-subject variability by sensitivity analyses on some of the beta coefficients contained in the MSS model. Such analyses would provide some insights on the intrinsic variation conveyed through genetic factors that may be contributing to this variation. Table 6-16 provides a good summary of the qualitative uncertainties, their likely direction and magnitude, and the extent of the knowledge base underpinning current understanding of the phenomenon being addressed.~~

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Discussion of major constituents of uncertainty and variability is well done. The current analyses provide insights on inter-subject variation but do not address intra-subject variation. Future review cycles may shed light on such variability if methods such as those employed in McDonnell et al. (2013) are used as their analysis showed that intra-subject variability is related to the magnitude of an individual's response rather than assuming that intra-subject variability is constant across individuals. Table 6-16 provides a good summary of the qualitative uncertainties, their likely direction and magnitude, and the extent of the knowledge base underpinning current understanding of the phenomenon being addressed.

Chapter 7: Characterization of Health Risk Based on Epidemiological Studies

13. *To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated epidemiology-based risk assessment to be technically sound, appropriately balanced, and clearly communicated?*

By and large, the decisions made in carrying out the exposure and risk assessment were either well justified or have been subjected to a sensitivity analysis. These included decisions to:

- base risk on total risk, not with respect to the lowest measured level;
- use core-based statistical areas (CBSA) rather than central urban areas;
- substitute the Bell et al. (2004) C-R functions for short-term exposure related mortality with the Smith et al. (2009) C-R functions;
- base exposure on peak exposure metrics.

The basis for estimating long-term mortality (respiratory) risks relies on a single study, Jerett et al. (2009), and the HREA should acknowledge the uncertainty and confidence in modeling results from the use of a single study, albeit a good one. On the face of it, the estimate of up to approximately 20% of chronic obstructive pulmonary disease (COPD) deaths attributable to ozone (page 7-68) based on the Jerrett C-R function, seems quite high, especially when one considers that the population at risk for dying of COPD is comprised of those who are unlikely to exercise and likely to spend less time outdoors. Nonetheless, the CASAC concurs that Jerrett et al. (2009) is an appropriate study to use at this time as the basis for the long-term mortality risk estimates given its adequacy and the lack of alternative data.

Errors in population totals for epidemiology risk analyses were identified and revised tables for Chapters 7 and 8 of the HREA were submitted to the CASAC for review. These revised tables (USEPA, 2014a) are the basis for the following evaluation and advice.

Because estimates of total attributable deaths and total morbidity counts, as well as estimates of changes in attributable deaths and morbidity counts are affected by population counts, the revised tables showed changes in these statistics. However, risks per 100,000 population and percent attributable risk estimates were largely unaffected when the errors were corrected. Importantly, most observations and conclusions contained in the 2nd Draft Ozone Policy Assessment (PA) arise from epidemiology-based risk estimates that focus on population-standardized metrics. Thus, the revised risk estimates did not substantially change any of the policy-related observations contained in the 2nd Draft Ozone PA.

Based on the revised analysis results (USEPA, 2014a) of the12 selected urban areas representative of the U.S. population, (particularly the revised Table 7-7 for premature mortality related to short-term exposure ~~and Table 7-12 for premature mortality related to long-term exposure~~ to ozone), the EPA has appropriately estimated that the annual mean number of premature deaths avoidable for short-term exposure to ozone ranges (based on differences in meteorology when comparing 2007 and 2009) from 140 to 270 at a level of 70 ppb, 650 to 990 for a level of 65 ppb, and 790 to 1170 for a level of 60 ppb, compared to just meeting the current standard. In light of the potential impacts of accounting for nonlinearity of the concentration-response function for long-term exposure reflecting a threshold of the mortality response, the estimated number of premature deaths avoidable for long-term exposure reductions for several levels of the standard need to be viewed with caution. ~~Similarly, the preventable annual mean number of premature deaths from long-term exposure to ozone is estimated to range from 330 to 440 for a level of 70 ppb, 910 to 1160 for a level of 65 ppb, and 1220 to 1500 for a level of 60 ppb, all compared to just meeting the current standard.~~ The estimated mean number of preventable premature deaths nationally for ~~both~~ short-term ~~and long-term~~ exposure would of course be larger if taking into account geographic areas other than the 12 that were analyzed. The relative reduction in mean annual premature mortality ranges from 2.1 to 3.6 percent ~~and 4.0 to 5.1 percent~~ for short-~~ and long-~~term exposure,~~ respectively,~~ at a level of 70 ppb compared to just meeting the current standard. The relative reduction increases to ranges of 9.3 to 13.3 percent~~ and 10.9 to 13.4 percent~~ for short-~~ and long-~~tterm exposures, ~~respectively,~~ at a level of 65 ppb, and to 11.2 to 15.7 percent~~, and 14.6 to 17.3 percent, respectively,~~ at a level of 60 ppb. Analogous estimates of relative reduction in mean annual premature mortality for long-term exposure again need to be viewed cautiously until results

of sensitivity analyses that explore the impact of potential nonlinearity of the concentration-response function are available. Although these estimates for short-term exposure impacts are subject to uncertainty, the data supports a conclusion that there are meaningful reductions in mean premature mortality associated with ozone levels lower than the current standard, that the absolute and relative reduction in mean premature mortality increases as the level is lowered, and that these mean estimates and the associated quantified uncertainties, are useful for policy analysis.

EPA models for extended urban areas show that health risks decline as alternative ozone NAAQS are made more stringent. These same models have been applied to smaller geographic areas which are consonant with those employed in the epidemiological study used to derive dose-response functions (Table 7C-1*). The results for the latter suggest that health risks in the smaller more urban areas can increase for many cities as NAAQS alternatives become more stringent. This is because ozone precursor sources would be reduced and allow less scavenging of oxygen from ozone in these areas. It would be important to characterize the populations in both the larger and more urban areas to determine whether there are any differences in the populations at risk in these areas and to determine whether there could be any environmental justice issues associated with these differences. Ideally if one were to investigate the latter issue, even smaller geographic areas with significant minority populations should be examined. Comparison of area characteristics should be undertaken for the epidemiological studies, but it would also be of interest to learn if there would be any children or outdoor workers in the more urban areas who would experience significantly higher exposures to ozone as a result of possible changes in ozone NAAQS.

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Taking into account the corrections made by the EPA described above, the CASAC finds that the input data, methods, and findings for the short-term morbidity and mortality risk estimates are scientifically appropriate and adequate for use in the PA.

Regarding overall confidence, in light of the reliance on a single study to estimate long-term respiratory mortality effects, and the seemingly large effect estimate, it is overly confident to conclude that there is a "reasonable degree of confidence" in these risk estimates (page 7-86). The text should also address a point raised in the ISA (ISA page 7-31) that there is "limited evidence" for an association between long-term exposure and respiratory mortality, presumably because the evidence is based on only one study.

In light of the central importance of respiratory (presumably COPD) mortality as an outcome of long-term ozone exposure, consideration should be given to estimating exposures in this group with APEX (if diary profiles are available). Presumably this population might be expected to spend a relatively smaller proportion of time in more exposed settings.

* It should be noted that this corrected Table is still in error as indicated by EPA Staff during the conference call. The lower confidence limits in the Table are 12.5% rather than 2.5% confidence limits. This error should be corrected in a final version.

The discussion of variability and uncertainty is generally sound and comprehensive. One aspect that is not included in the discussion of spatial variability in concentrations is the fine-scale spatial variability due to near-roadway O_3 gradients. ~~associated with titration of ozone by NO.~~ Near roadway ozone concentrations are considerably lower than city average values due to local

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NO_x/O_3 titration chemistry. Also, there are typically no roadside ozone monitors, so concentrations at these microenvironments cannot be quantified empirically in most regulatory monitoring networks. Depending on the city, a greater or lesser fraction of the population lives in close proximity to large roadways, and it is not certain, for short-term exposures, that the average city day-to-day concentration pattern is representative for people living near roadways. This has implications for population exposure misclassification which is not reflected in Table 7-4 (page 7-43) and that should be discussed. For long-term exposures, the importance of roadside gradients is equally important.

It is not clear why the HREA concludes that the mortality metric for short-term exposure is "not responsive to meeting the existing and alternative standard levels" (page 7-69). Mortality reductions seem to steadily increase with changes to the standard.

It is clear why some regions, namely those with low ozone concentrations, experience increases in estimated concentrations and therefore in health risk when concentrations in ozone precursors (NO_x) are lowered to meet the current standard. Nevertheless, it would be helpful if a sentence or two were inserted in each section where such findings are presented as a reminder that this is to be expected for regions having low ozone concentrations because of nitric oxide (NO) quenching. When NO concentrations are reduced, there is less ozone quenching in these regions and consequently higher ozone concentrations.

"Incidence" is used both to refer to death rates and absolute counts. The term should be reserved for rates.

There is a distinction between reducing ozone to a particular level and reducing ozone to meet a given standard through reduction in precursor emissions. The chapter should be clearer about what is being done in each case.

In Table 7-4 on uncertainty analysis, it is not clear why simulating ozone concentrations for "attainment of both existing and alternative standards" should be included here among other factors assessed in sensitivity analyses. These are simply different ways of expressing impacts of different regulations that provide different insights.

14. *To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources and appropriately characterized the relationship of those sources of uncertainty and variability to the risk estimates?*

See response to Charge Question 13 for comments on small-scale ozone spatial variability. Otherwise, the discussion is comprehensive and appropriate in presenting the sources and impacts of uncertainty and variability, to the extent possible. The sensitivity analyses are informative. Consideration could be given to shortening the discussion of sensitivity given that the same material is presented in tabular form.

15. *Adjusting the distributions of O_3 concentrations based on decreasing NOx emissions to just*

meet the existing and alternative O_3 primary standards resulted, in some cases, in substantial shifts in the spatial and temporal patterns of O_3 across case study urban areas relative to patterns of O_3 that existed for recent air quality, and presumably relative to the patterns present in the study locations of the epidemiology studies from which the concentration- response functions were drawn (see section 7.1.1 of the TSD, USEPA, 2012). What are the views of the Panel on the characterization of the degree to which these changes in spatial patterns of O_3 introduce uncertainty in risk estimates when effect estimates based on one spatial/temporal pattern of O_3 (the pattern in the epidemiology study) are applied to a substantially different spatial/temporal pattern of O_3 concentrations?

It is noted that the simulations used to estimate ozone levels under alternative standards result in spatial patterns different than those observed in the epidemiologic studies on which the health effects measures are based. This would result in different health impacts than those predicted from the epidemiologic studies if one or both of the following conditions are met: (a) factors associated with space modify the effects of ozone on health; or (b) spatial mobility of persons within the area is a key driver of individual-level exposures. The CASAC is confident that the impact of different spatial patterns should not be great, and should likely be substantially less than the other sources of uncertainty. The EPA has implicitly assumed that factors associated with space do not modify effects and that spatial mobility is not a key driver of individual level exposures. These assumptions should be explicitly stated and the robustness of results to the assumptions should be discussed.

In addition, the Bayesian ("shrunken") estimates should theoretically make each city C-R function less sensitive to the particular spatial-temporal pattern present during the place and time used for the epidemiological analysis. There is no ready alternative that is preferable. Furthermore, the assumption of a constant function is reasonable.

16. *In particular, what are the views on the Panel on the characterization of the level of uncertainty associated with estimates of risk associated with days with relatively lower composite (area-wide average) O_3 concentrations and those with relatively higher composite O_3 concentrations?*

The presentation in the chapter is appropriate in this regard.

Chapter 8: National Scale Mortality Risk Burden Based on Application of Results from Epidemiological Studies

17. *To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated national-scale risk analysis to be technically sound, appropriately balanced, and clearly communicated?*

Overall, this chapter is straightforward, well written, and covers all of the important aspects of the interpretation and presentation of the methods used. The approach is technically sound. The

rationale for the selection of the concentration-response (C-R) functions used in the analyses in this chapter should be provided. In addition, the chapter would benefit from information on why city-specific and national effects may differ. Referring to other sections of the overall document (e.g., Chapter 7) could point readers to the needed detail without causing the document to be too repetitive.

