

**Comments Provided for Consideration to the CASAC Ozone Review Panel on the EPA's first external review draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants to be held on May 19-20 2011.**

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We would like to make general and specific comments to Section 6.2.1.1 of this ISA. The section is generally well written and discusses almost all relevant papers. The focus of the section is on changes in FEV<sub>1</sub>, the endpoint considered by EPA a key health effects indicator of ozone exposure. Unfortunately, the other spirometric endpoints, such as changes in FVC and FEV<sub>1</sub>/FVC are completely ignored in discussion, although these endpoints might contribute to the elucidation of the extent of ozone-induced lung function impairment.

Based on our review, we are concerned about the following areas of the document:

1. The use of Filtered Air (FA) may not be an appropriate control exposure because the 0 ppb O<sub>3</sub> FA that is generated in the laboratory does not exist under ambient or indoor air conditions. Evidence continues to mount that the Policy-Relevant Background (PRB) hourly average O<sub>3</sub> concentrations are much greater than the 15-35 ppb levels that the EPA often cites. PRB O<sub>3</sub> hourly average concentrations frequently occur at some sites  $\geq$  50 ppb. An important issue that requires further attention is whether statistically significant effects observed at 60 ppb when compared to a FA control would provide the same significant effects if the effects were compared to O<sub>3</sub> hourly average concentrations (i.e., concentrations  $\geq$  50 ppb) measured under PRB conditions. No evidence is currently available to conclude that Kim et al. (2011) would have reported a statistically significant difference between the enhanced treatment of 60 ppb and a control that represented observed hourly average concentrations under PRB conditions.

2. Comparing changes across corresponding time intervals that take into consideration the absolute difference between the O<sub>3</sub> and FA responses and expressing them as "ozone-induced" is misleading. The FA responses in such adjustments are not "extraneous" as stated on page 6-3, line 22 since the FA responses may, in some studies, substantially though "artificially" enhance the magnitude of the O<sub>3</sub> response. If they are extraneous, why is it necessary to adjust ozone-induced changes? We do not recommend such FA adjustments. Again, we believe strongly that these adjustments can artificially enhance the responses.

3. The EPA's focus on end-of-exposure results ignores a wealth of information provided by hourly data. There are at least 10 studies that have reported hourly mean changes in FEV<sub>1</sub>. Yet, this information is persistently ignored by the Agency. The relevant subsection should compare and contrast various temporal phases of response and the dynamics of FEV<sub>1</sub> changes during exposure to a square-wave (S-W) and variable exposure profile. Such analysis should provide important information on health risk assessment (see Hazucha and Lefohn, 2007; Lefohn et al., 2010).

4. Even more important to health assessment than Intersubject variability (p.6-8) is Within-subject (intrasubject) Variability in Response. This area of concern should be discussed in a separate subsection. Currently, there is no subsection that deals with this important source of FEV<sub>1</sub> variation. Unfortunately, the peer-reviewed literature publishes only the mean values and not data on individual FEV<sub>1</sub> responses. However, because of the impact these data may have on individual's health risk assessment), EPA should requested such data from the principal investigators of respective studies. From the spreadsheets we have received from the investigators and subsequently analyzed, the intrasubject variability of response of various endpoints may be substantial. This may have an impact on how the end-of-exposure 10% decrement in FEV<sub>1</sub> (EPA responder) relates to within subject hourly variability of response. With considerable between and within exposure variability of FEV<sub>1</sub>, the utility of using only individuals' end-exposure FEV<sub>1</sub> value for health assessment is inadequate. We had no difficulty in obtaining such data from Drs. Adams and Schelegle in our detailed analyses (see Hazucha and Lefohn, 2007; Lefohn et al., 2010).

5. The ISA document is frequently referencing the Adams (1998) report. The report was (1) not subjected to peer review, (2) not published in the open literature, and (3) not available to public as indicated by the EPA. The experiment described in the report was a face mask study and the author reported no significant effects at the 60 ppb level. Based on very limited secondary information cited in other publications, it is not possible to evaluate the study and therefore, it should not be considered in the ISA document. We strongly recommend that any reference to Adams (1998) be deleted.

6. Post hoc statistical analyses, such as Brown et al. (2008) using Adams (2006) data, are questionable because they violate *a priori* statistical design. It is even more problematic, when a continuous variable such as FEV<sub>1</sub> is treated as an ordinal variable as in Brown's reanalysis. Approaches based on suppressing or enhancing the behavior of extreme responses within specific experiments, treatments, and measurement times do not provide confidence in attempts to reinterpret the analysis in a meaningful statistical sense. More recently, Lefohn et al. (2010) reanalyzed Adams (2006) data and confirmed the original conclusion of Adams (2006) (i.e., that the effects were not statistically significant). The discussion in the ISA requires additional balance and needs to present the available information in the literature in an unbiased manner.

7. A summary should be provided in the ISA that describes the controlled exposure studies.

### **Specific comments:**

Page 6-2, 2<sup>nd</sup> para: It should be clearly stated that most of the toxicological and controlled human exposure were at high ozone concentration (i.e., > 300 ppb).

