Memorandum

To: The Clean Air Scientific Advisory Committee (CASAC) **Date:** May 14, 2014

From: Julie E. Goodman, Ph.D., DABT, FACE and Sonja Sax, Sc.D.

Subject: Comments on the CASAC Review of the Health Risk and Exposure Assessment and the Policy Assessment for Ozone

This memo addresses specific comments that were provided by CASAC members related to the ongoing review of the primary National Ambient Air Quality Standards (NAAQS) for ozone. Specifically, the United States Environmental Protection Agency (EPA) asked the Clean Air Scientific Advisory Committee (CASAC) to review and comment on the second external draft Health Risk and Exposure Assessment for Ozone (REA) (US EPA, 2014a) and the second external draft of the Policy Assessment for the Review of the Ozone National Ambient Air Quality Standards (PA) (US EPA, 2014b). Individual CASAC members addressed specific sections of these documents and EPA charge questions in preliminary written comments, and during a meeting held March 25-27, 2014. Our comments below address some of the points regarding the health effects of ozone that CASAC members discussed with a focus on Chapters 5-9 of the REA and Chapters 1-4 of the PA. Additional comments on CASAC's draft PA and Health REA letters to the Administrator will be provided separately.

CASAC's Pre-meeting Response to REA and PA Charge Questions

Health Risk and Exposure Assessment (Chapters 5-9)

Most of the CASAC members commented positively on the second draft REA. Many explicitly stated that they thought it was a major improvement over the first draft, indicating that the data assessment was stronger and better formulated than in the past. While we agree that this effort represents a significant improvement over the previous draft, many issues remain that were not fully addressed by the CASAC panel. These issues pertain to the presentation and interpretation of the risk assessment, particularly in light of the significant amount of uncertainty in the modeled risk estimates.

Chapter 5: Characterization of Human Exposure to Ozone

As opposed to presenting the total number of people with ozone exposures or risks in a given urban area, EPA presented results in terms of (1) percentages of certain population groups (*e.g.*, children) with ozone exposures or ozone-related health risks and (2) percentage reductions in exposure or risk in these population groups at lower ozone levels. Mr. Avol commented on the use of percentages to describe populations affected in various cities, noting, for example, that 5% of the population in New York City is vastly different than 5% of the population of Baltimore (a less population-dense city). Mr. Avol went on to point out that the percentage perspective does not take into account any "vulnerability factor" (*e.g.*, race, access to health care) and that a discussion of proportional changes across a city fails to incorporate important public health indices.

While it is true that presenting results in terms of a percentage may limit comparisons across cities, the method EPA used was appropriate because it applies to the *simulated* population in the Air Pollutants Exposure Model (APEX) analysis (not the total population in any given urban area). To obtain an estimate of the total number of people with exposures or risks in a given urban area, EPA would have to extrapolate based on the APEX analysis. Owing to numerous assumptions used in the model, any extrapolated estimates would be highly uncertain; thus, the results of the APEX analysis are most useful as comparative estimates (*e.g.*, for comparing across different benchmarks or alternative levels of the standard, as EPA did in the REA). Regarding his comment on vulnerability, Mr. Avol did not appear to consider that EPA conducted a highly conservative analysis by focusing on exercising children and asthmatics to address issues of susceptibility, which likely led to overestimated risks in the urban populations as a whole.

Dr. Diez Roux found the methods and descriptions of the model inputs to be clearly presented, but she expressed confusion about the model output data. Using Figure 5-2 as an example, Dr. Diez-Roux commented that it is not clear what one ozone exposure means in the context of describing the percent of asthmatic children with at least one ozone exposure at or above 60 parts per billion (ppb)-8 hour. She wrote, "Does it mean that they were engaging in moderate of [*sic*] greater exertion at any time during an 8 hour period with an average of ≥60 ppb? 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?)." Dr. Diez-Roux noted this one example, but there are several more instances of this lack of clarity throughout Chapter 5. A related question not discussed by Dr. Diez Roux is concerned with how a single exposure relates to a standard that is based on a 3-year average of the 4th highest daily maximum 8-hr level. This needs clarification as well. These questions, together with Mr. Avol's line of questioning, suggest that there was confusion among CASAC members regarding EPA's APEX analysis that may have limited their ability to interpret the findings correctly.

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

Dr. Kleeberger concluded that the methods and results related to lung function risk analyses were "sound, balanced, and clearly communicated." He also noted that the use of the McDonnell-Stewart-Smith (MSS) model was appropriate for measuring changes in lung function in terms of forced expiratory volume in 1 second (FEV_1). While Dr. Kleeberger stated that the discussion of uncertainty and variability was adequate, he requested clarification regarding whether EPA included intrinsic variation (*i.e.*, genetic) factors in the models and, if not, an explanation of why EPA excluded them. Again, this comment suggests a misunderstanding of the general inputs into the APEX model, as data are not available to conduct such an assessment. CASAC should recommend that EPA provide clarification.