The EPA examined the threshold analysis contained in Jerrett et al. (2009) and found that the mortality model including a threshold at 56 ppb had the lowest log likelihood value of all models examined. However, it is not clear whether the 56 ppb threshold model is a better predictor of respiratory mortality than when using a linear model for the Jerrett et al. data. Different, but valid statistical tests produced different conclusions about the threshold versus linear models. The less stringent test judged the 56 ppb threshold model to be superior to the linear model, but the confidence interval indicates the threshold could occur anywhere from 0 to 60 ppb. Using the more stringent statistical test, none of the threshold models produce better predictions than the linear model. Given these results, the CASAC concurs with the EPA's planned approach (USEPA, 2014b) to conduct a sensitivity analysis evaluating potential thresholds in the C-R functions that relate long-term ozone exposures with respiratory mortality and to not make the threshold models the core analytical procedure in the PA.

18. *To what extent does the Panel find the risk and air quality representativeness analyses to be technically sound and clearly communicated?*

The HREA clearly communicates the representativeness of the urban study areas in a national context by examining the major determinants of ozone effect estimates, namely demographics, base-line health conditions, exposure determinants, and climate and air quality.

The HREA provides an excellent synopsis of the major findings concerning subcategories of risk attributes and the differences between the urban study areas and the U.S. dataset. However, one aspect that should be included as part of the discussion on spatial variability relates to fine scale spatial variability due to roadway gradients. Individual Panel member comments provide guidance on some specific technical points that, if addressed, would strengthen an already excellent chapter.

Chapter 9: Synthesis

19. *To what extent does the Panel find the synthesis to be a useful integration and summarization of key results and insights regarding the overall health exposure and risk assessment?*

The Synthesis is a bit long, and might be better described as a "Summary and Synthesis". As a summary and synthesis it contains the necessary information, although it would be more effective if it were more concise. A table would be helpful that integrates the findings across endpoints and analyses conducted at various standards, such as found in the Welfare Risk and Exposure Assessment (Table 8-1 in the WREA).

Chapter 3 clearly shows that the current NAAQS for ozone is not protective of human health and

needs to be revised. The HREA emphasizes the conclusion reached in the ISA that there is a causal relationship between short-term ozone exposure and a broad range of respiratory effects, including lung function decrements, respiratory symptoms, inflammation, hospital admissions, and emergency department visits – all of which are observed below the level of the current ozone NAAQS. This chapter presents ample scientific evidence from human controlled exposure studies and epidemiology studies that adverse health effects occur with exposure to 72 ppb of ozone. For example, the combination of decrements in FEV1 together with the statistically significant alterations in symptoms in human subjects exposed to 70~~2~~ ppb ozone meets the American Thoracic Society's definition of an adverse health effect (ATC, 2000).

20. *To what extent does the Panel find that the discussion of overall uncertainty provides an appropriate context for interpretation of the exposure and risk results?*

The discussion of uncertainty provides a good context for interpretation of the exposure and risk results, though the general confidence in the current analyses is not apparent as currently presented. In particular, it would be useful if Section 9.5 concluded with more direct statements as to how to interpret the overall uncertainties in the risk and exposure assessments for use in standard setting. The current last line seems to be more negative than the report would otherwise indicate. The HREA should also identify the specific uncertainties that are most important (e.g., contribute the most to their overall confidence/lack of confidence in the results) and that should be targeted for further reduction in future work. There is also concern about how the standard errors for each city were calculated, and the HREA should acknowledge that the regression approach used would benefit from further scrutiny as part of future work.

Executive Summary

21. *To what extent does the Panel find the Executive Summary to be a useful summary of the data and methods used to estimate human exposures and health risks and the key results of the assessment?*

The Executive Summary is very good, and is a very useful summary of the HREA. There should be more discussion of uncertainties. A map of areas meeting current and alternative standards would be helpful. In addition to BenMAP and APEX, CMAQ should also be mentioned, given the central role CMAQ plays in the analyses.

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Appendix A

Individual Comments by CASAC Ozone Review Panel Members on EPA's Health Risk and Exposure Assessment (Second Draft)

Mr. George Allen

These comments focus on Chapters 1-4 of the Health REA.

General Comments.

Overall these chapters, especially chapter 4 (Air Quality Considerations) are substantially improved over the first draft REA, and are generally responsive to CASAC comments on that draft. The implementation of the HDDM rollback method is particularly impressive in its scope.

Charge Questions.

Chapter 1: Introduction

Q #1. To what extent does the Panel find the introductory and background material, including that pertaining to previous reviews of the O3 standards and the current review, to be clearly communicated and appropriately characterized?

This brief chapter clearly summarizes the recent history of the O3 NAAQS process, including the legal challenges to the 2008 final O3 NAAQS rule and the "reconsideration" process that EPA unsuccessfully pursued in response to those challenges. My comments on the Policy Assessment 2nd draft discuss the implications of these legal challenges and court rulings in more detail.

Chapter 2: Conceptual Model

Q #2. To what extent does the Panel find that the discussions accurately and clearly reflect the air quality, health effects, exposure and risk considerations relevant for quantitative exposure and risk assessment, building from information contained in the final ISA? What are the views of the Panel on the additional flowchart provided for the overall assessment and the additional information regarding specific elements of the exposure and risk assessments?

This chapter provides a useful and accessible overview of the complex REA process. The flowchart in Figure 2-1 (page 2-2) is helpful in understanding how the various parallel components of both exposure assessment models (APEX) and risk assessment (BENMAP) support the overall risk characterization. Including the relevant REA chapters for each component in this flowchart is very useful. Each component of the REA process is clearly summarized in a well-structured manner; these summaries provide the reader with a contextual understanding of the more detailed discussions in later chapters. Figure 2-2 (page 2-11) is a very clear summary of the causal determinations of both long and short-term O3 health effects. Page 2-21, lines 24-29 provide a helpful discussion of "attributable risk" and how estimates of total risk remaining after meeting the existing standard form the "reference value" for evaluation of risk reductions from meeting potential lower standards.

Chapter 3: Scope

Q #3. To what extent does the Panel find the scope of the health risk and exposure assessment is

clearly communicated? To what extent does the panel find the additional flowcharts for each analytical component to be useful additions?

This chapter covers the scope of the key design elements of the REA in a well-organized manner. The various "Conceptual Diagram" flowcharts are very helpful in helping the reader to understand each of these major components of the REA. Section 3-4, Air Quality Characterization, page 3-12, lines 7-21 provide a good description of how this 2nd draft develops risk estimates referenced to zero O3 concentration and from all sources – a substantial change from how previous risk estimates were developed, and responsive to CASAC comments from the previous draft REA.

Chapter 4: Air Quality Considerations

Q #4. What are the views of the Panel on the appropriateness of the methods used to characterize O3 air quality for the exposure and risk assessment? What are the views of the Panel on the HDDM-based adjustment methodology used to adjust O3 concentrations to just meet the existing O3 standard and alternative standards?

This chapter describes and characterizes the results of the CMAQ-based HDDM adjustment method, as the CASAC recommended in the review of the first draft REA. This is a radical departure from the previous "rollback" mathematical-only simulations in previous O3 NAAQS reviews which while computationally simple were inadequate for this purpose. The HDDM approach takes into account the complex precursor O3 chemistry and how a given emission reduction scenario may result in both benefits and dis-benefits across the urban to suburban scales.

EPA staff are to be commended for undertaking this major effort and publishing the improvements made to the HDDM rollback method in the peer-reviewed literature (Simon et al. 2013, doi: 10.1021/es303674e), including 129 pages of supporting information. The detailed breakdown of the HDDM method in section 4.3.3.1, pages 4-15 to 4-19, along with the flowchart in figure 4-6, page 4-17 serve as a reasonably detailed description of how the method was implemented for this review.

It is sometimes unclear throughout this chapter if adjustments were based on the equal NOx/VOC emission reduction scenario or a NOx only scenario; see page 4-18 lines 10-27 for one example. The discussion of limitations of the HDDM approach encountered for the substantial emission reduction scenarios needed for New York City and Los Angles (page 4-18 lines 28-35) could be expanded upon – what % reduction of which scenario(s) was required to meet the lower alternative standard levels?

It seems counter-intuitive that the model's inability to estimate hourly O3 distributions would be encountered at a higher concentration in New York (65 ppb) than in Los Angles (60 ppb), given that Los Angles current O3 levels are substantially higher than for New York City. EPA staff noted during the meeting that NYC needed such large NOx reductions because of the high concentrations at a single NYC NOx monitor. It would be useful for future work in the next review cycle to compare NYC HDDM results without that one monitor. In general, as the new near-road NOx monitoring network is deployed, there may be new and higher maximum

concentration urban NOx sites in large cities that only reflect a micro to mid-spatial scale and could make the HDDM performance issues noted for NYC and LA for NAAQS targets of 65 ppb or lower more common.

Q #5. To what extent does the Panel find that the discussion of uncertainty related to the air quality inputs to the exposure and risk assessment appropriately covers important sources of uncertainty?

The specific limitations of the HDDM method for simulating lower alternative standards in New York City and Los Angles are discussed on page 4-18 lines 28-36 and page 4-19 lines 1-6. The "significantly more uncertain" risk estimates (due to the need to use the 95th percent CI lower bound estimates) is noted; a brief qualitative description of this uncertainty would be useful here.

Section 4.3.3.2, Resulting Air Quality (page 4-19), presents a good overview of how the HDDM adjusted distributions behave in general for both spatial and temporal patterns. A useful comparison of the quadratic rollback and the HDDM adjustment methods is presented in this section and figures 4-7 and 4-8. It is noted on page 4-20 line 1 that in general hourly O3 distributions are shifted upward with HDDM compared to the quadratic rollback method.

The more general limitation of the HDDM approach for cases where large emission changes (perturbations) are needed to meet lower alternative standard levels (60-65 ppb) is clearly explained in section 4.5, page 4-38 to 4-41. This section quantitatively presents the uncertainty for 50 and 90% NOx reduction conditions, and concludes that the uncertainty of the HDDM method "is small up to 90% emission cuts" (for NOx, page 4-39, lines 9-10). Specific uncertainties are presented for the 15-city case study areas for 75 and 65 ppb cases (page 4-39, lines 27-31). It is unclear if these are NOx-only emission reduction scenarios (as discussed earlier on this page) or not. Table 4-6 (pages 4-42 to 4-51) is a useful summary of qualitative uncertainty for key AQ elements of the risk analysis.

Specific comments.

Page 2-7 lines 24-27: just equal NOx and VOC emission reduction scenarios? or NOx only?

Page 3-12 line 1: "urban cast" typo.

Lines 2-3: NOx only emission scenarios were also considered and should be mentioned here since NOx reductions are likely to be the more effective approach in most scenarios.

Page 3-20 line 7: sentence ends prematurely. "causal relationship with." …

Page 4-2, lines 9-12: it is not "generally agreed" that Castnet O3 data going back to 2006 is of comparable quality to the data reported to AQS. While Castnet QA/QC requirements now (since 2011) meet those required for compliance monitoring by state and local air agencies, the older O3 data did not meet those requirements. See public comments by Alan Leston for more detail. This does not mean that those data cannot or should not be used in the REA; they fill a gap in rural

primarily eastern US regions and do have value in this process.

Page 4-5, footnote 6 says composite monitors do not always include the highest design value monitor in every urban area. Page 4-14 lines 12-14 says all monitors were used. This needs clarification.

Page 4-7, Figure 4-4, bottom plot: Sacramento 2008 is oddly elevated by ~ 20 ppb. Is this 4th highest value correct? If yes, a brief explanation in the text or a footnote may be useful.

Editorial Comments:

Pg 6-43 lines 4-5:
from the value at 36 linearly to zero at age 55, and set it to zero for ages above 55 (**see Error! 4 Reference source not found**.).

