Comments for Consideration by the CASAC Ozone Review Panel on the Reconsideration of the 2008 NAAQS for its teleconference deliberations on February 18, 2011

Milan Hazucha, M.D., Ph.D.
Department of Medicine, School of Medicine and
Center for Environmental Medicine, Asthma, and Lung Biology
University of North Carolina
Chapel Hill, NC 27599-7310

and

Allen S. Lefohn, Ph.D.
A.S.L. & Associates, 302 North Last Chance Gulch, Suite 410
Helena, Montana 59601
asl-associates.com/

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Last March 19, 2010 we submitted Comments for Consideration by the US EPA for its deliberations on the re-evaluation of the ozone (O_3) standard entitled "Clarification to Some of the Scientific Issues Raised by the EPA Concerning Human Laboratory Studies", Docket ID No.EPA-HQ-OAR-2005-0172.

In assessing the health effects, the proposed primary standard is based on the strength of evidence derived from human laboratory studies that, and as asserted by EPA, "provide data with the highest level of confidence" (75 FR, 2010, p.2945) because they provide human health effects data acquired under closely monitored conditions and can provide exposure-response relationships. As asserted by EPA, we fully agree that the informed judgment and conclusions about the health effects should be based on the nature and weight of the evidence, on biological plausibility, consistency, strength, and coherence of evidence. As indicated in the Federal Register (75 FR, 2010, p.2940), the reconsideration of the O_3 standards is based on the scientific and technical information and analyses on which the March 2008 O_3 NAAQS rulemaking was based. In the pages that follow, we have expressed concerns about some of the scientific issues summarized in the Federal Register (2010). We would also like to expand on our March 19, 2010 comments with focus on the Charge Questions (Wegman, 2011) to be discussed at the February 18 and March 3, 2011 CASAC teleconferences in the hope that our comments will provide more

accurate input into the decision making process associated with setting the level of the human health standard for O_3.

1. Comments to Charge Question 1.

What is your advice on the overall strengths and limitations of the evidence from controlled human exposure and epidemiological studies and the results of the exposure and risk assessments, in the context of EPA's selection of a standard level within the proposed range that would be requisite to protect public health with an adequate margin of safety, including the need to protect susceptible populations, such as children and people with asthma?

1.1 Controlled human exposure studies.

The first Charge Question on the overall strengths and limitations of the evidence from controlled human studies briefly summarizes the results of two Adams multi-exposure studies (2002, 2006) considered new for 2008 rulemaking. A point is made that these are "newly available in the 2008 rulemaking.... down to an exposure level of 0.060 ppm." Actually, these studies discuss exposure levels down to 0.040 ppm.

A more recent study that was not available in 2008 provides some guidance on the O_3 effects at 0.060 ppm level. It is a multi-exposure study of Schelegle et al. (2009) which reports lung function data effects following 6.6-hr exposure to 0.087, 0.080, 0.070, and 0.060 ppm. The authors used several parametric and nonparametric tests to analyze the data and found the effects of 0.060 exposure to be not significant from filtered air by any of the tests. All other O_3 exposure effects were significant from filtered air. Our reanalyzes of Schelegle and colleagues (2009) data agreed with the authors' findings (Lefohn et al., 2010).

As reiterated in the Memorandum (Wegman, 2011), the current EPA (75 FR, 2010, p. 2950) approach in evaluating the "health effects" is placing the emphasis in interpretation of effects on the number of individuals whose FEV_1 decrement at the end of exposure is greater than 10% (more specifically FEV_1 decrements $\geq$ 10 % but <20%). The Memorandum (Wegman, 2011) states that "7 to 20% of the subjects in the Adams studies experienced lung function decrements ($\geq$ 10%) at the 0.060 ppm exposure level" (75 FR, 2010, p. 2986). The 7% of the subjects represents 2 of 30 subjects in the Adams (2006) study population that experienced FEV_1 decrements with $\geq$ 10% with the square-wave exposure pattern at the 0.060 ppm exposure level