Dr. Miller stated that EPA's analysis of controlled human exposure studies was technically sound and an improvement in the overall ozone risk characterization. Dr. Miller and Dr. Kleeberger both stated that the discussion of uncertainty and variability was adequate; however, Dr. Russell stated that the uncertainty discussion was lacking. He discussed how the uncertainties in the MSS model are likely larger than 5% (as acknowledged in the REA) but only 5% were evaluated (referencing Fig. 6-12). However, Dr. Russell did not inquire further about this discrepancy or provide suggestions beyond that it should be noted in the figure caption. Also, the 2012 MSS model used by EPA assumes a constant variance, whereas the 2013 better-fitting MSS proportional variance model has a variance changing proportionally to exposure level, which is a more likely condition (McDonnell *et al*., 2013). EPA should consider using the updated MSS model. We agree that the treatment of uncertainty and variability was not adequate in the REA, and EPA should have evaluated how changes larger than 5% in the MSS parameters would have impacted the risk assessment results. Also, CASAC members did not question why EPA did not present confidence bounds (*i.e.*, confidence intervals, or CIs) for any of the exposure or lung function risk estimates. Importantly,

none of the CASAC members commented on how uncertainty should be considered in the interpretation of the risk results, particularly when comparing across different proposed levels of the standard. These are important issues that CASAC should have asked EPA to address.

Dr. Ulman pointed out that the analysis considered uncertainty with respect to intra-subject variation but not inter-subject variation. He stated that it is important to include a sensitivity analysis that incorporates this variation, which might be larger in at-risk populations (*e.g.*, asthmatics) than the general population. This is a particularly salient point, as EPA focused on at-risk populations in this analysis but did not consider this additional source of variability. Furthermore, Dr. Ulman stated that the changes to the intra-subject distribution in the sensitivity analysis (p. 6-41) increased the proportion of children with a change in FEV_1 > 10% from 31 to 92%. Unfortunately, Dr. Ulman did not offer an alternative approach or insight into what the implications of such assumptions mean to the usefulness of such analyses. In the REA, EPA also noted that it assumed a normal (Gaussian) distribution for this parameter, which was convenient for the analysis but likely wrong, without providing additional analysis to assess the impact of this assumption on the results. In addition, EPA tends to evaluate effects only in the adverse direction (FEV_1 > 10%) without balancing them against potential improvements in lung function.

Chapter 7: Characterization of Health Risk Based on Epidemiological Studies

In her written comments, Dr. Diez-Roux stated:

> 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 [ozone] 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. These issues need to be clarified. The extent to which the simulated increases of [ozone] at lower standards is realistic and to be expected in the real world needs to be discussed. How important is this possible increase in considering the health impact of alternative standards?

This is an important question that has yet to be fully addressed. CASAC should urge EPA to evaluate how increased ozone levels in urban areas as a result of lowering the ozone standards may actually result in increased health risks.

Dr. Miller said that using decreasing nitrogen oxide (NO_x) emissions as the driver for just meeting the current or alternative ozone standards is the only viable approach for lowering ozone levels. While this may be the most common approach for addressing ozone reductions, EPA appropriately considered several alternative approaches in its sensitivity analyses.

The urban area that EPA modeled is larger than the areas evaluated in the underlying epidemiology studies. Dr. Miller argued that the uncertainties associated with using this larger area are not likely to be any greater that those introduced by other factors. Increasing the study area, however, reduces the impact of NO titration that is evident by the EPA model in the core urban area, therefore indicating increased mortality. When the analysis is conducted using the core urban areas from the epidemiology studies, it shows that when NO_2 levels are reduced dramatically to attain lower ozone standards, ozone levels will actually increase. This results in increased risk estimates with a lower ozone standard – a scenario that is not health protective. CASAC should request that EPA more fully address this discrepancy.

Dr. Vedal made several points about this chapter of the REA. He noted that relying on Jerrett *et al*. (2009) as the only basis for estimating long-term mortality risks tempers confidence in the resulting concentration-response function (CRF). He disagreed with EPA's use of "reasonable degree of confidence" in the risk estimates for long-term respiratory mortality effects (p. 7-86), noting that this seems inconsistent with the Integrated Science Assessment (ISA) conclusion that there is "limited evidence" for an association between long-term exposure and respiratory mortality. This is an important point that CASAC should include in its letter to the Administrator.

Dr. Vedal also noted that there are issues regarding spatial variability in ozone with respect to proximity to roadways and how predicted risks increase for some study areas when standards are met. Overall, Dr. Vedal concluded that the discussion of uncertainty and variability in Chapter 7 of the REA was sound and comprehensive. However, we note that EPA did not highlight the quantified uncertainty (represented by the confidence bounds around the risk estimates) or that this only captures a small amount of the overall uncertainty. Also, EPA did not discuss how known and unknown uncertainties contribute to the overall confidence in the risk estimates and how these estimates should be interpreted in light of this.