Pg 7-19, line 11-12
estimates that were very close to those generated using the population-weighted O3 metric (**see 11 REFERENCE- Karen Wesson???**).

Pg 7-69, line 11:
As discussed in Chapter 4 **(section ???)**, after ...

Mr. Ed Avol

Comments EPA O3 Document, 2nd Draft REA

CHAPTER 4

Fig 4-9 & 4-10, pp4-26 on… I'm curious, and a little concerned, about the HDDM adjustment approach and its admission that downwind surburban sites are excluded from consideration of adjustment impacts. The HDDM adjustment admittedly does not completely account for or consider the downwind rural ozone concentration effects of NOx or VOC adjustments in the upwind urban areas. In several urban locations (like Los Angeles, where downwind reporting sites such as Lake Arrowhead may be excluded from assessment of ozone adjustment impacts evaluations), a potentially misleading picture of decreasing levels in the immediate and downwind vicinity may therefore be created. Since any single monitoring site in a region can place the region in non-compliance, (and locations like Lake Arrowhead have historically been the "high" site in the Los Angeles region), what does exclusion of persistently high downwind sites from the analysis imply for acceptance/endorsement/utility of the HDDM adjustment approach?

CHAPTER 5 MODELING

General Comment – Although I appreciate that one has to select some framework for discussing comparative reductions and portions of the population affected, there is at least one somewhat disquieting aspect to the presentation and interpretation of it for me, and that is the way in which the percentage of populations in the urban case study areas is used. The 15 Urban Case Study Areas represent (Table 4-1, p4-6) populations ranging from 2.7 million to 21 million people (2010 Data), an almost ten-fold range. The ensuing discussions and comparisons present these study areas in terms of percent of children or adults affected at some design value (60, 65,70, or 75 ppb O_3, for example), but 5% of the New York population (at 21+ million) arguably means something quite different, in terms of affected individuals, than 5% of Baltimore's population (at 2.7+ million). Moreover, the percentage perspective does not take into account any adjustment for a "vulnerability" factor (due to race, ethnicity, access to health care, pre-existing conditions etc), so discussion of proportional changes across urban case study areas glosses over some very important indices of public health. I realize that the intent of the presentation is not to compare Atlanta to Sacramento, but still, proportional changes in air quality will likely have disproportional changes in regional public health outcomes…and that observation or acknowledgement does not seem to be considered in any substantive way in the document portions I reviewed (and to my knowledge, is not included in the exposure-response function in the McDonnell-Stewart-Smith model referred to in the HREA).

CHAPTER 8 NATIONAL SCALE MORTALITY BASED ON EPI STUDIES

(nothing to usefully add here; BENMAP is not in my portfolio of expertise)

CHAPTER 9 SUMMARY

General Comment: This ~50 page chapter is a summary? There is a lot of detail and re-visiting of issues that could have arguably been housed in this detail in the other chapters. Additionally, there is no differentiation between key summary conclusions and more general information in this

chapter. Surely there must be some key (highlight-able?) summary points that the Reader should be aware of?

Section 9.2 is titled "Key Results", but it rambles on, showing tables and discussing approaches. With all due respect, this is NOT the way to present "Key Results"! This could and should be edited down to a paragraph or two per section, referring to the previous chapters wherein additional supporting details may be found. Key tables or figures should be included to emphasize critical points, not to reproduce them in much the same detail as in their respective home sections. In its current form, much of the important summary conclusions are lost in the morass of re-presentation.

Some Specific Comments

1. P9-1, lines 4 to 6: re-phrase to say, "…short-term O_3 exposures are causally related to both respiratory and cardiovascular effects, and that…"
2. P9-8, Section 9.22 Human Exposure Modeling (Chapter 5)
3. P9-9, lines 2 to 4: delete the second half of this sentence (it doesn't add anything here) and leave sentence to state that "Persons spending a large portion of their time outdoors during afternoon hours experienced the highest 8-hour O_3 exposure concentrations."

Dr. Michelle Bell

Chapter 5. Characterization of Human Exposure to Ozone

The section on APEX would benefit greatly from some discussion of its accuracy. Can a section on evaluation of APEX be included? As written, the section tells us what Apex does, but not how well it does it.

The overall point of the APEX analysis is not made clear in the introductory portions of Chapter 5. As the regulations and most health analyses will be or were based on ambient levels or controlled exposures. Just add more description and detail here for how the results will be used. In general, this chapter could use more discussion of the implications of the results, in addition to the numerical estimates.

The relation of these values, estimated by APEX, in comparison to clinical evidence for benchmarks (page 5-18), needs explanation as the health-based studies are typically based on an overall ozone level, not accounting for activity patterns and so on.

The section on meteorological data used (5.2.4) is a bit vague in places. E.g., "a few to several meteorological stations". Information on the imputed data (% imputed), etc. would be helpful.

Chapter 8. National scale mortality risk burden based on application of results from epidemiological studies

Overall, this chapter is well written and explained. The methods, interpretation and presentation of methods and results are technically sound and well communicated.

Provide the rationale for the selection for the concentration-response functions used in this section. The choice of these studies needs to be justified. This discussion may belong in Section 7, which gives some information on this (around page 7-18), but it's still unclear.

The chapter discusses that higher certainty exists for urban areas, so it may be useful to note such areas (the ones used on the original CRFS) on a map or some of the existing maps.

This chapter would benefit from information on why city-specific and national effects may differ.

In general, Chapter 8 would benefit from reference to sections in Chapter 7.

Dr. Joseph Brain

Chapter 1: Introduction

1. To what extent does the Panel find the introductory and background material, including that pertaining to previous reviews of the O3 standards and the current review, to be clearly communicated and appropriately characterized?

Chapter 1 is brief – six pages long – and yet it does an excellent job in introducing the entire document. The complex history of the ozone standard is well described, including the controversial decisions and legal challenges that occurred during the past decade. The essential facts are there and links to more detailed documents are given. The summary of the goals and approaches is helpful. The final section "Organization of Document" is a brief but useful guide.
What's missing? After informing the reader that the current standard is 75 ppb, based on the annual 4th-highest daily maximum 8-hour average concentration, averaged over three years, there is no comment as to exceedances. An important context early in the document is the status of the current ozone standard. Is it like CO that exceedances are few and far between, or is the current standard problematic?

Chapter 2: Conceptual Model

2. To what extent does the Panel find that the discussions accurately and clearly reflect the air quality, health effects, exposure and risk considerations relevant for quantitative exposure and risk assessment, building from information contained in the final ISA? What are the views of the Panel on the additional flowchart provided for the overall assessment and the additional information regarding specific elements of the exposure and risk assessments?

Chapter 2 has been rewritten and is clearer and more effective than in the previous draft. It clearly shows how this current model builds on information from the now final version of the ISA. I find the flow chart, Figure 2-1, clear and helpful. As indicated in my comments on Chapter 1, why not discuss the topic of exposure and risk assessment in the context of exceedances for the current ozone standard.
One topic that seems to be missing, but was prominent in previous discussions, was the policy-relevant background (PRB) and how that influences our interpretation of the available data. Is it appropriate to compare levels of ozone where health effects are observed to zero ozone, or should they also be compared to the PRB?
In regard to Section 2.2.5, when discussing "exposures of concern," the agency should better defend the three benchmark levels selected, 60, 70, and 80 ppb. One would have thought that one of the benchmark levels would be the current standard, 75 ppb. Why isn't that fourth level included? Don't we really want to know how these other three levels – one above and two below – differ in their consequences from the current standard?
Figure 2.2, "Causal Determinations for O_3 Health Effects," is simple and helpful, but I have several questions about it. Don't we need a brief definition of the three categories: suggestive, likely, and causal? It is true that these "strength of evidence" categories are defined in the ISA, but few readers will have the persistence to look them up. Shouldn't we add a brief definition here of

these important categories and what they mean?
Some issues remain unexplored that may be important. For example, what are the practical consequences of adaptation, a well-known phenomenon for ozone exposures? Is a high level of ozone more serious for individuals and communities that rarely encounter elevated levels of ozone compared to more adapted individuals who experience elevated ozone levels much of the time, and perhaps have greater exposures out-of-doors because of climate, and exercising more often outside? Animal data clearly suggest that responses to the same ozone level are influenced by ozone exposure history.
I like the discussion of at risk populations, 2.2.8. In previous documents, we had trouble with this, since at risk could point to increased likelihood of exposure as well as inherent reasons for greater susceptibility, e.g. age and preexisting diseases. A persistent problem is always the limits of at risk populations. To what extent do we base standards on more susceptible populations and to what extent do we want standards to be driven by small numbers of hypersusceptible groups or individuals? For an asthmatic in hospice because of cancer, any increase in ozone may be life threatening.
Overall, Chapter 2 is dramatically improved.

Chapter 3: Scope
3. To what extent does the Panel find the scope of the health risk and exposure assessment is clearly communicated? To what extent does the panel find the additional flowcharts for each analytical component to be useful additions?
I believe that Chapter 3 does a good job of clearly communicating the scope of the health risk and exposure assessment. In particular, the figures and flow charts provide an excellent summary and guide the reader to the more extensive text. Figure 3-1 fits well within the section on air quality characterization and helps the reader. Figure 3-2 accurately summarizes the accompanying text. Figure 3-3 is useful in terms of linking exposure to uptake of ozone in the lungs. It delineates the multiple factors that affect the link between exposure levels in the ambient environment and the exposure of lungs. I am less happy with the bottom oval, which has all this culminating in changes in the FEV1. Why single out that parameter and ignore other outcomes? Modest changes in FEV1 per se may be of less significance than related inflammatory changes, such as more neutrophils in the BAL. Those changes may be more tightly linked to the pathogenesis of chronic lung disease. Focusing on the FEV1 may lead to minimizing the consequences of ozone exposures on a chronic basis. It also focuses, through the symbol delta, in acute changes. As the text mentions, there is greater interest in how ozone and other air pollutants might affect lung growth as well as the long-term declines in pulmonary function as we age.

Figure 3-4 seems more complicated, and at least for me, was not a very helpful introduction to the text. I'm happy with the final figure, Figure 3-5.

Table 3-1 raises the issue of the empty boxes, the unfilled cells: Why were the categories of respiratory hospitalizations, respiratory ED visits, or respiratory symptoms measured in so few of these cities. Why, for example, were respiratory hospitalizations measured in Detroit, Los Angeles, and New York, but not in the other nine USA urban areas?

I would again point out lack of clarity in terms of background levels of ozone and the related PRB. In the policy assessment draft, especially in Chapter 2, Section 2.4, there is an extensive discussion

of nonanthropogenic sources/background ozone. Shouldn't this topic at least be mentioned here? What do we make of this ozone background? Should health effects at particular ozone levels (when estimating a delta) be related to zero levels of ozone (which never occur) or to our best estimates of background ozone? Moreover, how do we take into account varying background levels in time and space as we model health effects? I also ask why our estimates of exposure and health outcomes don't include the current standard of 75 ppb.

Dr. David Chock

CHAPTER 4: AIR QUALITY CONSIDERATIONS

Charge Questions:

4. What are the views of the Panel on the appropriateness of the methods used to characterize ozone air quality for the exposure and risk assessment? What are the views of the Panel on the HDDM-based adjustment methodology used to adjust ozone concentrations to just meet the existing ozone standard and alternative standards?

5. To what extent does the Panel find that the discussion of uncertainty related to the air quality imputs to the exposure and risk assessment appropriately covers important sources of uncertainty?

This Chapter is a substantial improvement over the first draft version. Replacing the Quadratic Rollback method with the HDDM procedure for estimating the ozone concentration distributions under "just meeting" the standard and alternative standards is an important improvement from the scientific perspective. Using the HDDM approach for adjusting the ozone concentrations to just meeting the existing standards or the alternative standards actually obviates the concern about how the background ozone concentrations should be defined. Another major improvement is the demonstration of the statistical superiority of the Downscaler approach to fuse the modelled and observed ozone concentrations over the whole nation when both sets of information are available (like in 2007). This approach helps improve the accuracy of the fused ozone concentration profile in monitored areas and the estimate of the national burden of mortality risk. The Appendices are also very well prepared with a wealth of supporting information.