(comparing pre- and post-exposures) when the results were adjusted for the effects of exercise alone in filtered air (FA). This number disagrees with data presented in Fig. 8-1B (US EPA, 2006) showing that only 3%, i.e., 1/30 subjects in Adams (2006) study experienced ≥ 10% decrement. Moreover, the upper range value of 20% (6/30) perpetuated throughout the EPA documents may apparently come from the 0.080 pm face-mask Adams (2002) study and, therefore, in this context is not relevant. However, it may also be possible that the 20% value (6 of 30 subjects), although cited as Adams (2002) by the EPA, originated from his earlier study in 1998, which was not published in the peer-reviewed literature and is neither referenced in the Criteria Document (US EPA, 2006) nor Federal Register (75 FR, 2010). In this face mask study, which according to Adams presented an "artificial burden" with minute ventilation 15% greater than used in his 2002 and 2006 studies and 0.060 ppm O_3 concentration, FEV_1 changes were not statistically significant. We believe that it is inappropriate for EPA to use the non-peer reviewed Adams' results from his 1998 report in its rulemaking considerations.

EPA subsequently states (Wegman, 2011; 75 FR, 2010, p. 2951) that such magnitude of lung function decrements is of concern because for active healthy people, moderate levels of functional responses (e.g., FEV_1 decrements of ≥ 10% but < 20%) and/ or moderate symptomatic responses would likely interfere with normal activity for a relatively few responsive individuals. Furthermore, CASAC indicated (75 FR, 2010, p.2973) that focus should be on the lower end of the range of moderate levels of functional responses for estimating potentially adverse lung function decrements in people with lung disease. The EPA then uses the concentration at which a small percentage of volunteers who responded with ≥ 10% decrement in FEV_1 to extrapolate to an entire population (US EPA, 2007). In the opinion of Prof. Smith[1,2] with which we concur the 2 out of 30 subjects "is an extremely small number of individuals from which to conclude that the response is significant" (Smith, 2007). Moreover, to quote: "Given the large uncertainty in the probability of response at 0.06 ppm ozone, I do not believe that staff paper's conclusions on this point are justified" (Smith, 2007).

EPA's approach overlooks numerous modulating/confounding factors that will impact health effects assessment. The use of FA is not an appropriate control exposure because the 0 ppb O_3

[1] Prof. Richard L. Smith is Director of Statistical and Applied Mathematical Sciences Institute, University of North Carolina–Chapel Hill, NC.

[2] Member of Health Effects Institute , Health Research Committee

“air” that is generated in the laboratory does not exist under ambient or indoor air conditions. For example, the FA FEV_1 responses associated with the controlled human exposure experiments show an improvement of FEV_1 (Adams, 2006). Comparing changes across corresponding time intervals and expressing them as "corrected values" that take into consideration the absolute difference between the O_3 and FA responses may perhaps “artificially” enhance the magnitude of the O_3 response. Such enhanced responses may not be necessarily observed at relevant background levels of hourly average O_3 concentrations with the result that statistically significant differences using FA may not be realized using actual ambient background levels. A comparison to a control that represents background O_3 concentrations is more appropriate.

The selection of the background O_3 level to be used as a control exposure is important. The EPA (75 FR, 2010, p.2980) has estimated, using a model that policy-relevant background (PRB) O_3 concentrations are in the range of 15-35 ppb. Empirical O_3 data collected at an O_3 monitoring site where PRB conditions predominate show that the O_3 concentration levels are frequently $\geq$ 50 ppb (Oltmans and Lefohn, 2005; Oltmans et al., 2008). The range of maximum hourly average concentrations for April for the period 2003 to 2010 is 54 – 65 ppb and the range of hourly average concentrations $\geq$ 50 ppb is 30 – 188 occurrences. Eurasian emissions associated with biomass burning and their easterly transport enhance O_3 concentrations at west coast O_3 monitoring sites under PRB conditions, as well as inland O_3 monitoring sites in Montana, Wyoming, and North Dakota (Oltmans et al., 2010). Thus, the EPA's modeled estimates of policy-relevant background O_3 concentrations in the range of 15 to 35 ppb is much lower than actual measured ambient values when PRB conditions predominate.

In assessing the relevance of the small number of individuals that experience moderate lung function decrements, important considerations that must be taken into account are: (1) lack of relevant background O_3 control profile in laboratory studies; (2) substantial intra-individual variability; (3) lack of coherence between responses of some individuals to a range of O_3 concentrations; (4) post hoc statistical analyses; and (5) inadequate standard-setting assessment when applying square-wave exposure patterns.