Chapter 9: Synthesis

Dr. Russell requested a deeper and more definitive discussion of uncertainty, suggesting it would be useful if Section 9.5 had more direct statements on how the reader should interpret the overall uncertainties in the risk and exposure assessments for use in standard setting. He also stated that the REA should identify the most impactful uncertainties and how they can be targeted for further reduction. Dr. Russell pointed out that the discussions of analyses dealing with seasonal ozone changes and the impact of different metrics used in the analyses were inadequate.

Aside from Dr. Russell's comments, CASAC members did not provide much of a discussion of uncertainty in the modeled risk estimates and how this should guide the interpretation of results. We note that, with respect to the risk assessment on lung function decrements, EPA's many conservative model assumptions compound uncertainty and most likely result in overestimated risks. Also, EPA did not provide CIs to indicate the uncertainty surrounding the risks estimated from either of its two models using controlled exposure study data, making it difficult to determine whether the observed small reductions in the percentage of individuals who would experience lung function decrements with lower ozone standards were statistically significant. With respect to the mortality risk assessment, EPA provided CIs for mortality estimates, which was an improvement over the first draft. However, these confidence bounds do not capture a large majority of the uncertainties associated with the risk estimates. Moreover, EPA's evaluation of these uncertainties could be stronger if it identified the key sources of uncertainty and stated the relative impact of each source more clearly, rather than defaulting to "both" as the direction and "low-medium" as the relative magnitude for the majority of these uncertainties. It would be more effective to provide examples and circumstances on how the uncertainties would 1) bias estimates low or high and 2) act cumulatively. Without this type of analysis, the uncertainty evaluation is not useful.

Policy Assessment: Health Effects (Chapters 1-4)

Overall, most CASAC members largely agreed with EPA's conclusions that the current standards should be revised. Many members agreed with the evidence EPA put forth in support of health effects at levels at 75 ppb ozone, as well as the potential need to consider the upper bound of the proposed range (*i.e.*, 70 ppb). The preliminary comments of individual CASAC members addressed several issues with the draft PA, some of which are summarized below.

Chapter 2: Ozone Monitoring & Air Quality

Mr. Allen, Mr. Avol, Dr. Jacob, and Dr. Russell all mentioned that there is confusion regarding how EPA considered background ozone levels in the PA. Mr. Allen pointed out that it is unclear how EPA will navigate between the need to consider background ozone levels and the feasibility of new regulations. Dr. Jacob stated that it is unclear whether the analysis of the background contribution to ozone will be utilized for both scientific and policy purposes. Mr. Avol asked whether measurements from human chamber studies should be compared to 0 ppb or background levels. He stated that these considerations clearly affect the magnitude of outcomes attributable to ozone and the nature of the dose-response curves at low ozone levels. As discussed in the next section, when controlled human subjects were exposed to fresh air (*i.e.*, 0 ppb), FEV_1 improved compared to baseline levels. Therefore, any FEV_1 decrements attributable to ozone in these studies, when compared to fresh air controls, may actually be overstated. Overall, although these important issues were raised, there was no resolution or additional discussion as to how EPA should address them. The issue of background ozone levels remains a concern, particularly when the low end of the recommended range of the ozone standard is close to observed background in some areas. CASAC should ask EPA to clarify how it will ensure that background will be adequately considered.

Chapter 3: Adequacy of the Primary Standard

In discussing the adequacy of the primary standard, Dr. Miller attributed the lack of consistent statistically significant group mean decrements in various controlled human exposure studies at 60 ppb ozone to low statistical power among the studies. He also stated that Section 3.4 provided strong evidence that indicates a revision of the current standard is appropriate. Dr. Miller also wanted to revisit 70 ppb as an upper level based on the scientific body of evidence. Dr. Neufeld concluded that EPA's analysis of the evidence, uncertainty, and variability was thorough and complete and, ultimately, strengthened its conclusions that the current standard is inadequate. Overall, Dr. Miller, Dr. Neufeld, and Dr. Russell all similarly concluded that EPA was justified in proposing a revised standard. As discussed in the next section, Dr. Miller's comments are not supported by the evidence across all the controlled exposure studies. EPA is correct in stating that there is a lack of consistency in the statistical significance across controlled studies and some of the statistical significance is a result of the way the data are analyzed. Furthermore, as discussed in detail in Goodman *et al*. (2013), the studies do not support *adverse* effects at 70 ppb.

Dr. Vedal commented that evidence provided by EPA on long-term exposure effects on lung function are largely based on "relatively weaker studies" and the studies of the highest quality (those of the Children's Health Study cohort) did not demonstrate any effects. Indeed, studies of the Children Health Study cohort are comprehensive and consistently have shown no ozone effects in children on respiratory endpoints, including lung function, lung function growth, and asthma (*e.g.*, Peters *et al*., 1999; Gauderman *et al*., 2000, 2002, 2004; McConnell *et al*., 2002, 2010; Berhane *et al*., 2004). Despite this, Dr. Vedal concluded that EPA's discussion in Section 3.4 provided an appropriate and sufficient rationale to support EPA's suggestion to revise the current NAAQS for ozone.