P.6-2, L.37: Simply, this association is not "less clearly indicated" but "not clear". Please correct.

P.6-3, L.21-23: Ozone FEV<sub>1</sub> data "adjusted" for FA FEV<sub>1</sub> responses should not be called "ozone-induced" but "FA adjusted ozone-induced" so there is no misunderstanding by the reader. Moreover, if for whatever reason, one were to adapt the "adjustment" approach to spirometric data, the same approach should be used consistently in adjustment of other physiologic endpoints as well, because the same cofounders will affect those outcomes as well.

Without an adjustment for FA, the post-ozone effects of many studies may not have been statistically significant and, therefore, the results would have had a substantially diminished weight in consideration of the health risk assessment.

P. 6-4, L.7: Similar rapid recovery was reported by Schelegle et al. (2009) following 6.6-h exposure. Add a sentence to this effect.

P.6-5, Fig. 6-1: This figure needs to be updated with more recent data. In addition to the predicted curve, a true fitted curve should be calculated and plotted. With the addition of new data points, the two curves will differ significantly.

P. 6-5, L.3: As we already pointed out in our general comment #6, the Brown et al. (2008) reanalysis using Adams (2006) data is not appropriate. Such post-hoc analyses violate *a priori* statistical design. Brown et al. (2008) recommended that the Bonferroni procedure be used as the preferred multiple comparison correction, although they have not used it in their analyses. However, the Bonferroni procedure is considered to be too conservative and more sophisticated

procedures, such as Tukey's test is appropriate (Norman and Steiner, Biostatistics, B.C. Dekker 2000). Lefohn et al. (2010), using the Tukey's studentized range approach, reanalyzed Adams (2006) data and confirmed Adams' (2006) original conclusion i.e., the effects were not statistically significant at the 60 ppb level. The Lefohn et al. (2010) re-analysis is important and the EPA should evaluate the findings and compare the authors' results with those of Brown et al. (2008).

P. 6-6: This page begins with a description of a variable ozone exposure profile studies. There are 5 studies that used variable exposure profile and we recommend that they be discussed together in one newly created and titled subsection. Lefohn et al. (2010) focused on these studies because of the relevance of the variable exposure profiles simulating ambient-type exposures instead of applying the unrealistic square-wave exposures. Although the EPA may not be interested in the hour-by-hour responses that occur over a 6.6- and 8-h period, we believe that because of potential health impact others should be concerned about the interim responses versus just focusing on the post-exposure responses.

P. 6-6, L.31-37: It is important to clearly state that the overall ozone dose following the application of S-W and variable exposure profiles appeared to be equivalent in these studies. Lefohn et al. (2010) describe for the variable and step-wise exposure studies at 80 ppb and greater concentrations, there appear to be three FEV<sub>1</sub> response phases: (i) a 2-h initial "induction phase," (ii) a subsequent nonlinear statistically significant FEV<sub>1</sub> "response phase," and (iii) a final "reversal phase," with an improving FEV<sub>1</sub> decrement as O<sub>3</sub> concentration decreases. The reversal phase is not observed in any of the S-W studies. Although EPA states that a variable exposure results in greater spirometric and symptomatic responses "is not unexpected" (line 35), the EPA appears to not be interested in this phenomenon. The Agency ignores the intermediate effects when applying its current analytical methodology of using only the end-of-exposure data.

P. 6-7, L.3-6: The statement should be revised and moved to line 30, following the Schelegle et al. (2009) variable exposure study discussion.

Although the preceding sentence (L.1-3) again asserts correctly that variable at S-W dose-equivalent ozone level exposures induce greater effects, the focus of subsequent sections are unfortunately only on the end-of-exposure effects. The follow-up section (line 30+) should not only include a discussion of the end-exposure data "where the influence of triangular and S-W concentration patterns are minimal" (line 4) but more significantly a discussion of generally ignored but important hourly data where the "influence" is the most pronounced. For example, if only end-exposure effects are considered by EPA, a possible decrement of e.g., 10% in FEV<sub>1</sub> experienced by an asthmatic breathing a peak concentration of 120 ppb in ambient air is of no concern to EPA because at the end of 6-8 h exposure his/her decrement may be only 2%. However, if a 10% decline occurs at the end of exposure, it is of a concern to EPA. Should not these concerns be equal? Lefohn et al. (2010) discuss this observation.

P.6-7, L7-19: The Schelegle et al. (2009) study is the most recent variable exposure study, thus it should be the last study of the subsection which we suggest be created on Variable Exposures.

P.6-7, L.21-29: This study should have been discussed with similar S-W studies on page 6-5 and not mixed with variable exposures.