1.2 Questionable post-hoc statistical analyses of data.

In considering the weight of the evidence gained from the two Adams studies EPA has commented that although the two studies are by one investigator the studies are well designed

(Wegman, 2011). The 0.040 ppm exposure showed non-significant improvement of lung function (FEV_1) in both studies. The 0.060 ppm effects in 2006 study were also found to be non-significant by the author. The EPA, however, has considered statistical analyses of this study to be "inconclusive" and did its own reanalysis finding the not significant 0.060 ppm square-wave exposure effects as statistically significant (Brown, 2007; Brown et al., 2008). This re-analyses was done "because of potential regulatory implications of the presence or absence of effects" (Brown et al., 2008), implicitly referring to statistical significance or non-significance of effects. Commenting on the EPA's criticism of Adams (2006), Smith (2007) states that in considering the statistical aspect of Adams' analysis "the evidence for a response at 0.06 ppm ozone level is still very uncertain". Subsequently, Smith (2007) commented that "In my judgment, when all the comparisons are taken into account, there is insufficient evidence to conclude that there is any well-defined response to ozone exposure below the 0.08 ppm level". Surprisingly, the effects of average 0.060 ppm step-wise exposures reported in the same study, which were also found not to be significant by the author, were not reanalyzed by EPA.

The approach of Brown et al. (2008) is problematic. ***The selection of statistical method to analyze data is closely tied to and dependent upon study hypotheses***. In all of the relevant Adams studies, the key interest was in hourly changes and not solely the end-exposure effects. Thus, Brown et al. (2008) reanalyzes of only end of exposure changes ignoring intermediate hourly changes is questionable. Our reanalyzes of Adams (2006) data using a statistical method different from both Adams (2006) and Brown (2008) found the effects of 0.040 and 0.060 ppm to be in agreement with Adams analyses, i.e., not significant from filtered air (Lefohn et al, 2010). It is apparent that several statistical approaches are claimed to be appropriate for analyses of the same data by different investigators, even though they result in conflicting statistical significance of reported changes. ***The appropriate statistical test is the one that is in conformity with the study hypotheses*** and that would be Adams' analyses as well as that of Lefohn et al (2010). To re-analyze data because the original statistical outcome did not produce desired results and expected "implications" of such outcome is inappropriate.

1.3 The risk assessment based on infrequent square-wave-like exposure profile and not on a typical diurnal concentration pattern is troubling.

The NAAQS (US EPA, 2006) document states that "the controlled exposure (or "clinical") studies provide the clearest and most compelling evidence for human health effects directly attributable to acute exposures to O_3 per se" (page E-9). Implicitly, such acute O_3 exposures mean exposures to diurnal (i.e., variable) concentration encountered by general public in ambient air.

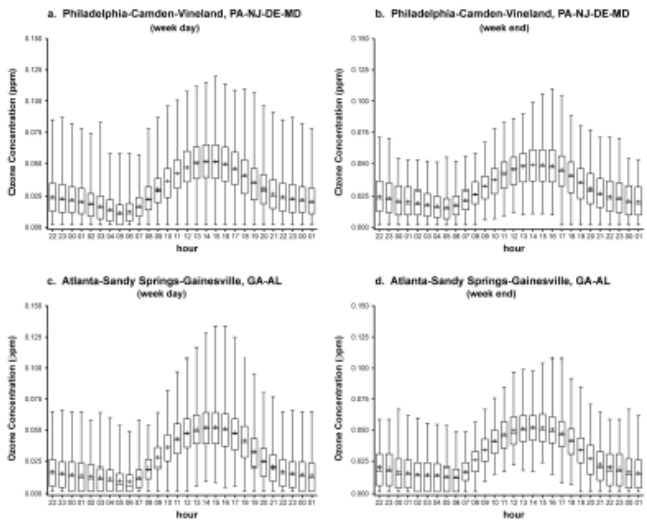

Figure 3-12a-d. Diurnal variations in hourly averaged O_3 on weekdays and weekends in four cities. Values shown represent averages from May to September of 2004. Boxes define the interquartile range and the whiskers, the minima and maxima.

Source: Fitz-Simons et al. (2005).

One of the key topics discussed in Chapter 3 of the same document entitled "Environmental Concentrations, Patterns, and Exposure Estimates" is characterization of ambient O_3 concentrations, particularly section 3.4 entitled "Diurnal and Seasonal variability of ozone". More than 25 pages including 13 figures each with 4-6 panels show plots of a typical diurnal concentration pattern recorded across various US cities (US EPA, 2006). In our perusal of Chapter 3 we have not found any reference to a square-wave concentration profile occurring in the ambient atmosphere in the US. The figures and related discussion in this Chapter leave no doubt that the diurnal O_3 profile across the US has a variable form with bell-like concentration pattern reaching peak in the early afternoon (see the Figure 3-12a-d). Therefore, one would expect that the health risk estimate would be based on real diurnal ambient atmosphere concentration profiles and not on an occasional occurrence of a near steady-state concentration.