Chapter 4: Consideration of Potential Alternative Primary Standards

Dr. Diez-Roux provided detailed evaluations of the PA and brought up important points on the clarity (or lack thereof) and logic behind many of EPA's conclusions. For instance, Dr. Diez-Roux commented on the approach used in Chapter 4 to summarize associations in cities meeting various alternative ozone

standards. She stated that the point of this analysis is not clearly stated and the overall conclusion is confusing. Specifically, in questioning the conclusions from Table 4-1, Dr. Diez-Roux asked, "If studies conducted in areas that have met lower standards do not show an effect do we conclude then that the standard produces appropriate health protection? But if they do does this suggest that an even lower standard is necessary?" Similarly, Dr. Diez-Roux also found conclusions from Table 4-2 to be confusing with respect to what EPA was concluding about ozone levels below 70 ppb and the justification for such conclusions. This is an important point that calls into question this analysis in the PA.

Overall, it appears that most CASAC members agreed with EPA's conclusions that the current standard should be revised, with many members agreeing that the evidence put forth supports health effects at levels at or below 70 ppb ozone. However, in general, CASAC members provided little evidence to support their conclusions, particularly when commenting on the inadequacy of the current standard and residual health impacts below the standard.

March 25-27, 2014, CASAC Meeting

In general, the CASAC discussion echoed the comments presented in the pre-meeting comments. There was a general consensus that the second REA and PA drafts were an improvement over the first drafts, and there was general agreement with EPA's approach and presentation of the results. A large majority of the discussion focused on editorial changes or points of clarification that EPA should consider in the final document. Below, we comment on the more substantive scientific discussions regarding the human health effects evidence discussed on Days 2 (REA) and 3 (PA, Chapters 3-4). We also comment on specific suggestions by CASAC members regarding what should be included in the letter to the Administrator. Specific comments on the draft letters to the Administrator will be provided separately.

Health Risk and Exposure Assessment (Day 2 – March 26, 2014)

Chapters 2 and 3

In the discussion of Chapters 2 and 3, panel members specifically requested that EPA include a discussion of background ozone and how it was used it in the analysis (or, if not, an explanation of why it was not considered). Panel members also suggested that EPA discuss the uncertainty associated with background and the implications for the risk findings in the REA. As noted above, the issue of how background should be considered in the process of setting the ozone NAAQS remains critical and unresolved.

Panel members also discussed the issue of susceptibility, and where to draw the line for standard setting. Specifically, a panel member provided the example of an asthmatic *vs*. cancer patient in hospice care as demonstrating a wide range of susceptibility. Although the second draft REA focused a great deal more on what it called "at-risk" populations, these primarily included children and asthmatics and not highly compromised individuals; neither CASAC nor EPA acknowledged that focusing on these groups in the risk evaluation would lead to highly conservative estimates.

Chapter 4

Panel members generally agreed that the discussion of uncertainty was essentially complete, but there were still issues with the application of the calculated Higher-Order Decoupled Direct Method (HDDM) sensitivities, based on only eight months of data from 2007, to data for other years (2008-2010). Specifically, Dr. Chock stated that this approach underestimated potential variability in exposure

estimates and EPA was incorrect to characterize this source of uncertainty as low-to-medium. The EPA approach introduced a considerable amount of uncertainty because the 2007-based coefficients likely do not capture ozone reactions under different environmental conditions (*e.g.*, meteorology) that would occur in different years, and therefore results in more uncertain simulated ozone concentrations for meeting current and alternative levels of the ozone standard in other years.

The panel members also had concerns about the analyses of New York City and Los Angeles because of the large NO_x reductions needed to achieve lower ozone standards in these cities. EPA acknowledged that it has far less confidence in the risk estimates for these two cities compared to other cities because drastic NO_2 reductions were needed to achieve alternative ozone standards, causing model instability. Based on these modeling issues in these two cities, CASAC should recommend that the results for these two cities be excluded from consideration when evaluating the risk results, as well as in the summary tables in the executive summary, synthesis chapter, and policy assessment.

Chapter 5

The CASAC panel generally thought that EPA characterized uncertainty and variability well, but uncertainty should have been propagated for all steps in the modeling. Specifically, Dr. Suh suggested that it may be misleading to say that uncertainty factors were "low-to-moderate." Also, she suggested that a discussion of which factors were the greatest drivers of uncertainty was needed. We agree that the discussion of uncertainty was generally inadequate and needs to be expanded to address these issues. Further, there needs to be an assessment of how uncertainty should be considered in the interpretation of the results.