The key assumptions in this Chapter that allow the incorporation of the HDDM approach in actual applications is the linear relation between the first-order sensitivity coefficients and the ozone concentrations, and between the second-order sensitivity coefficients and the first-order sensitivity coefficients. These assumptions arguably allow the transfer of the statistical relations based on the modeling results for 2007 to the real world by using the observed ozone concentrations at the monitors to replace the modeled ozone concentrations for the grids containing the monitors at the same hours and in the same seasons but for the years different from but not too distant from 2007. These relations of model-run results must be considered strictly empirical. Actually, there is no theoretical basis to justify this regression linking the sensitivities to ozone concentrations. The notion of NOx-limited and VOC-limited conditions may help empirically but far from being reliable across all monitoring sites and all hours of the day in an urban area. The only basis the current approach relies on is the hope that the regression patterns remain relatively unchanged for the corresponding sites and time of day and season for the period not too distant from the year the regressions are established. Yet this approach may well be the only sensible way presently to apply the HDDM results to adjust the ozone concentration distributions by precursor emission reductions to meet the current and alternative ozone air quality standards for the different areas under consideration

It is actually a bit surprising that some of the linear fits between the first-order sensitivity coefficients and the ozone concentrations look pretty good, as illustrated in Appendix 4-D. The empirical relations between the first and second sensitivity coefficients are more tentative, as expected. But at least the generally anticipated negative slopes are observed as we expect the ozone concentrations to eventually decrease and level off as emission controls become more stringent.

In the case of high NOx emission reductions, the authors devise a three-step approach by first determining the sensitivity coefficients generated by the 0%, 50% and 90% NOx emission reduction base runs, and applying the correct sets of sensitivity coefficients or their linear combinations to the appropriate region of NOx emission reduction. (See p. 19 of Appendix 4-D.).

There are two other issues that need mentioning, both may be relatively minor at present in comparison to the drastic linear-relation assumptions described above, but still worthy of mention. One is the implicit assumption of local emission reduction. The sensitivity coefficients are built on the assumption that the emission perturbation is described by a uniform, across-the-domain percent US anthropogenic emission reduction. But the resulting sensitivity coefficients are applied only locally for a given urban area without regard to the emission reduction levels of the upwind areas. The resulting errors may be somewhat alleviated if all or most upwind areas also require similar levels of emission reduction to achieve a given ozone air quality standard, or if the high ozone concentrations of an area are dominated primarily by the ozone chemistry of emissions from within the area. The other issue is the predominant use of NOx emission reductions to meet a given standard. Emission reductions by NOx alone is more straightforward but may not be a robust or preferred control strategy in practice in some areas and may lead to an upward shift of the lower portions of the ozone concentration distributions as seen in many metropolitan areas in Figs. 4-9 and 4-10. In these cases, the present or alternative ozone air quality standard may be met, but perhaps at the expense of an increased health hazard due to higher ozone exposures in the more densely populated districts where the VOC-limited conditions tend to prevail, at least initially.

The use of the Downscaler for fusing the observed data and modeling results yields the best performance compared to the eVNA approach. This is not surprising since, in the case of the Downscaler, a large number of parameters are introduced to enable optimization of the fit, whereas eVNA simply invokes a set of straightforward scaling factors for interpolation. Using the estimated parameters for the Downscaler approach to estimate the nationwide "fused" ozone concentrations that just meet the current ozone standard or alternative standard may not be readily justified.

In Table 4-6, the authors provide an extensive list of sources of uncertainty in the generation of the air quality output for health risk assessments. The list is very well thought out and thorough. And their assessments on the directions and magnitudes of the uncertainty impacts of these sources are reasonable. The knowledge-based comments and comments on the influence of uncertainty from these sources on risk estimates are cogent and reasonable. There is one exception: the size of the knowledge-based uncertainty in item F (Applying modeled sensitivities to un-modeled time periods) is actually uncertain in itself. A designation of "low-medium" may be a bit optimistic. It

may be more appropriate to designate it as "to be determined" or "probably medium".

On p. 4-47, the statement regarding the underestimation of benefits of reducing high ozone and disbenefits of increasing low ozone is confusing. It appears that the authors are referring to the underestimation of the variability of benefits of reducing high ozone and of the disbenefits of increasing low ozone since these regions are at the extreme ends of the "data" used to construct the linear regressions for the sensitivity coefficients.

In conclusion, I find this chapter to be very well prepared and the authors need to be congratulated for their effort.

Minor Comments:
In the Methods section (4.3.3.1), the text ought to mention the modeling domains and the horizontal grid size used in the model.

For better clarity, the pink and turquoise colors in Figs. 13-27 need to be explained in the text or figure captions in Appendix 4-D.

In Appendix 4-D, it would be useful to mention in the figure caption of Figure 2 that the "75%" mark is used in the illustration instead of the "90%" used in the text.

CHAPTER 5: CHARACTERIZATION OF HUMAN EXPOSURE TO OZONE

Charge Questions:
6. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded population-based exposure analysis to be technically wound, appropriately balanced, and clearly communicated?

7. Chapter 5 includes several evaluations of key APEX inputs and model outputs, including for example analysis of time-activity data and comparison of actual personal exposures with modeled exposures. What are the views of the Panel on the appropriateness and usefulness of these evaluations and the conclusion drawn from these evaluations?

8. Chapter 5 includes several scenario-based exposure simulations that focus on specific populations or behaviors. What are the views of the Panel on the design, results and interpretation of these additional scenario-based exposure simulations?

9. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the exposure estimates?

This chapter, together with its accompanying appendices, is a result of the EPA's best-effort projection of population exposure under existing and alternative ozone air quality standards. The assessment, interpretation, and presentation of the methods and results are excellent. New material

and methodologies have been incorporated, together with a large amount of cross-checkings, verifications, sensitivity tests that significantly enhance the credibility of the conclusions. Noteworthy improvements include the use of the HDDM methodology in place of the quadratic rollback approach, incorporation of new activity data base in CHAD, estimated exposure impact of averting behavior for all school-aged children and for asthmatic school-age children, among others. The attached appendices are quite detailed and comprehensive.

Appendix 5F contains the results of a large number of exposure simulations for different population subgroups under different ozone standards. The presentations of the results are clear and concise. Overall, this exposure analysis is fair and credible, and is an impressive achievement. It most definitely is an enormous improvement over the first draft.

Figure 5-1 is an excellent summary of the conceptual framework used in the exposure study. Section 5.2.3 indicates that the census tract ambient hourly ozone concentrations come from the monitors coupled with the VNA estimation when extrapolations beyond the range of 30 km from a given monitor becomes necessary. However, it should also describe how the air quality modeling results are used to replace the monitored concentrations when cases of achieving the existing or alternative air quality standards are to be modeled. Is the spatial resolution of the monitors retained or replaced by that of the modeling grid? For clarity, a very brief description is in order on how eVNA parameters are used in projecting the concentration distributions for cases that just meet the existing or alternative standards.

The presentation of the exposure assessment results (Section 5.3, pages 5-23 to 5-34) is excellent. The figures are clear, informative and concise. It may be helpful to explain why there are two disconnected lines overlapping 2008 in Figures 5-5 through 5-9. This is a result of two different sets of design value, one for 2006-2008 and one for 2008-2010. The set for 2008-2009 was not used in the analysis. The different levels of design value trigger different levels of emission control, which leads to different levels of exposure.

The chapter provides some discussions on the analysis of time- location-activity data. It is reassuring that the majority of diaries from CHAD comes from surveys conducted in the past decade and that the pre-1990s diaries represent less than 15% of the total diaries available in CHAD. Even in the case where there are some noted differences in activities, like the children's outdoor participation rates of 50% in the 1980's and 35-40% in later decades, the inclusion or exclusion of the 1980's data causes a change in outdoor participation rate of only 3%. (p. 5-37, lies 25 to 36). The authors also indicate an average of 30-minute increase in time spent outdoors in the 1980's data compared to the 2000's data. But when an afternoon outdoor time of at least 2 hours is considered, inclusion of these old data have little adverse influence on the exposure outcomes due to the large variability in the data. Accordingly, it looks reasonable that inclusion of these old diary data would not strongly influence the exposure estimates.

The EPA compared the CHAD diary results with literature on the time spent outdoors and the levels of exertion while outdoors for both asthmatics and non-asthmatics and found little difference between the two groups. This is separately true for school-age children and for adults. However, there seems to be some inconsistency in the literature regarding the *range* in percent of outdoor time spent on strenuous activities by asthmatics. (See p. 5-40, lines 3 to 14.) It would be

helpful if this difference could be resolved soon. But this percent *range* difference in the literature is not necessarily grounds to negate the EPA's conclusions, which are based on the analysis of newer available data (See p. 5-39).

It is interesting that there seems to be persistent relative magnitude differences among exposure estimates derived from using ozone concentrations based on the original air monitor values, VNA values and eVNA values. In general, the design of an interpolation scheme ought not to introduce a systematic bias, unless there are some persistent spatial patterns that distinctly favor some biases, like having the highest concentrations constantly occurring in the regions with the highest population density. But these spatial patterns may not be true or persistent in many urban areas. In the case of eVNA, because the modeled concentrations are also involved, some biases may indeed exist, and the difference may in fact reveals the disadvantage of using the monitor values alone to characterize the spatial concentration distributions over the whole urban area.

The explanation for the differences in exposure between the Quadratic Rollback and HDDM is excellent. Indeed, Quadratic Rollback adjusted the high-quantile portion of the concentration distribution with some fixed rules which are not based on science.
Table 5-6 characterizes the major uncertainties encountered and their potential impacts on the APEX exposure assessments. The list is comprehensive and the estimated impacts look reasonable to the extent of our current understanding. Evidence to challenge the impact assertion is not available. The table also indicates which uncertainties are newly evaluated. This is helpful.

Appendix 5-D contains and extensive list of types or components of exposure variability like simulated individuals, microenvironments, and physiological characterizations, and how APEX incorporates them. Components that may co-vary with the input are also incorporated as necessary. The APEX incorporates the impacts of variability and covariability reasonably and quite thoroughly. One item that is worth mentioning that is also outside the control of APEX is the variability of input meteorological conditions and the resulting ozone concentrations beyond those described in Table 5D-1. Presently, the APEX results on exposure outcome are based on the explicit input of meteorological variables and adjusted ozone concentrations for the period of 2006 – 2010, which may or may not be representative of future scenarios for ozone.

CHAPTER 9: SYNTHESIS

Charge Questions:
19. To what extent does the Panel find the synthesis to be a useful integration and summarization of key results and insights regarding the overall health exposure and risk assessment?

20. To what extent does the Panel find that the discussion of overall uncertainty provides an appropriate context for interpretation of the exposure and risk results?
This chapter is an excellent summary and analysis of findings presented in this Assessment report. The description is comprehensive, accurate and well thought out, even though it is a bit on the lengthy side.

In describing the improvement of the HDDM air quality adjustment methodology over quadratic rollback on p. 9-4, it would be useful to add as part of the first point or as a separate point that the quadratic rollback requires an assumed background ozone concentration which serves as the "floor" for each area. How to set this "floor" can be controversial. The HDDM approach, on the other hand, removes this problem since the background emissions are explicitly included in the model simulations and the predicted ozone concentration changes are directly linked to the US anthropogenic emission reductions alone.

