Dear Administrator Jackson:

This letter provides comments of the Clean Air Scientific Advisory Committee (CASAC) in response to the charge questions submitted in the January 26, 2011 memorandum from the Office of Air Quality Planning and Standards (OAQPS). The questions are related to the current reconsideration of the 2008 proposed National Ambient Air Quality Standard (NAAQS) for Ozone.

Previous Comments by CASAC

As you know, CASAC has an extensive, recent record of providing independent peer review on the Agency's technical documents related to the Ozone NAAQS. From 2005 to 2008, CASAC reviewed two drafts of the Staff Paper (now called the Policy Assessment), two drafts of the Criteria Document (now called the Integrated Science Assessment), two drafts of the risk assessment and two drafts of the exposure assessment. As stated in our letters of October 24, 2006, March 26, 2007 and April 7, 2008 to former Administrator Stephen L. Johnson, CASAC unanimously recommended selection of an 8-hour average ozone NAAQS within the range proposed by EPA (60 to 70 ppb). On March 12, 2008, EPA published its decision to revise the National Ambient Air Quality Standards (NAAQS) for Ozone, revising the 8-hour "primary" ozone standard[1], designed to protect public health, to a level of 75 ppb. In response, CASAC offered comments in a letter to former Administrator Johnson on April 7, 2008 to the effect that CASAC did not endorse the new primary ozone standard (75 ppb) as being sufficiently protective of public health.

In response to EPA's reconsideration of the 2008 Ozone NAAQS and the proposal published on January 19, 2010, CASAC reaffirmed its support for the selection of an 8-hour average ozone NAAQS within the 60 – 70 ppb range. In our letter of February 19, 2010, we reiterated support for this range and referred to the supporting evidence as presented in *Air Quality Criteria for Ozone and Related Photochemical Oxidants* (March 2006) and *Review of the National Ambient Air Quality Standards for Ozone: Policy Assessment of Scientific and Technical Information* (OAQPS Staff Paper, July 2007).

While we are concerned that EPA's most recent request for additional CASAC advice is redundant with our past reviews, we nonetheless are pleased for the opportunity to reaffirm our previous advice and we are submitting this letter and the attached consensus advice to further assist EPA as it takes action following this additional scientific input from CASAC.

Here we reaffirm that the evidence from controlled human and epidemiological studies strongly supports the selection of a new primary ozone standard within the 60 – 70 ppb range for an 8-hour averaging time. As enumerated in the 2006 Criteria Document and other companion

[1] An 8-hour averaging time and a form based on the annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years, were adopted in 1997 and retained in the 2008 rulemaking.

assessments, the evidence provides firm and sufficiently certain support for this recommended range for the standard.

Key Findings

Although the Clean Air Act mandates the selection of a standard that has an adequate "margin of safety," the practical application of this term requires a policy judgment. The scientific evidence that was assembled by EPA and reviewed by CASAC shows no "threshold" or level below which there is no risk of decrement in lung function following short-term exposure to ozone.

As you give consideration to the revision of the NAAQS, we offer the following summary of findings in the evidence available through 2006:

- The evidence available on dose-response for effects of ozone shows associations extending to levels within the range of exposures currently experienced in the United States.

- There is scientific certainty that 6.6-hour exposures with exercise of young, healthy, non-smoking adult volunteers to concentrations ≥ 80 ppb cause clinically relevant decrements of lung function.

- Some healthy individuals have been shown to have clinically relevant responses, even at 60 ppb.

- Since the majority of clinical studies involve young, healthy adult populations, less is known about health effects in such potentially ozone sensitive populations as the elderly, children and those with cardiopulmonary disease. For these susceptible groups, decrements in lung function may be greater than in the healthy volunteers and are likely to have a greater clinical significance.

- Children and adults with asthma are at increased risk of acute exacerbations on or shortly after days when elevated ozone concentrations occur even when exposures don't exceed the NAAQS concentration of 75 ppb.

- Large segments of the population falls into what EPA terms a "sensitive population group,'' i.e., those at increased risk because they are more intrinsically susceptible (children, the elderly, and individuals with chronic lung disease) and those who are more vulnerable due to increased exposure because they work outside or live in areas that are more polluted than the mean levels in their communities.

- CASAC unanimously reaffirms its support for the previously recommended selection of an 8-hour average ozone NAAQS within the range proposed by EPA (60 to 70 ppb).

Public Comments

There were over 55 public comments presented during the teleconferences in February and March of 2011. As always, we welcome public input into our deliberations. Some commentators pointed out that even in the range of 60 – 70 ppb, there would be selected members of the population who would continue to be at risk, and thus a standard set in this range would contain a reduced margin of safety for these vulnerable populations. Other public comments touched upon topics outside the scope of our specific deliberations around the charge questions. For your information, concerns were expressed about potential deleterious economic consequences of a more stringent NAAQS, including adverse impacts on jobs and commerce, and the practical issues of implementation. Other comments touched on the possibility of deferring any change in the 2008 standard until the newer evidence has been considered. The difficulty of establishing "policy relevant background" for this naturally occurring internationally-transported pollutant also received comment.