Chapter 6

Panel members discussed the findings from the most recent controlled exposure study by Kim *et al.* (2011), noting that this is probably the only study with adequate statistical power to detect ozone effects. Kim *et al.* (2011) exposed 59 healthy exercising, non-smoking young adults, a larger group than other similar studies (which typically included 30 subjects) to filtered air (FA) and 60 ppb ozone over six hours and evaluated the change in FEV_1, forced vital capacity (FVC), and total symptom scores (TSS). The authors analyzed and reported only pre-exposure measurements and post-exposure values after the sixth hour of exposure, ignoring measurements also taken at the 3rd-5th hours. They reported a statistically significant group mean percent change in FEV_1 of -1.7%. The authors also reported a pre-/post-exposure increase in neutrophilic inflammation but no statistically significant increase in TSS.

The study was limited by a selective data analysis and choice of the statistical approach more than statistical power. In contrast, Adams (2006) conducted a similar smaller study and reported no statistically significant effects when he assessed all of his hourly FEV_1 data. However, in their re-analysis of this study, Brown *et al.* (2008) reported statistical significance at 60 ppb considering the pre-/post-exposure data only. What is important to note in both the Kim *et al.* (2011) and Adams (2006) studies is that reported lung function decrements were so small that they do not constitute an adverse effect, regardless of the statistical significance of the results, particularly when not accompanied by other symptoms.

The CASAC members also discussed Schelegle *et al.* (2009), which is a chamber exposure study of 31 healthy, non-smoking young adults using a similar exposure/exercise profile and evaluating ozone concentrations of 63, 72, 81, and 88 ppb, as well as FA. A particular strength of the Schelegle *et al.* (2009) study is that the authors used three different statistical approaches addressing repeated measurements, multiple comparisons, and non-parametric data. Unlike the Kim *et al*. (2011) and Brown

et al. (2008) studies, none of Schelegle *et al*.'s statistical methods yielded statistically significant group mean FEV_1 decrements at 63 ppb ozone. Dr. Miller noted that this may have been due to lack of statistical power from fewer subjects, but as discussed above, it may also have been due to more appropriate statistical methodology and inclusion of all data. Schelegle *et al*. (2009) specifically noted that:

> [L]imiting the analysis to the immediate postexposure [*sic*] FEV_1 data and restricting the mean comparisons to the filtered air control would increase the power of the analysis and allow for the detection of significant differences when differences between means are small…however, we also recognize that when doing so caution should be exercised to ensure that the approach used is consistent with the original study design. In this case the individual subject FEV_1 responses induced by each exposure protocol are not independent and therefore any analysis should consider the effect of multiple comparisons.

Also, at 63 ppb, Schelegle *et al*. (2009) reported no increases in TSS and that FEV_1 decrements were very small, indicating a lack of adversity. Another important fact is that FEV_1 improved over the course of the exposure periods in FA-exposed individuals, magnifying perceived FEV_1 changes and overestimating FEV_1 decrements with ozone exposure – an issue only mentioned in passing during the CASAC meeting. Dr. Miller noted that some of the individuals in the Schelegle *et al*. (2009) study experienced an adverse FEV_1 decrement > 10%, with symptoms at 72 ppb. From the reported results in the Schelegle *et al*. (2009) study, it is unclear if this small number of individuals also experienced symptoms; therefore, these FEV_1 decrements may not necessarily constitute adversity (ATS, 2000). As a whole, results across all of the controlled exposure studies indicate that effects are not adverse below 80 ppb; therefore, there is a great deal more support for a protective standard at 75 ppb. Although he did not acknowledge this point, Dr. Miller also commented that there is increased uncertainty regarding ozone effects at exposures below 70 ppb. If this is the case, it is unclear how evidence could support a standard below this level.

Some CASAC members questioned the appropriateness of using only FEV_1 decrements as a measure of respiratory effects and suggested that more chronic indicators (such as inflammation) may be more appropriate. We agree that FEV_1 decrements alone should not be the sole indicator of the potential toxicity of ozone. However, even based on FEV_1 decrements alone, the limited available data show that effects of ozone below 80 ppb are transient and reversible and, even if caused by ozone, not clinically adverse. Only one study evaluated inflammation, providing very limited evidence. Additional studies are necessary to confirm these findings and to assess whether inflammation constitutes an adverse effect as measured in these studies.

Chapter 7

EPA justified estimating risks down to zero ozone levels by asserting that there is no evidence of a threshold for ozone effects, and CASAC panelists generally agreed with this justification, with the exception of Dr. Miller, who argued that there is likely to be a biologically effective threshold for ozone. We note that toxicological and controlled human exposure study evidence indicates that there is a threshold for ozone effects. In addition, several researchers have reported thresholds for ozone in epidemiology studies, including Stylianou and Nicolich (2009), Xia and Tong (2006), Smith *et al*. (2009), and Moolgavkar *et al*. (2013). As discussed by Rhomberg *et al*. (2011), the challenge in identifying a threshold for ozone effects in epidemiology studies is mainly a result of exposure measurement error, which can linearize CRFs and mask the true threshold. In addition, assessing risks down to zero does not reflect the reality that a zero ozone level is unattainable. CASAC should urge EPA to evaluate excess risks above threshold ozone levels.