P. 6-7, L.30: As suggested earlier, this section should include discussion of hourly patterns of spirometric response to variable and S-W exposures. There are at least 10 studies that have reported hourly mean changes in FEV<sub>1</sub>. However, this wealth of information has not been considered. The principal investigators of these studies have recognized the importance of measuring the progress of FEV<sub>1</sub> changes during an exposure in an overall assessment of health effects. We believe that the EPA should discuss the various phases of FEV<sub>1</sub> response (see Schelegle et al., 2007 and 2009; Lefohn et al., 2010). We also believe that the different dynamics of FEV<sub>1</sub> changes during S-W and variable exposures provide important information for health risk assessment that the EPA appears to be overlooking.

P.6-7, L.35: Please delete reference to Adams (1998) in the ISA document. The report was not subjected to a peer review. It was not published in the open literature and is not available. It was a face mask study and the effects of 60 ppb were not statistically significant. Apart from citing the report in some peer-reviewed papers, the details from the report are not available and it is impossible to evaluate the study.

P.6-8, L.5: The n value should be 91. The results from Adams (1998) should not be included and the Adams (2006) subjects were double counted (the same subjects were exposed to both triangular and S-W exposure).

P. 6-8, L.10-13: The key measure of central tendency in Brown's et al. (2008) reanalysis is median (see page 1024 of the original paper) and the Wilcoxon sign test was the primary statistical test. As the secondary data, the authors provide mean values. Therefore, we suggest that the discussion when referring to Brown et al. (2008) include the primary measure (i.e., the median). To better balance the continuing reference to the Brown et al. (2008) re-analyses, we recommend that these results be compared to the re-analysis described in Lefohn et al. (2010).

P.6-8, L.29-31: This sentence describes within and not intersubject variability. Suggest replacing "over several months" with more accurate "within season".

We suggest a new subsection entitled "Within-subject Variability in Response" that would follow the Intersubject subsection be developed for the ISA document. It would be highly desirable to discuss individual's variability of baseline/pre-exposure values as well as variability of FA and ozone hourly spirometric response during exposure. The individual's variability in FEV<sub>1</sub> is considerable and exceeds the average decrement reported at ozone concentration at and below 70 ppb. Though none of the studies have published individual's responses, the data can be requested from the investigators. The authors of several review studies (Hazucha and Lefohn,

2007; Brown et al., 2008; Lefohn et al., 2010) obtained such data directly from the principal investigators, Drs. Adams, Schelegle, and Hazucha. We suggest that the EPA request such data from other studies and other principal investigators as well.

P.6-8, L.31-36: Although there is a tendency by the investigators to interpret their findings of repeated exposures as *reproducible*, closer examination shows that for many individuals the differences in FEV<sub>1</sub> response may be substantial and, in some cases, different by as much as 40 percentage points. This should be included the discussion.

P.6-9, L.15-18: The information from the Adams (1998) study cannot be verified and should be deleted. Consequently, the proportion will be 8% and not 10%. Please correct. Footnote #5 is missing.

P.6-9, L.19-24: Please replace the word “corrected” with “adjusted” in the text of this paragraph and the document as well. The improvement of lung function following FA exposure should not be called typical because of a couple of studies have reported so. Revise the subsequent sentence to read: ”For example, ozone-induced versus FA adjusted ozone-induced proportions of individuals.....”. Delete the last sentence of the paragraph since it is not necessarily true for other studies. It is possible that an alternative conclusion can be reached. If the PRB hourly average ozone concentrations were  $\geq 50$  ppb, it may be possible that the statistically significance reported for some of the studies at specific levels might disappear with the result that the human health risk would be overestimated using EPA’s current methodology. Evidence is mounting that PRB O<sub>3</sub> hourly averaged concentrations are  $\geq 50$  ppb at some locations and times during the year and that these concentrations are not infrequent (see Lefohn and Oltmans, 2011).

P.6-10, whole paragraph: Delete Adams (1998) study, correct the weighted-average values, and revise the discussion, e.g., n=61 and 3.1 % (line 4). As we already pointed out earlier, the data from these and other studies by Adams and Schelegle cited in the ISA are very important for the health risk assessment. We believe that the discussion of these studies and subsequent conclusions would be different if the complete set of hourly data were to be evaluated.

P.6-10, L. 13-14: The study of Adams (1998) is inadmissible and should be deleted. The proportions for Schelegle et al. (2009) study are cited on page 6-9, line 10. Please correct the statement.

P.6-13, L.19: Please cite the sources for the reported diminished symptomatic response in children. The elderly may have diminished symptomatic response, but they also have diminished lung function response. Please expand the discussion.

**Additional references:**

Hazucha, M., Lefohn, A.S., 2007. Nonlinearity in Human Health Response to Ozone: Experimental Laboratory Considerations Atmospheric Environment. 41:4559-4570.

Lefohn, A.S., Hazucha, M.J., Shadwick, D., Adams, W.C., 2010. An Alternative Form and Level of the Human Health Ozone Standard. Inhalation Toxicology. 22:999–1011.

Lefohn, A.S., Oltmans, S.J., 2011. Comments Relating to Section 3.4 (Policy-Relevant Background Concentrations) in the March 2011 Draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants. Submitted to the Docket ID No. EPA–HQ–ORD–2011– 0050.