On p. 9-12, line 1, "Table 5-6" should be "Table 5-7." And on line 25, "Figure 9-2" should be "Figure 9-3." Also, it would be useful to provide additional clarifications in the figure caption or the footnote of Figure 9-3 that the highest value across the years 2006-2010 in the percent of children with at least one ozone exposure that exceeds 60 ppb for each of the cases of just meeting given air quality standards actually comes from the maximum of each pair of red curves shown in Figure 9-2. A similar linkage is also indicated for Figure 9-5 and Figure 9-4.
The authors highlight two sources of uncertainties in modeling ozone responses to meeting different levels of the standard. (See p. 9-39, lines 15-34) One is the applicability of HDDM sensitivities over large emission perturbations. The other is the variability in data used to create regressions linking the sensitivity coefficients to observed concentrations. The first source of uncertainty can be controlled and is relatively small. But the authors indicate that the second source of uncertainty is also small. The authors stated that the uncertainty introduced from the *application* of regressions to determine sensitivities were quantified by propagating uncertainties in the sensitivities through to uncertainties in the final predicted ozone concentrations which had standard errors less than 1.4 ppb for all adjustment scenarios (p. 9-39, lines 26 to 29). This statement may well be true. But the problem is that the regression steps themselves have high uncertainty because there is no theoretical underpinning to justify the general applicability of these relations. One cannot tell from the level of the ozone concentration alone whether the slope of the first-order sensitivity coefficient relative to the concentration will be positive or negative, let alone the magnitude of the slope. The notion of NOx-limited and VOC-limited conditions may help empirically but far from being reliable across all monitoring sites and all hours of the day in an urban area. It would be helpful if the authors acknowledge that the generality of the regression approach needs further scrutiny.

Section 9.6 is an excellent conclusion for the overall integrated characterization of health risk associated with different ozone standards based on the enormous tasks undertaken by EPA to date.

EXECUTIVE SUMMARY

Charge Questions:
21. To what extent does the Panel find the Executive Summary to be a useful summary of the data and methods used to estimate human exposures and health risks and the key results of the assessment?

The Executive Summary is well written and is sufficiently comprehensive to cover all the new approaches used and the major findings. It is most definitely useful for readers who are experts in their respective fields. But it may be too lengthy and too technical for non-experts. There are

some items below where clarifications would be helpful.

Item 4 of the left bottom paragraph on p. ES-2 is too general and vague. Do the authors refer to uncertaintiey associated with various inputs and how and to what extent these uncertainties influence the risk estimates?

At the bottom of the right column on p. ES-4, the text says, "Based on this information, no more than 26 percent ….." But the readers cannot see anything close to the 26% in the two figures shown. The 26% refers to the maximum percent estimated for the 15 urban areas. But the figures refer to the average percent estimated. I recommend to just show the average percent to maintain consistency between the text and the figures. Otherwise, clarify that the 26% refers to the maximum estimated percent not plotted in the figures. Similar issues exist in the case of 70-ppb in the text.

The caption for the figures on p. ES-5 is confusing. It is better to change "average percent increases in percent of …" to "average incremental increases in percent of …" as in p. 5-69 of Chapter 5. (There is a similar issue in the caption of the figure on p. ES-7.) Also, they are arranged as top and bottom, not left and right as indicated in the caption.
The caption of figures on p. ES-8 needs to indicate that the bottom figure for respiratory HA is also for short-term exposure.

Dr. Ana Diez-Roux

Chapter 5

6. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded population-based exposure analysis to be technically sound, appropriately balanced, and clearly communicated?

Overall I found the methods to be clearly presented. Figure 5-1 was especially useful in summarizing the various inputs to the modeling process. The document does a very good job of describing the various sources of data that went into the modeling process and how the data were used.

I also found the description of the model output useful, although some relatively minor editing would improve clarity. For example, the title of Figure 5-2 says "Percent of asthmatic school-age children in all study areas with at least one O3 exposure at of above 60ppb-8 hour while at moderate or greater exertion…" . It is not clear what "one O3 exposure" means in this context. Does it mean that they were engaging in moderate of greater exertion at any time during an 8 hour period with an average of >=60ppb? In order to count as "one exposure" is there a minimum time requirement (for example, must they be engaging in moderate or greater exertion during a least one hour at any time during the 8 hour averaging period?) Perhaps I am misinterpreting the output measure reported here, if so this needs to be clarified.

Figure 5-3 was very helpful as a way to present the results but a bit more clarity in the labeling would help readers better interpret the graphics. For example the labeling of the bottom panel could be "Percent of asthmatic school age children with at least one exposure [see my note above regarding clarifying this metric] at or above 60ppb, 70 ppb and 80 ppb (red, green and blue lines) when air quality was adjusted to just meet standards of 75, 70. 65 and 60 ppb (panels left to right).

Section 5.3.3 provides a very good description of the results. A summary at the end of the section highlighting the key points (especially those that will be of relevance to the PA) would be very helpful.

7. Chapter 5 includes several evaluations of key APEX inputs and model outputs, including for example analysis of time-activity data and comparison of actual personal exposures with modeled exposures. What are the views of the Panel on the appropriateness and usefulness of these evaluations and the conclusions drawn from these evaluations?

I found the evaluations presented in section 5.4.1 useful and well described and the conclusions reasonable. The document has been greatly strengthened through the incorporation of this section. Section 5.4.4 was also useful although the lack of agreement wit the Detroit data in section 5.4.4.1 needs to be explained or at least further discussed with respect to the implications of this for the exposure estimates previously presented.

8. Chapter 5 includes several scenario-based exposure simulations that focus on specific

populations or behaviors. What are the views of the Panel on the design, results, and interpretation of these additional scenario-based exposure simulations?

Sections 5.4.3 included very useful information. It would benefit from a concise summary at the end highlighting the key conclusions and their implications from the exposure estimates previously presented.

9. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the exposure estimates?

All important sources of variability and uncertainty are addressed in the text or extensive tables. The document does a very good job of discussion all potential sources of uncertainty and evaluating the extent to which they can be addressed.

Chapter 7: Characterization of Health Risk Based on Epidemiological Studies

13. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated epidemiology-based risk assessment to be technically sound, appropriately balanced, and clearly communicated?

Overall I found the presentation of the methods clear and well justified. The criteria used to select the epidemiologic studies and metrics used in the risk assessment are well described. The limitations of the approach are also adequately noted.

The chapter generally does a good job of describing the results and sensitivity analyses. In general the presentation of results is markedly improved over the prior version. The sequence of results presented in tables and figures for each health endpoint is informative and well described. However some additional editing of the language would further improve clarity. The chapter repeatedly refers to "incidence" or "mortality" when what it is referring to (if my interpretation is correct) are actual counts of deaths or events (epidemiologically incidence and mortality are by definition a proportion or a rate, not a count). In contrast Figure 7-4 does present true mortality estimates (incidence of death). This language needs to be corrected throughout so that counts of deaths are not referred to as incidence. For example, the column headers of Table 7-7 could be modified to "Total number of o3- attributable deaths" and "change in total number of O3 attributable deaths" (if there is a reduction the number should be preceded by a negative sign). Similar language referring to "events" can be used for morbidity tables.
The titles for figures 7-2 and 7-3 are identical.
The section on short term attributable mortality (pg 7-69) indicates that "the mortality risk metric is generally not responsive to meeting the existing and alternative standard levels". It is argued that this occurs because of simulated increases on O3 on some days and regions, even when the standard being met is lower. It is noted that this contrasts with clinical study-based risk estimates. Later in the same section it is noted that "the magnitude of the risk reduction increases as lower alternative standards are simulated". This seems to contradict the previously quoted statement in the same section. Perhaps the initial statement should be modified to indicate that the impact of alternative standards on changes in short term attributable mortality is small but increases as the

standard is lower. Then go on to discuss why the impact may be small (this is because of possible increases in ozone in some areas as a result of the way in which meeting the alternative standard was simulated but also because a lot of the attributable deaths occur at lower levels of the distribution which are not largely impacted by the alternative standards).

It is noted here (and later on in the PA) that based on the approach used to model ozone reductions under alternative standards, ozone levels may actually rise in some areas when meeting lower overall standards. This is because of the dynamics used to model ozone reductions. It should be noted that as a consequence the estimates of the health effects are not precisely the health impacts of reducing ozone to a certain level, but rather the health impact of meeting an alternative standard *through a postulated set of changes to precursors* (some of which results in reductions and some of which result in increases in ozone). This is a subtle but important difference I think. It may be useful to at least note this. Also, is the approach used to model meeting alternative standards (which results in increases in some locations but decreases in others) realistic? The extent to which the simulated increases of O3 at lower standards is realistic and to be expected in the real world needs to be discussed.

14. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources and appropriately characterized the relationship of those sources of uncertainty and variability to the risk estimates?

The discussion of variability and uncertainty covers the main sources of variability and uncertainty and addresses them appropriately to the extent possible with available data.
The section also appropriately describes sensitivity analyses that have performed to at least partly assess the plausible impact of some of these uncertainties. The table included is thoughtful, comprehensive, and informative.

15. Adjusting the distributions of O_3 concentrations based on decreasing NOx emissions to just meet the existing and alternative O_3 primary standards resulted, in some cases, in substantial shifts in the spatial and temporal patterns of O_3 across case study urban areas relative to patterns of O_3 that existed for recent air quality, and presumably relative to the patterns present in the study locations of the epidemiology studies from which the concentration response functions were drawn (see section 7.1.1 of the TSD, USEPA, 2012). What are the views of the Panel on the characterization of the degree to which these changes in spatial patterns of O_3 introduce uncertainty in risk estimates when effect estimates based on one spatial/temporal pattern of O_3 (the pattern in the epidemiology study) are applied to a substantially different spatial/temporal pattern of O_3 concentrations?

It is noted that the simulations used to estimate Ozone levels under alternative standards result in spatial patterns different than those observed in the epidemiologic studies on which the health effects measures are based. This would result in different health impacts than those predicted from the epidemiologic studies if one or both of the following conditions are met (a) factors associated with space modify the effects of ozone on heath or (b) spatial mobility of persons within the area is a key driver of individual-level exposures. If we are confident that the impact of these two conditions is absent or negligible then we can be confident in the expected health benefits as predicted despite the change in the spatial pattern.

In the absence of a clear rationale for effect modification by space, I would argue that the impact of the changing spatial patterns can be ignored. If we believe the effect estimates are capturing the underlying causal effect, then this effect should be approximately generalizable over space.

16. In particular, what are the views on the Panel on the characterization of the level of uncertainty associated with estimates of risk associated with days with relatively lower composite (area-wide average) O_3 concentrations and those with relatively higher composite O_3 concentrations?

This is mentioned in the chapter but is not given much relevance. I am not sure there is much more to say about this than what is already included.

Dr. Daniel Jacob

Chapter 4: Air Quality Considerations

4. What are the views of the Panel on the appropriateness of the methods used to characterize O_3 air quality for the exposure and risk assessment? What are the views of the Panel on the HDDM-based adjustment methodology used to adjust O_3 concentrations to just meet the existing O_3 standard and alternative standards?

I view the methods as appropriate and a major improvement over the quadratic rollback method. A few points seem worth clarifying:

4.1 Pages 4-15,16. It seems that a very important aspect of improving the accuracy of the HDDM analysis for large emissions perturbations is the calculation of sensitivities for three emission levels, thus allowing better representation of the non-linearity. However, I had to wait until the uncertainty analysis in section 4-5 to learn that this calculation at three emission levels was done, and even there it did not tell me what these emission levels were. I recommend that this information be brought up here in the initial description.

4.2. Page 4-16, lines 4-7: how successful are these linear regressions at capturing the variability of the response? The rationale behind a linear fit is not clear.

4.3. Page 4-17: it would be worth clarifying that although nationwide emission decreases were imposed, different levels of emission decreases were used for the different urban areas. I presume that's what was done.

4.4. Page 4-18, paragraph starting on line 28: I did not understand that paragraph at all.

4.5. Figures 4-9 and 4-10: what percentiles correspond to the boxes and whiskers? It would be good to show the design value in those figures. I don't understand why many of the distributions fall far below the design value, even though the emission reductions targeted just meeting the design value. For example, Atlanta in Figure 4-10 seems to show a maximum concentration of only ~50 ppb for a NAAQS of 60 ppb. I'm obviously missing something important here.