Results from controlled laboratory exposures (e.g., variable concentration profile) of human volunteers indicate that higher O_3 hourly average concentrations elicit a greater effect on hour-by-hour physiologic response (i.e., FEV_1) than lower hourly average values, which implies a nonlinear dose-response relationship (US EPA, 2006; Adams, 2006b; Hazucha and Lefohn, 2007). Thus, identical 8-h average dose produces different responses, depending on the hour-by-hour O_3 concentration pattern. The current 8-h average human-health O_3 standard is not adequate

for describing this nonlinear FEV_1 hour-by-hour pattern of response. For developing a consistent standard to protect human health, it is important to identify those ambient-type concentration patterns that elicit adverse human health effects. The EPA appears to be focused on the square-wave regimes to establish the lower-level of response although it is clear that a ***variable pattern is typical of outdoor ambient conditions*** (US EPA, 2006, page AX6-19). Diurnal patterns predominate in urban, suburban, and low-elevation rural areas (US EPA, 2006). Using EPA AQS data for 2002, out of 28,148 8-h sequences, only 426 (1.51%) were classified as a square-wave ambient O_3 concentration profile (Lefohn et al., 2010). Consequently, the prevalence of a variable O_3 concentration profile in ambient air associated with greater spirometric effects should make the variable exposure studies "the highlights of evidence" and the key studies for standard setting. However, such is not the case; EPA has focused only on the 0.06 ppm square-wave results from Adams (2006) and possibly the 1998 non peer reviewed report by Adams that is cited in Adams (2002). ***We are concerned that by omitting data from the variable profile studies, the EPA has provided an inadequate assessment for the human health considerations.***

2. Comments to Charge Question 2:

Recognizing that controlled human exposure studies at 0.080 ppm O_3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV_1, how should the results of these studies inform our understanding the health effects to healthy adults at exposures levels from 0.060 to 0.070 ppm?

Human O_3 studies at concentration $\geq$ 0.08 ppm exploring changes in inflammatory variables show much greater intra- and inter-individual variance of measured endpoints than spirometric variables. At this time we do not have a sufficient number of human controlled studies exploring these endpoints to make a definitive statement concerning the importance of these observations in the standard-setting process. A recent study by Kim et al. (2011) reports on both spirometry and inflammatory cell changes to square-wave 0.060 ppm and perhaps may provide some general guidance as to the magnitude and individual variability of inflammatory endpoints following square-wave 0.060 exposures. However, for future rulemaking activities, we believe that variable/stepwise exposures and the application of realistic background O_3 levels as a control would be required to provide specific guidance to the EPA.

3. Comments to Charge Question 3.

How should the results of the controlled human exposure studies at 0.060 ppm O_3, showing effects on FEV_1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?

EPA recognizes that the intra-individual variability of various endpoints may be substantial but believes that the variability tends to be reproducible (75 FR, 2010, p. 2949). Although there is a tendency by the investigators to interpret their findings of repeated exposures to the same concentration as "reproducible" since the group averages are similar and correlations between two separate exposures are high (i.e., for some spirometric endpoints), closer examination shows that for many individuals, the differences in FEV_1 response may be substantial and, in some cases, different by as much as 40 percentage points. Hazucha et al. (2003) noted that many individuals, who were initially classified as weak responders, became strong responders on the second exposure and vice versa. Such a shift in an individual's O_3 responsiveness has a direct bearing on the current approach to data interpretation and usage by EPA in support of a lower O_3 standard.

Furthermore, there is a considerable intra-individual inconsistency of response within an exposure period. Some individuals show no response during, for example, 6.6-h exposure, but a sudden decrease in FEV_1 at the end of exposure. Others show an up and down response during exposure with a chance FEV_1 decrement of $\geq$ 10% at the end of exposure. Other individuals may respond with $\geq$ 10 % or even 15% decrement at the first hour, but minimal or no response at the end. With such individual variability, the utility of using only individuals' end exposure FEV_1 value for health assessment is questionable. These findings illustrate the large individual variability of response. Thus, because of the large intra-individual inconsistencies in response between and within exposures observed in the controlled health experiments, it is our opinion that the end of exposure value of an $FEV_1 \geq 10\%$ decrement may not be indicative of a detrimental health effect.

