

**Comments Provided for Consideration to the US EPA on the second external review draft of the Integrated Science Assessment for Ozone and Related Photochemical Oxidants**

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We would like to restate some of our comments dated May 5, 2011 which we submitted to the first draft of the ISA and are still relevant to the second draft of ISA as well as to make additional general and specific comments to Chapter 6 (p. 6-1 to 6-23) of the second external review draft ISA released on September 2011.

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. We recommend that the Agency address in the ISA 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 Policy-Relevant Background (PRB) conditions. The original assumption that PRB concentrations range from 15-35 ppb was incorrect and the more recent literature indicates that PRB *hourly* average O<sub>3</sub> concentrations at some locations in the US are much higher than EPA's original estimates. PRB O<sub>3</sub> hourly average concentrations frequently occur at some sites in the US at levels  $\geq$  50 ppb. 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 observed at some locations 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 may, in some studies,

substantially though “artificially” enhance the magnitude of the O<sub>3</sub> response. This presents a potentially misrepresentation of the results.

3. The EPA’s focus on end-of-exposure responses persistently ignores a wealth of information provided by hourly data published in numerous studies. Temporal pattern of changes provide important information on intra-subject 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.
4. Even more important to health assessment than inter-subject variability is within-subject (intra-subject) variability in response. Although the intra-subject variability of response by various endpoints may be substantial, this important source of variation has not been adequately discussed.
5. 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.
6. In the past, the EPA has focused its review on peer-reviewed published material. However, unsettling to us is that the Agency appears to have modified this policy by depending upon both peer-reviewed material as well as non peer-reviewed material. The Adams (1998) study that the Agency references in both the first and the second ISA (1) was not published in the open literature, (2) was not subjected to a peer review, and (3) is not available for evaluation. In contrast, two highly relevant articles published in two peer-reviewed journals have not been discussed in either of the ISA drafts (Hazucha and Lefohn, 2007; Lefohn, Hazucha, Shadwick, Adams, 2010). It is a matter of concern that these two articles have not been reviewed in the ISA even though the papers have raised a number of important questions and issues regarding (1) current research approaches involving human studies and (2) the form of the current O<sub>3</sub> standard.
7. There are a number of important similarities between human health and vegetation research results in the mechanisms as well as the pattern of response. We recommend that these important similarities for the results for human health effects and vegetation effects be discussed in the ISA. We believe that a discussion of these similarities to O<sub>3</sub> exposures may provide important clarifications concerning the form and level of the O<sub>3</sub> standard. For example, vegetation researchers have concluded the following:
  - Ozone effects are cumulative;

- Peak O<sub>3</sub> concentrations appear to be more important than lower concentrations in eliciting a response;
- Sensitivity to O<sub>3</sub> varies with time of day; and
- Exposure indices that cumulate hourly O<sub>3</sub> concentrations and preferentially weight the higher concentrations have better statistical fits to growth/yield response data than do the mean and peak indices.

The US EPA reached the above conclusions based on research experiments that evaluated the importance of the higher O<sub>3</sub> concentrations in plant response based on results from (1) controlled conditions in the laboratory and in the field, and (2) uncontrolled conditions in the San Bernardino National Forest. These studies provided a framework from which the EPA developed biologically relevant exposure-response models that provide a consistent relationship between O<sub>3</sub> conditions and vegetation biological endpoints.

Most data on exposure-response of vegetation to O<sub>3</sub> has relied on experiments conducted in open-top fumigation chambers (OTCs) as a part of the National Crop Loss Assessment Network (NCLAN) and EPA National Health and Environmental Effects Research Laboratory, Western Ecology Division (NHEERL-WED) forest program in the US. Plants were fumigated with various levels of O<sub>3</sub> to obtain exposure-response functions for injury and/or damage assessment. Support for the importance of the higher concentrations in affecting vegetation comes from retrospective studies reported in the using open-top fumigation chambers to compare different types of indices (Lefohn et al., 1988; Lee et al., 1988). These studies demonstrated that cumulative exposure indices, which emphasized higher concentrations, were best related to plant response. In reviewing whether to use the current form of the primary standard (i.e., 8-h average concentrations), the EPA (2011) noted the inadequacy of using the 8-h average metric as a surrogate for exposure-response for predicting vegetation effects. The Agency noted that the current 8-h standard is not biologically relevant for vegetation protection purposes because it is not cumulative.

Similarly, Hazucha and Lefohn (2007) and Lefohn et al. (2010) have described the nonlinearity (i.e., important of peak hourly average O<sub>3</sub> concentrations) in human health response as well as the cumulative nature of the responses associated with enhanced hourly average concentrations. Controlled human laboratory studies have shown that there is a disproportionately greater pulmonary function response from higher hourly average O<sub>3</sub> concentrations than from lower hourly average values and thus, a nonlinear relationship exists between O<sub>3</sub> dose and pulmonary function (FEV<sub>1</sub>) response. The nonlinear dose-response relationship affects the efficacy of the current 8-h O<sub>3</sub> standard to describe adequately the observed spirometric response to typical diurnal O<sub>3</sub> exposure patterns. Lefohn, Hazucha, Shadwick, and Adams (2010) reanalyzed data from five controlled human response to O<sub>3</sub> health laboratory experiments as reported by Hazucha et al. (1992), Adams (2003, 2006a, b), and Schelegle et al. (2009). These investigators exposed subjects to multi-hour variable/step-wise O<sub>3</sub> concentration profiles that mimicked typical patterns

of ambient O<sub>3</sub> concentrations. The authors' findings indicated a common response pattern across most of the studies that provides valuable information for the development of a lung function (FEV<sub>1</sub>)-based alternate form for the O<sub>3</sub> standard. Based on their reanalysis of the realistic exposure profiles used in these experiments, the authors suggested that an alternative form of the human health standard, similar to the proposed sigmoidally weighted secondary W126 vegetation standard form, be considered. The suggested form is a cumulative concentration weighted O<sub>3</sub> exposure index, which addresses both the delay associated with the onset of response (FEV<sub>1</sub> decrement) and the nonlinearity of response (i.e., the greater effect of higher concentrations over the mid- and low-range values) on an hourly basis. The Hazucha and Lefohn (2007) and Lefohn et al. (2010) papers highlighted the similarities between human health and vegetation results and pointed out the importance of peak O<sub>3</sub> concentrations versus the mid- and low-level values and the difficulties of using multi-hour average concentrations as a metric for predicting effects.

Similar human health effects results as summarized by Hazucha and Lefohn (2007) and Lefohn et al. (2010) point out the importance of the following:

- Ozone effects are cumulative; and
- Peak O<sub>3</sub> concentrations appear to be more important than lower concentrations in eliciting a response;

The similarities between the results for human health effects and vegetation effects are important. These similarities provide researchers and policy makers with essential information that is necessary to help guide future research as well as decisions concerning clarifications about the form and level of the O<sub>3</sub> standard. A section added in the ISA that describes the similarities of the responses of vegetation and human health to cumulative exposure/dose and peak versus mid-and lower level concentrations (i.e., nonlinear response) would add to the current version of the document.

## References

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