4.6 Page 4-31: I don't understand why the national mapping was done only for mean ozone statistics and not for more extreme ozone statistics, in particular the design value. These mean statistics are not well correlated with the design value (Page 4-36, Figure 4-18). I don't get the point of this national mapping.

5. To what extent does the Panel find that the discussion of uncertainty related to the air quality inputs to the exposure and risk assessment appropriately covers important sources of uncertainty?

5.1 The discussion covers different factors of uncertainty but is lacking in synthesis. The general point of an uncertainty analysis is to quantify the important sources of error and to determine how the errors are expected to add (in quadrature if uncorrelated) to arrive at an overall uncertainty estimate. Without that overall estimate it is not clear how this uncertainty analysis can be propagated to the REA.

5.2 One missing factor of uncertainty that needs some discussion is the ability to quantify the sensitivity of ozone to emission reductions through CMAQ. The standard evaluation of CMAQ with observed ozone concentrations may not help in characterizing that error. There has been some recent literature on comparison of simulated and observed ozone responses to SIP emission reductions (e.g., Dan Cohan's work at Rice) that would be useful to cite.

5.3 The calculation of HDDM sensitivities at three different NOx emission levels is obviously important to better capture the non-linearity in the dependence of ozone on emissions. It must be critical to explain the low errors in applying HDDM to 50% and 90% NOx emission reductions. The text should tell us the three emission levels at which HDDM calculations were done.

Dr. Steve Kleeberger

Chapter 6:

10. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded lung function risk analysis to be technically sound, appropriately balanced, and clearly communicated?

The methods and results of the expanded lung function risk analyses are sound, balanced, and clearly communicated. A minor comment: the header for 6.2.3.6 should indicate that the section refers to 'inter-individual variation' and not 'variability of responses' as this may leave readers to think that this is measurement error/variability and not specific intrinsic and extrinsic factors that lead to differential responsiveness to ozone effects between individuals.

11. What are the views of the Panel on the implementation of the McDonnell-Stewart-Smith model to specify the exposure-response function linking the change in FEV1 to O3 exposure?

The implementation of the McDonnell-Stewart-Smith model is appropriate for exposure/response and change in lung function (FEV1).

12. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the risk estimates?

In my estimation, the discussion of the uncertainty and variability was adequate. Although staff mentions potential causes of variability in response to ozone exposure (p 6-8), it is not clear to me that intrinsic variation (e.g. genetic factors that contribute to wide inter-individual variation) was included in the models. If not, then some discussion is warranted to explain why this is so (e.g. limited reproducibility).

Dr. Fred Miller

Chapter 1: Introduction

1. To what extent does the Panel find the introductory and background material, including that pertaining to previous reviews of the O3 standards and the current review, to be clearly communicated and appropriately characterized?

Response: The material on the current approach and the organization of the HREA is clearly communicated and is of the appropriate length.

Chapter 2: Conceptual Model

2. To what extent does the Panel find that the discussions accurately and clearly reflect the air quality, health effects, exposure and risk considerations relevant for quantitative exposure and risk assessment, building from information contained in the final ISA? What are the views of the Panel on the additional flowchart provided for the overall assessment and the additional information regarding specific elements of the exposure and risk assessments?

Response: The flow chart provided in Figure 2-1 is a useful addition that enables the HREAder to see how the different elements of this complicated assessment fit together and how they are covered in the various chapters that comprise the HREA. The reference to Fig. 2-1 at the top of page 2-11 is incorrect as Fig. 2-2 is the relevant figure.

The authors do an excellent job of accurately and clearly discussing the key elements of air quality, health effects, etc that collectively form the risk characterization. They bring key findings in the ISA forward into this chapter to support what their formation of the conceptual model used in the HREA.

Chapter 3: Scope

3. To what extent does the Panel find the scope of the health risk and exposure assessment is clearly communicated? To what extent does the panel find the additional flowcharts for each analytical component to be useful additions?

Response: This chapter is very well written and clearly communicates the scope of the HREA. Elements of the HREA are discussed in a logical order, and the additional flowcharts help the reader understand the key components of each phase (i. e., the characterization of air quality, the exposure assessment, the controlled human exposures, etc.).

Chapter 4: Air Quality Considerations

4. What are the views of the Panel on the appropriateness of the methods used to characterize O3 air quality for the exposure and risk assessment? What are the views of the Panel on the HDDM-based adjustment methodology used to adjust O3 concentrations to just meet the existing O3 standard and alternative standards?

5. To what extent does the Panel find that the discussion of uncertainty related to the air quality

inputs to the exposure and risk assessment appropriately covers important sources of uncertainty?

Response: No comments

Chapter 5: Characterization of Human Exposure to Ozone

6. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded population-based exposure analysis to be technically sound, appropriately balanced, and clearly communicated?

7. Chapter 5 includes several evaluations of key APEX inputs and model outputs, including for example analysis of time-activity data and comparison of actual personal exposures with modeled exposures. What are the views of the Panel on the appropriateness and usefulness of these evaluations and the conclusions drawn from these evaluations?

8. Chapter 5 includes several scenario-based exposure simulations that focus on specific populations or behaviors. What are the views of the Panel on the design, results, and interpretation of these additional scenario-based exposure simulations?

9. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the exposure estimates?

Response: This chapter is the first of many successive chapters where the figures are so small that they are of limited value to the reader as one can only deduce overall trends in most of the panels comprising the figures. In addition, the color schemes for 70 and 80 ppb of O_3 are essentially indistinguishable in the figures.

Chapter 6: Characterization of Health Risk Based on Controlled Human Exposure Studies

10. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded lung function risk analysis to be technically sound, appropriately balanced, and clearly communicated?

11. What are the views of the Panel on the implementation of the McDonnell-Stewart-Smith model to specify the exposure-response function linking the change in FEV1 to O3 exposure?

12. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the risk estimates?

Response: The updated and expanded lung function risk analysis is technically sound and represents a significant improvement in the approach to this component of the overall O3 risk characterization. The authors clearly describe the main differences between the MSS model for individual responses versus the population model used in this and past assessments. The MSS model is scientifically and biologically defensible, particularly the use of the threshold version of the model even though major differences in risk do not result between the threshold and non-threshold model. The implementation of the MSS model in the HREA is clearly described, and the

comparison of the MSS model results to those obtained with the exposure-response model is of tremendous importance. One of the most important statements in the HREA is found at the bottom of page 6-29 where it is stated

> "In most cases, the MSS model gives results about a factor of three higher than the exposure-response function model for school a-aged children. This is expected since, as discussed above, the MSS model includes responses for a wider range of exposure protocols (under different levels of exertion, lengths of exposures, and patterns of exposure concentrations) than the exposure-response model of previous reviews".

As noted earlier, the panels comprising the figures are too small and lessen the quality of the chapter. In Fig. 5-10, the colors used for 60 and 70 ppb of O3 are too close to each other and would cause confusion to a reader until they figured out the "stacking" of ppb bars in the different rows.

The description of the additional time activity pattern data recently acquired addresses a concern raised previously by CASAC concerning how activity patterns should be brought up to date.

Discussion of major constituents of uncertainty and variability was well done by the authors. Table 6-16 provides a good summary of the qualitative uncertainties, their likely direction and magnitude, and the extent of the knowledge base underpinning current understanding of the phenomenon being addressed.

Chapter 7: Characterization of Health Risk Based on Epidemiological Studies

13. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated epidemiology-based risk assessment to be technically sound, appropriately balanced, and clearly communicated?

14. To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources and appropriately characterized the relationship of those sources of uncertainty and variability to the risk estimates?

15. Adjusting the distributions of O3 concentrations based on decreasing NOx emissions to just meet the existing and alternative O3 primary standards resulted, in some cases, in substantial shifts in the spatial and temporal patterns of O3 across case study urban areas relative to patterns of O3 that existed for recent air quality, and presumably relative to the patterns present in the study locations of the epidemiology studies from which the concentration response functions were drawn (see section 7.1.1 of the TSD, USEPA, 2012). What are the views of the Panel on the characterization of the degree to which these changes in spatial patterns of O3 introduce uncertainty in risk estimates when effect estimates based on one spatial/temporal pattern of O3 (the pattern in the epidemiology study) are applied to a substantially different spatial/temporal pattern of O3 concentrations?

16. In particular, what are the views on the Panel on the characterization of the level of uncertainty associated with estimates of risk associated with days with relatively lower composite (area-wide average) O3 concentrations and those with relatively higher composite O_3

concentrations?

Response: The material in Section 7.3 on the selection of model inputs and assumptions is well done and useful in helping the reader understand the overall issues involved with the use of the epidemiological studies in the HREA. While the discussion of uncertainty and variability in Section 7.4 covers the important sources and their relationships to risk estimates, the section could be shortened significantly by a more limited discussion in the text given the same material is essentially provided in Table7-4 in a more succinct manner.

Using the decreasing of NOx emissions as the driver for just meeting the current standard or alternative standards is reasonable and the only really viable approach to lowering O3 levels. While this results in the shifting of spatial and temporal patterns across case study urban areas, the overall effect should cancel out relative to a comparison of the area covered in the epidemiology studies as one would have to invoke that the area not included in these studies are not representative of the broader geographical and socioeconomic area that were included in the epidemiology studies. The uncertainties introduced in risk estimates when effect estimates are based on one spatial/temporal pattern of O3 and are applied to a substantially different spatial/temporal pattern of O3 concentrations are not likely to be any greater than the uncertainties introduced by other factors that are discussed in Chapter 7. Moreover, the central tendency of statistical theory should work to prevent the uncertainties in risk estimates from going only in one direction.

Chapter 8: National Scale Mortality Risk Burden Based on Application of Results from Epidemiological Studies

17. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated national-scale risk analysis to be technically sound, appropriately balanced, and clearly communicated?

18. To what extent does the Panel find the risk and air quality representativeness analyses to be technically sound and clearly communicated?

Response: This chapter is a straightforward and well-written one that covers all of the important aspects of the interpretation and presentation of the methods used. The approach is technically sound. The authors clearly communicated the representativeness of the urban study areas in a national context by examining the major determinants of O3 effect estimates, namely demographics, base-line health conditions, exposure determinants, and climate and air quality. Table 8-6 provides an excellent synopsis of the major findings concerning subcategories of risk attributes and the differences between the urban study areas and the U.S. dataset.

Chapter 9: Synthesis

19. To what extent does the Panel find the synthesis to be a useful integration and summarization of key results and insights regarding the overall health exposure and risk assessment?
20. To what extent does the Panel find that the discussion of overall uncertainty provides an appropriate context for interpretation of the exposure and risk results?

Response: The Synthesis chapter is about the right length for condensing the salient points and issues that were dealt with in the HREA. The figures provide a good summary of the major findings for the 4 primary health endpoints that were assessed in a manner that shows the distributional changes among the 15 cities that were assessed.

In Section 9.5, on the overall assessment of confidence in the exposure and risk results, the authors seem to "back off" on the usefulness of the short-term risk based modeling results for the larger study areas using the multi-city times series based estimates compared to what is presented and discussed in Chapter 7. This "backing off" is particularly present in the statement on page 9-42 where the authors write

> "Overall, these sources of uncertainty cause us to have reduced confidence in estimates of short-term risk based on modeling the larger (CBSA-based) study areas using the multi-city time series-based effect estimates. This reduces the utility of the risk assessment in directly informing the decision regarding the level of the standard since we have lower confidence in estimates of absolute risk associated with a given standards level. However, the risk assessment can still be useful in providing estimates of the general magnitude and direction of changes in risk associated with an alternative standard level."

Executive Summary

21. To what extent does the Panel find the Executive Summary to be a useful summary of the data and methods used to estimate human exposures and health risks and the key results of the assessment?

Response: Overall, the Executive Summary is well written and clearly brings out the most salient points and findings of the HREA. The balance between sections is good. The legend to the figure on E-5 needs to be changed to "top" and "bottom" instead of "left" and "right" if the final version keeps the same publication layout as is currently used. In the section of health based risks for controlled human studies, the authors should eliminate the use of "potentially" when describing the implications of a 20 percent decrease in FEV_1 for persons with existing lung disease – can cause more serious effects needs to be the thrust of this point. On page E-7, the explanation of how to interpret the stacked bars and their colors is excellent and reflects the kind of wording that should be used more frequently in the document.