Adams (2006) reported no statistical significance at the 0.06 ppm level using both variable and square-wave profiles. Similarly, Schelegle et al. (2009) reported similar results using a variable profile. Lefohn et al. (2010), using the data from Adams (2006) and Schelegle et al. (2009) and a different statistical approach, reported no statistical significance. Using almost

double the number of subjects as Adams (2006) and Schelegle et al. (2009), Kim et al. (2011) reported statistical significance using 0.06 ppm square-wave profiles. However, the resulting FEV_1 effects were compared with FA instead of realistic ambient variable exposure pattern that represented background O_3 concentrations. Actual PRB O_3 concentrations have been reported to frequently occur at some monitoring sites ≥ 50 ppb (Oltmans et al., 2008; Oltmans et al., 2010). An important issue to consider is whether Kim et al. (2011) would have observed a statistically significant difference between the square-wave 0.06 ppm exposure and a control that reflected observed PRB O_3 concentrations (i.e., concentrations ≥ 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 0.06 ppm and a control that represented observed PRB concentrations.

4. Comments to Charge Question 4.

With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean FEV1 decrements relative to the findings that 7 to 20% of the subjects experienced FEV1 decrements ≥ 10%? Please consider this question from both a public health and a clinical perspective.

To date EPA has used only selected data (square-wave) from a few controlled human exposure studies that have reported on the effects of O_3 at 0.060. The available database could be substantially enhanced if (1) the variable/stepwise concentration profile studies were included, and (2) the hourly responses data were considered as well. However, addition of these data to the database may require a modified approach to risk estimation based on a cumulative approach as described in Lefohn et al. (2010).

As we already pointed out in comments to Charge Question 1, Adams (2006) and Fig. 8-1B (US EPA, 2006) reported only 1/30 subjects (3%) showing FEV_1 decrement ≥ 10% following exposure to 0.060 ppm O_3. This becomes 7% (2/30) when adjusted for filtered air response by EPA (Brown et al., 2008), which we do not necessarily consider appropriate because of enhancements at FA, which is not a relevant background O_3 concentration. The upper limit of 20% is misleading because it is either based on the 0.080 ppm results of face-mask exposure (Adams, 2002) or on a non-peer reviewed Adams (1998) report. Consequently, the use of such data is highly questionable. Thus, for 0.060 ppm exposure (square-wave), we do not have a range but 1 or possibly 2 subjects with ≥10% decrement. Considering "the large uncertainty in the

probability of response at 0.06 ppm ozone" (Smith, 2007) and considering that 2/30 subjects " is an extremely small number of individuals from which to conclude that the response is significant" (Smith, 2007), we find the available evidence of pulmonary function effects, based on the Adams (2006) study, to be inadequate and believe that an extrapolation to a general population is inappropriate.

5. Conclusions

EPA in its current approach in evaluating the "health effects" is placing the emphasis in interpretation of effects on the number of individuals whose FEV_1 decrement at the end of exposure is greater than 10%. The EPA states that this is of concern because for active healthy people, moderate levels of functional responses (e.g., FEV_1 decrements of $\geq$ 10% but < 20%) and/ or moderate symptomatic responses would likely interfere with normal activity for a relatively few responsive individuals. However, in assessing the relevance of the small number of individuals that experience moderate lung function decrements, important considerations must be taken into account. Based on our analysis, we conclude:

1. The use of FA may not be an appropriate control exposure because the 0 ppb O_3 "air' that is generated in the laboratory does not exist under ambient or indoor air conditions. Actual PRB O_3 concentrations are greater the 15-35 ppb levels modeled by the EPA and PRB hourly average concentrations frequently occur at some sites $\geq$ 50 ppb. Comparing changes across corresponding time intervals and expressing them as "corrected values" that take into consideration the absolute difference between the O_3 and FA responses may perhaps "artificially" enhance the magnitude of the O_3 response.

2. Intra-individual variability of various endpoints may be substantial. 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_1 response may be substantial and, in some cases, different by as much as 40 percentage points. With such individuals, between and within exposure inconsistencies, the utility of using only individuals' end exposure FEV_1 value for health assessment is questionable.

3. The lack of coherence between responses of many individuals to a range of O_3 concentrations further reflects on instability of these effects.