Instead of conducting its risk assessment using the central core areas defined in the underlying epidemiology studies, EPA used larger urban areas. CASAC concluded that EPA's rationale for doing so was sound, but using larger study areas resulted in a mismatch between the estimated ozone concentrations and health functions derived from the epidemiology studies. This approach was inappropriate as it introduced a potentially large error in the risk estimates. CASAC should suggest that EPA present approaches in its core analyses that match the scenario in the underlying epidemiology studies as closely as possible to evaluate such alternative scenarios in its sensitivity analyses.

EPA calculated risks of long-term respiratory mortality using Jerrett *et al*. (2009) as the basis for the analysis. CASAC concluded that a threshold model from the Jerrett *et al*. (2009) study should have been included as a sensitivity analysis.[1] It is notable, however, that several CASAC panelists had questions regarding the rationale for including long-term respiratory mortality at all, mainly because of the limited evidence for this endpoint and because it was based primarily on the single Jerrett *et al*. (2009) study. We agree that evidence is too limited to justify calculating risk estimates for this endpoint. In fact, there are two other studies that reported null results (Abbey *et al*., 1999; Lipsett *et al*., 2011); because the weight of available evidence does not support a causal relationship between ozone and long-term respiratory mortality, this endpoint should not have been evaluated in the REA. Regardless, if EPA considers the inclusion of the long-term risk estimates, it should consider presenting results based on the threshold analysis as the core results, and alternative models as secondary information in the appendix. Dr. Vedal and Dr. Miller both argued for a threshold model.

Chapter 9 and Executive Summary

Several panelists noted that the executive summary needed to include more discussion of uncertainty and how EPA addressed it. As noted above, this is an area where EPA needs to indicate more clearly how uncertainty impacts its results and, more importantly, its interpretation of those results.

Discussion of the CASAC Letter to the EPA Administrator

Dr. Miller voiced a general conclusion on behalf of CASAC: "[T]he analyses that are presented in the health risk assessment showed that the current standard is not protective of public health." However, as discussed below, EPA's own analysis suggests that the standard is protective and little would be gained from lowering it.

EPA's exposure assessment indicates that the current level of the ozone standard is health protective, but this is not evident from the way it is presented in the second draft REA. EPA highlighted estimated simulated children's exposures in excess of a 60 ppb benchmark – a level that has not been shown to be associated with adverse respiratory effects in the large majority of controlled exposure studies (Goodman *et al*., 2013). Taking an even more conservative approach, EPA highlighted the percent of children experiencing a single exceedance of this benchmark in a given year or ozone season. Instead, EPA should have focused on multiple estimated exposures allowed by the NAAQS above 70 ppb. These results show that, on average, less than 1% of children had at least two exposures greater than 70 ppb. This latter analysis, which shows that few of the most highly exposed and "at-risk" children would be exposed to levels above the recommended high end of the ozone range if the current standard were attained, should have been highlighted in the report as opposed to being relegated to an appendix.

[1] A memo was released by EPA on April 28, 2014, indicating that it will do the analysis and include results in the final draft REA. Available at: http://yosemite.epa.gov/sab/sabproduct.nsf/9440700C4560F06385257CC80062ADC0/$File/Threshold+Memo+to+CASAC.pdf

Similarly, EPA estimated very small reductions in risk with a lower-than-current ozone standard, particularly when considering outcomes that are more likely to be adverse (*e.g.*, multiple daily FEV_1 decrements *vs*. a single day). Furthermore, EPA did not highlight that if confidence bounds had been considered, its analysis would indicate that the current standard is health protective and no significant additional benefits would be achieved from lower ozone standards.

In addition, Dr. Miller noted that "the scientific evidence of human controlled study [*sic*] showed there are adverse effects on human health from exposures to 70 parts per billion ozone." Dr. Miller was likely referring to the study by Schelegle *et al*. (2009), which found significant FEV_1 decrements at a group mean exposure to 72 ppb. As noted above, this study did not indicate that adverse effects occurred at these exposure levels. Our independent review of all controlled studies that evaluated exposures to ozone below 80 ppb showed that below 72 ppb, lung function effects were isolated, independent, and not statistically different in subjects exposed to ozone compared to those exposed to FA, indicating a lack of causation. In addition, lung function effects at these levels are not adverse because they do not interfere with normal activity, nor do they result in permanent respiratory injury or progressive respiratory dysfunction (Goodman *et al*., 2013).