Dr. Ted Russell

Review of Ozone REA-Health 2nd Draft.
This REA is a marked improvement over the prior Draft, and over the REAs from years past. It shows a very positive evolution in the approach and the presentation. There can still be some improvements, but it has come a long way from the first one I read during the last review. It also represents a tremendous amount of work. The work that has gone in to the air quality characterization and the development of ozone changes in response to emissions controls as described in Appendix 4 is a remarkable amount of effort. While I might have done a few things a bit differently, and likewise interpreted some of the results a bit differently, that could be from my ignorance and not having spent so much time trying to pull off what was done.

From an air quality characterization and analysis standpoint, my view is that the largest step forward in their analysis is their ability to capture ozone responses to emissions controls using an advanced air quality model-based approach, e.g., using CMAQ with HDDM. This has allowed EPA to capture not only the reductions in peak ozone, but also the increases in lower level ozone levels in response to controls. Both of these have been observed, and this gives much greater confidence to their ensuing analyses. One concern was that too much of the important concepts from the Appendix that supports their approach is left in Appendix 4. It is very necessary to read Appendix 4 to have a reasonable view what is being done, and what are the particular strengths and weaknesses (Appendix 4, discussed below, however, is still a bit rough and could use some work). In this REA, they have also added additional ozone response models.

A major general concern was that the figures/figure captions were often not complete and/or clear. It took me a while to see what was being presented, and I often had to go back and forth between the figure and the text to figure out what was being shown. Make each figure/table almost stand alone, i.e., it could be a single slide in a presentation and need little explanation. The more comple figures, in particular, need a more informative caption.

Chapter 2:

Overall, the chapter adequately conveys the first parts of the conceptual framework for conducting a risk and exposure assessment for ozone.

The end of section 2.2.1 should be modified to note that the NOx-limited conditions are found in the summer/high ozone levels. Much of the year, cities can be radical limited due to the lack of sunlight. You may want to characterize these areas as being where "high ozone levels are NOx-limited".

Chapter 4:

1. Question 4. The use of HDDM-based adjustment is a major step forward. Reading this chapter and the supporting Appendix demonstrate a considerable amount of work, thought

and analysis. It also provides results that are much more in line with observations. Kudos to the staff in pulling this off.

There are some concerns, however. First, many important aspects of the method are relegated to Appendix 4, which I can both justify (it gets very technical and is likely of limited interest to many), but also criticize (there are rather important outcomes of using the method and how specific approaches to using the sensitivities). It is appreciated that the staff was able to develop, and have reviewed, a manuscript describing much of their approach, but there are some differences.

One comment that should be made is that, at present, their approach shows some bias in that they primarily utilize a NOx-oriented control approach (e.g., they prefer using a NOx-only set of sensitivities, not the NOx-VOC results, and do not even provide VOC-only approaches). This should be further discussed and defended, e.g., potentially a few analyses showing that a VOC-only approach is largely ineffective in most locations and/or that a VOC-only approach buys little benefit over a NOx-VOC approach. However, I do support the use of a limited number of non-source specific sensitivities as there are a huge number of source-specific analyses that could be done, the choice of which is not apparent at this time. How close would a VOC-only strategy get New York to the 60 ppb level?

A comment between this chapter and Appendix 4 is that I probably would not have chosen the same approach to estimating sensitivities and ozone levels at intermediate control levels, i.e., when control levels are not 50% or 75%. The current approach appears a bit ad hoc, and shows a few major deviations (though limited, and they have an adjustment approach). I might have done the maximum simulations at, say, 85% controls (more towards the extreme end of the controls) and used a cubic spline fit to provide sensitivities at intermediate levels. The spline could provide each of the first and second order sensitivities. Something to think about next time.

The next question I had was exactly how the sensitivities are being applied at each location in the domain. Are they being applied to the CMAQ-simulated value, or (I think) to the VNA/DS-derived value? Figures 3-1 and 4-6 (and Figure 1 in Appendix 4-3) should be edited to make this clear. Fig. 4-6 should explicitly show how VNA or DS is being used. Both might show how/where VNA and DS are being used in the process. Having calculated the location/time specific ozone value, the next question is how to develop the appropriate sensitivity. Should one use the sensitivities calculated directly as described in Appendix 4 specific to the simulated ozone value, or should those sensitivities be adjusted for the difference between the simulated and observed ozone levels. If the base simulated ozone is 80 ppb (and, thus the sensitivities are consistent with that simulated value), and the observed value is 100 ppb, should the sensitivities be adjusted upwards? One could give reasons both ways, and this should be discussed as well as support for their choice. I would probably adjust, but it is a tough call. (There are other approaches one might consider as well.) I suspect this would make rather little difference, but it should be discussed.

Section 4-5. Section 4-5 is comprehensive and I generally agree with their assessments of the levels of uncertainties, though with a few exceptions. The uncertainty in CMAQ modeling is probably "medium" based upon the model evaluation (which was very extensive). Likewise, the HDDM sensitivities are likewise about medium given that CMAQ results are about medium, and

that they also have undergone less extensive review and you cannot directly evaluate the sensitivities using observations. Further, it is not apparent the best way to scale sensitivities when the simulated observation does not match the observations. On page 4-47, it is stated that "… in general we expect that the that the benefits of reducing high ozone concentrations and disbenefits of increasing low ozone would be underestimated." This should be further explained and supported.

Chapter 4 needs a Summary/Key Observations section consistent with the other chapters.

Chapter 6

I am still not wild about how Eq. 6-2 is shown. The assumption is that C and V do not change over the time period, so they are not really a function of t, which is what is shown. Showing that they are varying along with X is inappropriate. One could just as well use t_0 or t_i, indicating that the choice is for time period I, or show that they choose an average over the time period (use a bar over the term).

The uncertainty discussion in this chapter also needs a bit of work. It is noted that the uncertainties in the MSS model parameters are likely larger than 5%, but with little more discussion. Then, Fig. 6-12 uses 5%. Thus, the uncertainties shown are likely greater than shown. This should be noted in the caption. Also, I do not believe that 6-12 should be labeled as elasticities. Elasticity has a specific definition. Those are responses to a 5% increase (as the caption notes). I think an elasticity would be 20 times what is shown (if you still use %, but I might use a fractional elasticity).

Chapter 9

Question 19. Certainly the Synthesis is useful, and the document would suffer without it.
Question 20. The discussion of uncertainty does provide a good context for interpretation of the exposure and risk results. However, I was hoping that the uncertainty discussion would be deeper and more definitive. In particular, it would be useful if the section (9.5) concluded with more direct statements as to how a reader should interpret the overall uncertainties in the risk and exposure assessments for use in standard setting. They could also identify the specific uncertainties that are most key (e.g., contribute the most to their overall confidence in the results) and that should be targeted for further reduction. With those two answers in mind, while the synthesis is valuable and insightful, it is not without additional problems.

Chapter 9 should deal more with synthesizing the results from the application of various responses over different seasons and different levels. While some analyses dealt with ozone during the warm seasons and only higher exposure levels, others were over the whole range. The discussions that are present are a good start. However, to state "The implications of this is that our estimates of mortality and morbidity risk reductions… are likely to understate…" should be qualified in that the seasonal application can add bias in the other direction.

Page 9-43: l 10-19. This paragraph says things are different and it is important to understand the differences, but does not provide how they are different and what that means. The next paragraph does similarly. It would be good if both of the paragraphs were more informative as to what differently really entails. Use of different metrics will lead to different results, but are they

meaning differences? Do they conflict? Are they problematic when the results are interpreted for use in standard setting, e./g., raise concerns about uncertainties, or are they consistent and support the use of the metrics? In general, the synthesis could be more definitive.

9-23, l 2: It is not just one reaction that is of importance. The consumption of radicals also reduces ozone.

9-38, l3-5. Does this statement agree with the analysis found in the ISA? Please link to the ISA.

Appendix 4

Appendix 4 (particularly 4-D) represents a huge amount of work and a major step forward. It also needs a fair amount of work to harmonize the chapters. In particular, the figure numbering and equation numbering should be more specific as to the specific appendix. One might even think about an Introduction to the Appendices overall. Certainly, there needs to be an overall Table of Contents for the Chapter 4 appendices either up front and/or in the HREA Table of Contents.
The evaluation is extensive.
In Appendix 4-D, Section 3.2.3 could be a bit more clear in what is being done to modify observed concentrations. Sections 4-5 and 4-6 could use their own flow diagram specific to that component of the analysis, and with more detail.
I might recommend EPA having a more extensive discussion with the modeling community about how to use sensitivities in adjusting ozone values to meet various air quality metrics. There was not time this time.

Dr. Helen H. Suh

Charge Questions for Chapter 5: Characterization of Human Exposure to Ozone
General Comments

The Chapter was generally well written, well organized, and comprehensive, representing a significant improvement over the previous draft. Its presentation of the REA goals and background on the APEX model were very useful, as they helped to frame the discussion of the model outputs and results.

In addition, the Chapter's addition of the targeted evaluation of the quality and relevance of the model inputs was terrific and should be expanded to include an evaluation of the 2000 US Census data and its relevance to the 2006-2010 study period. It is possible that this evaluation could be made from a comparison of 2000 and 2010 US Census data that examines whether and how the number and spatial distribution of the four at-risk study populations have or have not changed. This comparison may help to further characterize uncertainty resulting from population distributions.

6. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded population-based exposure analysis to be technically sound, appropriately balanced, and clearly communicated?

Presentations of the methods and results sections were technically sound and for the most part clear. The section describing the model output, however, was often difficult to follow and seemingly overcomplicated. Specific comments and suggestions include:

- A column should be added to Table 5-3 to indicate the number of subjects included in each study. Also, if an activity pattern study did not include data for all microenvironments, it should be noted (either as a footnote if rare or as a separate column if more common).
- The definition of benchmark level should be defined when it first appears.
- As mentioned starting on page 5-20, the discussion of temporal and spatial variability in exposures for each of the five air quality scenarios is complex. This complexity may require the results to be presented in multiple figures, rather than in condensed or summary figures, as represented in Figure 5-3 and 5-4. The summary figures are too confusing and require too much explanation in the text. Further, this explanation in the text is very confusing.
- The figures should be careful to display information consistently. For example, in Figure 5-3 the bottom row of graphs should be presented from left to right for 60, 65, 70, and 75 standard levels to match the order in the top row of boxplots. Perhaps this is to match the column order for Figures 5.5-5.9, for which standard levels are also presented in columns that move left to right from higher to lower standards. It seems contrary to convention to present them this way. Is there a reason for this?
- All results are presented as the percent of the at-risk group. Should the absolute number be presented as well for the city comparisons (e.g., 5-7 or 5-8) , since is possible that the percent for a given city is small but the number is high relative to another city.

7. Chapter 5 includes several evaluations of key APEX inputs and model outputs, including for example analysis of time-activity data and comparison of actual personal exposures with modeled exposures. What are the views of the Panel on the appropriateness and usefulness of these evaluations and the conclusions drawn from these evaluations?

The addition of evaluations of key APEX inputs and model outputs was appropriate, useful, and extremely important to demonstrate the validity/relevance of the exposure analysis and to address issues related to uncertainty in the model outputs. A factor that is not considered but should be at least discussed is whether activity pattern data should be linked to simulated individuals based not only on age, sex, day-of-week, and ambient temperature, but also on geographic variability, as it seems likely that activity patterns differ by geographic regions. Relatively minor suggestions include:

- In addition to the number of diary days, how many people were included in the database? By geographic region?
- Figure 5-10 needs additional explanation in the text and in its label. To what do the 1, 2, and 3 groupings refer?