4. Post hoc statistical analyses are questionable because they may violate *a priori* statistical design. Approaches based on the behavior of extreme responses within specific experiments, treatments, and measurement times have not been presented in a way to have any confidence in attempts to reinterpret the analysis in a meaningful statistical sense.

5. Focusing on square-wave versus realistic variable exposures provides an inadequate assessment for the human health considerations.

6. Inflammatory variables show much greater intra- and inter-individual variance of measured endpoints than spirometric variables. At this time we do not have a sufficient number of human controlled studies exploring these endpoints to make a definitive statement concerning the importance of these observations in the standard-setting process.

5. References

Adams, W. C., 2002. Comparison of chamber and face-mask 6.6-hour exposures to ozone on pulmonary function and symptoms responses. Inhalation Toxicol. 14:745-764.

Adams W.C., 2006. Comparison of chamber 6.6-h exposures to 0.04-0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. Inhal. Toxicol. 18:127-136.

Adams W.C., 2006b. Human pulmonary responses with 30-minute time intervals of exercise and rest when exposed for 8 hours to 0.12 ppm ozone via square-wave and acute triangular profiles. Inhal. Toxicol. 18:413-422.

Brown, J.S. The effects of ozone on lung function at 0.06 ppm in healthy adults. June 14, 2007. Memo to the Ozone NAAQS Review Docket. EPA-HQ-OAR-2005-0172-0175. Available online at: http://www.epa.gov/ttn/naaqs/standards/ozone/s_o3_cr_td.html.

Brown, J.S., Bateson, T.F., McDonnell, W.F., 2008. Effects of exposure to 0.06 ppm ozone on FEV_1 in humans: a secondary analysis of existing data. Environ. Health Perspect. 116:1023-1026.

Federal Register, 2010. National Ambient Air Quality Standards for Ozone: Proposed rule. 40 CFR Parts 50 and 58 (EPA-HQ-OAR-2005-0172; FRL-9102-1). RIN 2060-AP98. Vol. 75, No. 11, p. 2938-3052.

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

Hazucha, M., Lefohn, A.S., 2010. An alternative form and level of the human health ozone standard. Inhal Toxicol 22:999-1011.

Kim, C.S., Neil E Alexis, Ana G Rappold, Howard Kehrl, Milan J Hazucha, John C Lay, Mike Schmitt, Martin Case, Robert B Devlin, David B Peden, and David Diaz-Sanchez. Lung Function and Inflammatory Responses in Healthy Young Adults Exposed to 0.06 ppm Ozone for 6.6 Hours. Am J Respir Crit Care Med, prepubl. Jan, 7, 2011.

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.

Oltmans, S.J., Lefohn, A.S., 2005. Using empirical data to estimate policy relevant background for ozone exposures. Submitted to the U.S. EPA as part of the comments on the second draft of the Ozone Criteria Document.

Oltmans, S.J., Lefohn, A.S., Harris, J.M., Shadwick, D., 2008. Background ozone levels of air entering the west coast of the U.S. and assessment of longer-term changes. Atmospheric Environment 42:6020-6038.

Oltmans, S.J., Lefohn, A.S., Harris, J.M., Tarasick, D.W., Thompson, A.M., Wernli, H., Johnson, B.J., Novelli, P.C., Montzka, S.A., Ray, J.D., Patrick, L.C., Sweeney, C., Jefferson, A., Dann, T., Davies, J., Shapiro, M., Holben, B.N., 2010. Enhanced ozone over western North America from biomass burning in Eurasia during April 2008 as seen in surface and profile observations. Atmos Environ 44:4497-4509.

Smith, R.L. Public Comments to CASAC Ozone Review Panel, March 7, 2007.

U.S. Environmental Protection Agency, 2006. Air Quality Criteria for Ozone and Related Photochemical Oxidants. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC. U.S. EPA report no. EPA/600/R-05/004bF.

U.S. Environmental Protection Agency, 2007. Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information. OAQPS Staff Paper, Report EPA-452/R-07-007. Research Triangle Park, NC:Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency. Available online at: http://www.epa.gov/ttn/naaqs/standards/ozone/s_o3_cr_sp.html.

Wegman L.N. Memorandum: Solicitation of CASAC Advice on EPA's Reconsideration of the 2008 Primary Ozone National Ambient Air Quality Standard, EPA, HEID, OAQPS, January 26, 2011.