Policy Assessment (Day 2 and 3 – March 26-27, 2014)

Chapter 3: Adequacy of Current Standard

The general consensus among panel members was that the current standard was not adequately protective and the PA provided strong evidence to justify a revision. Most of the panelists commented that the scientific evidence presented in this chapter was stronger than in the past draft, and it convincingly presented data to support adverse health effects occurring at exposure to 70 ppb ozone. The panelists indicated that the controlled human exposure studies provided the strongest evidence.

As noted above and reviewed in detail in Goodman *et al*. (2013), lung function effects from ozone exposures below 80 ppb have been investigated in several controlled human exposure studies (Adams, 2002, 2006; Schelegle *et al*., 2009; Kim *et al*., 2011). Of these, only Schelegle *et al*. (2009) reported a statistically significant, but small, decrease in lung function at 72 ppb, using appropriate statistical methods. Based on ATS (2000), European Respiratory Society (Pellegrino *et al*., 2005), and US EPA (2007) guidelines, mean decrements in FEV_1 are considered adverse when they are greater than 10% and accompanied by other respiratory symptoms. Although Dr. Miller argued that some of the subjects in the Schelegle *et al*. (2009) study experienced greater than 10% FEV_1 decrements, it is unclear from the data presented in the paper whether these individuals also had a concomitant increase in symptoms.

Several members of the panel argued that high-risk individuals, such asthmatics and children, are expected to be more sensitive to the effects of ozone and have more significant decrements in lung function after exposure. However, there is little evidence of differential effects of ozone exposure on susceptible populations, including asthmatics and children. For example, several controlled human exposure studies have found no differences in lung function between asthmatics and non-asthmatics at elevated ozone exposures of 200-400 ppb (Basha *et al*., 1994; Scannell *et al*., 1996; Alexis *et al*., 2000; Mudway *et al*., 2001). With regard to children, several controlled exposure studies have reported that ozone responsiveness is similar or lower in children than in adults, and that there are no statistically significant effects of age on the FEV_1 responses to ozone exposures (McDonnell *et al*., 1985, 2012). This was not discussed by CASAC.

With respect to children and asthmatic children being susceptible populations, Dr. Vedal noted EPA's disregard of the high-quality camp study of almost 900 asthmatic children by O'Connor *et al*. (2008) and the largest cohort study (the Children's Health Study) that reported no effect of ozone on respiratory health endpoints. Dr. Vedal made this point in an overall comment on EPA's tendency in the PA to overreach when discussing the adversity of ozone-related health effects. He also noted that conclusions about asthma based on primate data may not be appropriate. However, even though Dr. Vedal identified these problems with the scientific evidence provided in Chapter 3, he ultimately concluded that there is sufficient evidence to justify revising the current ozone NAAQS.

We note that in the Health REA, EPA used a very conservative approach. This included a focus on children who spend a significant amount of time outdoors engaged in exercise and applying assumptions for children in the MSS model, which was based on data obtained from adults. Even assuming these hypothetical worst-case scenarios, EPA reported that less than 0.6% of children would experience at least two days of 8-hour maximum ozone concentrations above 70 ppb (in an ozone season) at the current level of the ozone standard (75 ppb), and less than 0.1% of these children would have these exposures if the standard were 70 ppb. Furthermore, the largest percentage of children that would experience greater than six days of FEV_1 decrements > 10% was 6% at the current level of the standard, and falls to 5% at a 70 ppb standard. Therefore, considering the highly conservative nature of the analysis, and no confidence bounds around these estimates (that would reflect the uncertainty in the model), these results show that exposures and effects at the current level of the standard are small, and lowering the standard to 70 ppb does not provide significant additional health benefits (*i.e.*, that are greater than the uncertainty in the models).

Interestingly, in pre-meeting comments, Dr. Vedal noted that "it was difficult to accept" that the percentage of children with FEV_1 decrements > 10% was the same as the percentage of children exposed at least once above 60 ppb in an ozone season. Although he did not elaborate on this point, the results appear to reflect the conservative nature of the model and the high likelihood that the model is overestimating the risks in children and in the urban populations as a whole.

Chapter 4: Consideration of Potential Alternative Primary Standards

For this chapter, the panelists generally agreed that the current standard is not adequate for protecting the health of all individuals. While they concluded that the evidence supports adverse health effects in people at 70 ppb, there was no general agreement on suggestions for a new standard or levels that would actually provide public health benefits. As discussed throughout these comments, current scientific evidence, as well as EPA's risk assessment, does not support lowering the current ozone standard.

Discussion Points for the CASAC Letter to the Administrator

In the discussion of the main points that should be included in the letter to the Administrator, there were two major discussion points. The first point was that the panel agreed that adverse health effects have been observed at ozone exposures of 70 ppb, and new evidence since the last review supports this assertion. The second point was that EPA should consider a standard below 70 ppb, not inclusive of 70, to provide an adequate margin of safety for susceptible populations, but there was no consensus as to what the upper bound should be. Some panelists argued that this should be a policy consideration, as there was less scientific evidence to suggest adverse health effects, and more uncertainty, below 70 ppb. Only Dr. Vedal dissented, suggesting to the panel that it consider supporting EPA's recommendations of a range between 60 and 70 ppb to "simplify things."