8. Chapter 5 includes several scenario-based exposure simulations that focus on specific populations or behaviors. What are the views of the Panel on the design, results, and interpretation of these additional scenario-based exposure simulations?

The additional scenario-based exposure simulations were useful, clearly explained, and an important addition to the analysis.

For these analyses, however, it would be helpful to take into account or discuss whether the amount of time spent outdoors varies by geographic location, for example may be higher in Los Angeles or Houston as compared to New York City. The impact of geographic variability may be important for these scenario-based exposures, since they calculate percent of Detroit (and in some cases Atlanta and Philadelphia) populations above benchmarks but do so using adjusted activity diary pools from the entire country. This geographic variability may explain differences in the personal exposure comparisons for DEARS participants.

9. To what extent does the Panel find that the discussion of uncertainty and variability has covered important sources of uncertainty and variability and appropriately characterized their relationship to the exposure estimates?

Most sources of uncertainty have been characterized as low or low-to-moderate, with a few sources characterized as moderate. While reasons for this categorization are provided, the categorization seems to underestimate uncertainty and to give the false impression that uncertainty in the exposure results is also low or low-to-moderate. This is notable given the fact that comparison of simulated exposures to measured exposures in Detroit showed systematic bias in the simulated exposures. Further, uncertainty characterization was defined based on available data and did not consider data gaps. For example, data on activity patterns and home air exchange rates for individuals of low socioeconomic status (SES) were generally not included in exposure simulations. These data gaps create uncertainty in the risk estimates, especially in what may be an important at-risk group.

Dr. James Ultman

Chapter 6: Characterization of Health Risk Based on Controlled Human Exposure Studies

- To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated and expanded lung function risk analysis to be technically sound, appropriately balanced, and clearly communicated?

The staff is to be commended on the both the breadth and depth of the technical analyses, and the effective and concise manner in which they are presented.

- What are the views of the Panel on the implementation of the McDonnell-Stewart-Smith model to specify the exposure-response function linking the change in FEV1 to O3 exposure?

The basis of the MSS model is clearly communicated as is its application to the exposure-response risk estimation. As pointed out in the document, several largely unsubstantiated assumptions had to be made (e.g., extension of young adult age coefficient to children, identical response models for asthmatic and non-asthmatic children). Nevertheless, it is clear that the incorporation of time-dependent inhaled dose and detoxification dynamics as well as inter- and intra-subject variability in the MSS model is, in concept, a substantial improvement over the mean population responses at fixed exertion used in the previous E-R model.

- To what extent does the Panel find that the discussion of uncertainty and variability have covered important sources of uncertainty and variability and appropriately characterized their relationship to the risk estimates?

The qualitative summary in table 6-16 is effective in defining the key uncertainties as well as indicating their effect on the risk assessment. In addition, a quantitative sensitivity analysis (Fig. 6-12) shows how large an uncertainty is produced in the risk estimate by a given uncertainty in each parameter of the MSS model. It is encouraging that model predictions are relatively insensitive to the age parameter for which little information regarding children is available.

A continuous normal distribution was used in the MSS model to represent intrasubject differences. In the final risk assessments, this distribution was truncated beyond two standard deviations of its zero mean in order to avoid unrealistic results for individuals. In assessing the uncertainty of this truncation, it was found that the proportion of children with $\Delta FEV > 10\%$ was predicted to be 31% using a two standard deviation cutoff (i.e., a percent FEV1 difference of ±8%) and 92% using a cutoff reflecting "actual" values (i.e., a FEV1 difference of ±20%). Thus, the selection of the cutoff is an important element in the risk assessment, and there needs to be a better discussion of what is meant by "actual" values and what rationale was used for selecting a two standard deviation cutoff.

Also, it is stated on page 6-41 that "…we truncate the variability term distribution at ±2 standard
4 deviations (±8.27), a convention we use for the distributions of several physiological variables

input to APEX …" How large are the uncertainties introduced by these cutoffs in the exposure risk assessment?

Dr. Sverre Vedal

Ch. 7. Characterization of Health Risk Based on Epi Studies

13. To what extent does the Panel find the assessment, interpretation, and presentation of the methods and results of the updated epidemiology-based risk assessment to be technically sound, appropriately balanced, and clearly communicated?

Random points:

- It's good that risk is based on total risk, not just to the lowest measured level.
- Core-based statistical area (CBSA) used rather than central urban is justified (7-6), although risk estimates are in some instances very sensitive to this choice.
- Substitution of Bell et al. (2004) with Smith et al. (2009) seems OK.
- Exposure based on peak exposure metrics is justified.
- Jerrett et al. (2009) as the only basis for estimating long-term mortality risks is risky, but it's the only game in town. This fact should temper confidence in C-R function.
- It's not surprising that differences in effect estimates drives the cross-city differences in risk reductions (7-74), but it's reassuring to see that.

Points for discussion:

- The estimate of up to approximately 20% of COPD deaths attributed to ozone (7-68) just seems implausible, especially when one considers that the population at risk for dying of COPD is composed of those who are unlikely to exercise and to be outdoors. I know that's what the effect estimate says, but ….
- Use of effect estimates pertaining to the larger populations - in some cases this results in using very a different effect estimate, e.g., NY, 0.0009 vs. for NJ, 0.0001 and 0.0005 (7-28, Table 7-3). Sensitivity to this choice is shown in 7.4.2 and 7.5.3.
- The discussion of variability and uncertainty is general sound and comprehensive. One aspect that is not touched on in discussion of spatial variability in concentrations is the fine-scale spatial variability due to roadway gradients. Near roadway ozone concentrations are considerably lower than city-average values. Also, there are typically no roadside ozone monitors, so concentrations there cannot be captured by most regulatory monitoring networks. Depending on the city, a greater or lesser fraction of the population lives in close proximity to large roadways, and it is not certain, for short-term exposures, that the average city day-to-day concentration pattern is reflected in those living near roadways. This has implications for population exposure misclassification and isn't reflected in Table 7-4 (7-43). For long-term exposures, the importance of roadside gradients is obvious.
- In Table 7-4 on uncertainty analysis, it isn't clear why simulating ozone concentrations for "attainment of both existing and alternative standards" should be included here among other factors assessed in sensitivity analyses. These are simply different ways of expressing impacts of different regulations that provide different insights.
- I don't understand the conclusion that the mortality metric for short-term exposure is "not responsive to meeting the existing and alternative standard levels" (7-69). Mortality reductions seem to steadily increase with changes to the standard.

- Does not the predicted increase in risk for some study areas (when concentrations are low) when meeting standards (7-70) call into some question the mechanics of the air quality model simulations on how air quality standards are met?
- Observation: A substantial fraction of short-term attributed risk remains after meeting the most stringent alternative standard (7-71).
- As noted, use of regional effect estimates for long-term exposure risk has dramatic impacts on risk (7-79 and Table 7-14), ranging from 0 to 40% of baseline risk, and 27% in Denver – the latter, as others, seems to stretch plausibility – see first bullet in this section.
- Regarding Overall Confidence, in light of the reliance on one study to estimate long-term respiratory mortality effects, and the seemingly large effect estimate, I would have been reluctant to conclude that I had a "reasonable degree of confidence" in these risk estimates (7-86). It also seems inconsistent with the ISA conclusion (ISA 7-31) that there is "limited evidence" for an association between long-term exposure and respiratory mortality, presumably because it is based on only one study.
- In light of the central importance of respiratory (presumably COPD) mortality as an outcome of long-term ozone exposure, consideration should be given to estimating exposures in this group with APEX (if diary profiles are available), not just in asthmatics, the young and the old. Presumably this population might be expected to spend a relatively smaller proportion of time in more exposed settings.

14. To what extent does the Panel find that the discussion of uncertainty and variability has covered important sources and appropriately characterized the relationship of those sources of uncertainty and variability to the risk estimates?

- See above for comments on small-scale ozone spatial variability.
- Otherwise, very good.

15. Adjusting the distributions of O3 concentrations based on decreasing NOx emissions to just meet the existing and alternative O3 primary standards resulted, in some cases, in substantial shifts in the spatial and temporal patterns of O3 across case study urban areas relative to patterns of O3 that existed for recent air quality, and presumably relative to the patterns present in the study locations of the epidemiology studies from which the concentration-response functions were drawn (see section 7.1.1 of the TSD, USEPA, 2012). What are the views of the Panel on the characterization of the degree to which these changes in spatial patterns of O3 introduce uncertainty in risk estimates when effect estimates based on one spatial/temporal pattern of O3 (the pattern in the epidemiology study) are applied to a substantially different spatial/temporal pattern of O3 concentrations?

Well, the Bayes estimates should theoretically make each city C-R function less sensitive to the particular spatial-temporal pattern present during the place and time used for the epi analysis. I don't see any ready alternative now to using the same C-R function, although the assumption of a constant function is a strong one.

16. In particular, what are the views on the Panel on the characterization of the level of uncertainty associated with estimates of risk associated with days with relatively lower composite (area-wide average) O3 concentrations and those with relatively higher composite O3

concentrations?

This characterization is not based on epidemiology (where the confidence interval around the effect smooth widens at both extremes) but rather on findings from human experimental and toxicological findings, which seem to me to pretty sound in this regard.

Dr. Ronald E. Wyzga

Chapter 1: To what extent does the Panel find the introductory and background material, including that pertaining to previous reviews of the O_3 standards and the current review, to be clearly communicated and appropriately characterized?

By and large this Chapter is well-written and clearly satisfies its objectives. My only comment refers to the sentence on p. 1-5, ll. 23-24; I am unclear about the objective here. Is it to make sure that there is some consideration of the worst conditions in the US or is it to demonstrate that the urban areas studied reflect the distribution of estimated ozone exposures seen throughout the US?

Chapter 2: To what extent does the Panel find that the discussions accurately and clearly reflect the air quality, health effects, exposure and risk considerations relevant for quantitative exposure and risk assessment, building from information contained in the final ISA?

This chapter largely reflects earlier considerations. There are a few areas where more clarity could be helpful. For example, I am unclear what is meant by "recent" O_3 concentrations. Could a specific timeframe be given?

On page 2-6, l. 28, the analysis will apparently employ the 2005 NEI. At the recent NOx Panel/CASAC meeting, data were presented for the 2011 and 2008 NEIs. Are these available and could they be used in the analysis? If not, how will the use of the 2005 data impact the results?

p. 2-7, l. 20. It would be helpful to name the models to be used.
l. 26: How sensitive will the results be if NOx and VOCs are not reduced in equal proportions. A limited sensitivity analysis could prove useful.

p. 2-8, l. 9: The antecedent of "those" is not clear.

p. 2-9 and following pages: The averaging times should be indicated for the various study results.

p. 2-14, l. 34: Consideration of the impact of repeated exposures could also mention the possibility of adaptation, which will not be explicitly considered.

p. 2-20. L. 20: The document may want to clarify that unexposed assumes a zero background exposure.

p. 2-21, ll. 8-10: Use of multiple areas will help address uncertainties for variable O_3 concentrations/exposures and for different populations. It will not address the uncertainty associated with various C-R and E-R functions as implied by the text. How will the latter uncertainties be addressed?

p. 2-22, ll-26-29: How or why is the new approach "more realistic"? This paragraph could be expanded to address this issue more clearly.

p. 2-23, ll. 31-34: Could the definition of "adverse" be given here?

Chapter 3: To what extent does the Panel find the scope of the health risk and exposure assessment is clearly communicated? To what extent does the panel find the additional flowcharts for each analytical component to be useful additions?

This Chapter is also well-written and communicates the scope of the work undertaken clearly. The flowcharts are helpful and consistent with the text.

A few clarifications could be helpful. For example, p. 3-6, l. 20 and elsewhere, specific years could be indicated in place of "recent".

p. 3-16, ll. 7-14: In consideration of the American Thoracic Society's definition of adversity (Am J Respir Crit Care Med, 161:665-673, 2000), could there also be a consideration of a joint response in lung function and symptoms in addition to the analyses outlined here?

p. 3-23, ll. 18-20: How will the confidence interval across studies be estimated?