With regard to adverse health effects, the panelists listed the following health effects for which there is evidence of adversity at 70 ppb: FEV_1 decrements, respiratory symptoms, inflammation, asthma, diminished immune function, respiratory hospital admissions, and respiratory emergency room visits. The panelists also listed groups of sensitive populations that would be anticipated to have greater adverse effects with exposure to ozone, including children, newborns, the elderly, and people with pre-existing health conditions (*e.g.*, asthmatics) and certain genetic determinants.

As discussed in more detail in Goodman *et al*. (2013), based on evidence from controlled human exposure studies, the data are limited for FEV_1 decrements at 70 ppb and these effects are not adverse. There is even less evidence of respiratory symptoms and inflammation at this level. The large majority of data show that effects are consistent and potentially adverse at levels well above 80 ppb. This indicates that the current standard of 75 ppb is protective.

There is even less evidence that other health effects occur at or below the current standard. With regard to asthma, there is a lack of consistency across epidemiology studies of short-term ozone exposure. For example, associations between ozone and respiratory symptoms among asthmatic children and adults have been studied, yet most of the studies reported null associations in both single- and multi-pollutant models (US EPA, 2013). Schildcrout *et al*. (2006) found no association between ozone and respiratory symptoms and rescue inhaler use in asthmatic children. In another study of children at summer camps, the authors reported no decreases in lung function (measured by FEV_1 and FEV_1/FVC) associated with higher daily ozone exposure (Nickmilder *et al*., 2007).

Other studies have reported mixed findings. Gent *et al*. (2003) reported that increased symptoms, including wheezing and chest tightness, were increased in ozone-exposed children taking maintenance medication but not in ozone-exposed children not on medication. Gent *et al*. (2003) suggested that this may have occurred because children on medication are more vulnerable to the effects of ozone than non-medicated children. Hernández-Cadena *et al*. (2009), on the other hand, reported that non-medicated asthmatic children experienced greater ozone-induced lung function decrements than medicated asthmatic children.

In one of the largest multi-city studies of asthmatic children, O'Connor *et al.* (2008) reported effects of ozone on lung function decrements in asthmatic children that were not statistically significant, and the magnitude of the response for ozone was considerably smaller compared to other pollutants. The authors also reported no association between ozone exposure and asthma symptoms or school absences. The authors concluded that the associations observed for ozone were weak compared to those in their previous study (Mortimer *et al*., 2002).

The evidence for hospital admissions and emergency room visits is equally mixed and inconsistent, with several studies reporting negative association, no associations, or statistically insignificant associations between ozone and either general or more specific (*e.g.*, asthma) respiratory health endpoints (US EPA, 2013, see Figure 6-19).

Regarding immune function effects, the large majority of findings are from animal studies (US EPA, 2013). These studies are conducted at highly elevated ozone exposures (much higher than the proposed ozone standard) that are not relevant to the ozone concentrations being considered by CASAC (*i.e.*, 70 ppb). In addition, it is unclear whether results from these studies can be extrapolated to humans. As acknowledged by EPA, the findings from controlled exposure studies and epidemiology studies are mixed and, in some cases, conflicting; thus, the available scientific literature provides little support for immune effects in humans at current ozone levels (US EPA, 2013).

Overall, many key studies that are discussed in the ozone ISA do not provide compelling support for the respiratory or immune function effects that CASAC has concluded are associated with ozone exposure at 70 ppb. In fact, the epidemiology evidence is so mixed that it calls into question a causal association with these health endpoints at current ozone levels. As noted by Dr. Vedal, the long-term effects are even less compelling, particularly because of consistent null findings for ozone in one of the largest and longest cohort studies of children in the US (*i.e.*, the Children's Health Study).

The current evidence from controlled exposure and epidemiology studies for respiratory health effects does not indicate that current ozone levels, which do not meet the current ozone standard in many areas, are adverse to public health. Therefore, the current standard, when met, should provide an adequate margin of safety to protect any potentially vulnerable population groups. In addition, to date, there is no consistent evidence that the groups identified by CASAC are actually more susceptible to ozone effects than others.

While there is some support for increased risk of mortality in elderly populations, EPA's analysis suggests that very few elderly people would be exposed to ozone levels above 70 ppb. The evidence is not consistent for increased risk of health effects in children or other groups identified by CASAC. More specifically, while some studies reported positive associations for children of varying ages, others showed inconsistent or null results. Furthermore, controlled human studies suggest that children are not as responsive to the respiratory effects of ozone as young adults. Finally, animal data do not inform the relationship between ozone effects and increased susceptibility in children or the elderly because of the high ozone concentrations used in animal studies; these concentrations are not applicable to typical exposures experienced by the general population.

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