Evidence Considered by CASAC

At EPA's request, our deliberations were constrained to the evidence assembled in the prior review that ended in 2008, i.e. a science record that closed in 2006. This constraint imposed an artificial boundary on our discussions. The public comments, however, were not so limited. While we appreciate the depth and scope of the public's interest in ozone regulation, we recognize that the topics raised and newer information could not be incorporated into our deliberations given our instructions from EPA and the process that has been used for assembling and reviewing evidence in considering a NAAQS revision. Although some written comments from individual panelists include more recent studies, our consensus responses to the charge questions and this letter are based on the literature considered in the last ozone NAAQS review that ended in 2008.

Conclusion

Again, we reaffirm our unanimous recommendation, given in Chairperson Henderson's 2008 letter to the Administrator, to set the ozone NAAQS within the range of 60 to 70 ppb for an 8-hour averaging time. In that range, CASAC finds that the evidence is sufficiently certain to be confident of public health benefits and additional protection for susceptible groups.

Draft Responses to Charge Questions

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?**

The controlled human exposures to ozone were carried out in rigorous fashion by established investigators at distinguished institutions. They used state-of-the-art techniques to measure pulmonary function changes and changes in lung inflammation based on biomarkers in bronchoalveolar-lavage fluids. These studies have produced substantial data on the acute effects of short-term exposures to this respiratory irritant and the results were quite consistent over a wide range of ozone concentrations and exposure durations. While CASAC did not consider the findings of recent publications (post-2006) in reaching this judgment, it was aware that the results of these more recent studies were consistent with those of the earlier studies that formed the basis for our judgments on the effects produced by controlled human exposures.

In interpreting these findings, we note that most of the studies that influenced our judgments on the proposed range involved healthy adult subjects and required exercise as a necessary factor for revealing adverse responses to ozone. Exercise promotes higher levels of ventilation as well as switching from predominantly nasal to oral breathing. These factors increase the penetration of ozone into the lungs, thereby increasing respiratory responses relative to quiet breathing. Since many Americans have occupations that require them to work outdoors while others exercise outdoors for recreation, these studies reflect the exposure circumstances of many people in the United States. This is an important consideration in establishing the primary NAAQS. There is also a substantial literature demonstrating that children with asthma participate in team sports and other forms of strenuous exercise as a regular part of their school and after-school activities. For such children, who represent a sensitive population, the pulmonary function decrements and inflammation observed in exercising healthy adults most likely underestimate the effects of a given ozone exposure.

There are substantial complementary epidemiological data that have the strength, compared with clinical studies, of being based on responses in generally much larger numbers and more diverse subjects. In chamber studies, exposures are limited to ozone alone. While ambient ozone measurements used in epidemiological studies are reasonably specific to ozone, there are other strong photochemical oxidants in the ambient air as well. This is considered a strength of the epidemiological data since ozone is not, *per se*, a criteria pollutant. Rather it was selected to serve as an indicator for the Photochemical Oxidant NAAQS, and the health effects of the mixture in natural settings

may be larger than if the exposure were only to ozone. The health-related functional and inflammatory changes measured in panel studies of people exposed to ozone outdoors are also seen in the controlled chamber exposure studies with ozone alone. Since these effects are not known to occur with ambient air exposures to realistic concentrations of these other photochemical co-pollutants, their presence may serve to exacerbate rather than simply add to the effects of the ozone in the ambient mixture. Thus, within the range of ozone concentrations under consideration (60 to 70 ppb), where the ratio of ozone to other photochemical oxidants is unlikely to change, reducing ozone concentrations is likely to reduce the effects of the photochemical oxidant mixture as a whole.

The effects observed in epidemiological studies are reasonably specific to ozone. However, as discussed above, they can also be influenced by the presence of other strong photochemical oxidants in the ambient air, and thus the health effects in natural settings may be larger than expected from clinical experiments with exposure only to ozone. Another potential difference between controlled exposure and epidemiological studies is the reaction products from ozone once it enters indoor environments. These reaction products include a wide range of gas-phase respiratory irritants and ultra-fine particles. Epidemiological studies take these other oxidants into account to some greater or lesser extent with respect to the covariance of the other ambient oxidants with ozone. It should also be noted that central monitors, particularly those placed in urban areas, have ozone concentrations that are lower than those further from the urban core because nitric oxide in motor vehicle emissions scavenges ozone, thereby lowering ozone concentrations within traffic corridors. Thus, ozone levels recorded by central site monitors may not accurately portray the near-ground exposure of most individuals in the population.

Taken together, controlled human studies and the epidemiological studies strongly support the selection of a new primary ozone 8-hour concentration limit that is well below the 1997 limit of 80 ppb over an 8-hour averaging time. There is scientific certainty that 6.6-hour exposures to ozone at concentrations $\geq$ 80 ppb with intermittent exercise, cause clinically relevant decrements of lung function in groups of young, healthy volunteers, and in one controlled human exposure study there were clinically relevant effects in some individuals at 60 ppb. The results of multiple epidemiological studies also show that children and adults with asthma are at increased risk of acute exacerbations of asthma on or shortly after days when ozone concentrations are elevated above background but less than 80 ppb, and there is no evidence of a threshold concentration limit below which there are no adverse effects in sensitive subpopulations. Given the results of EPA's exposure and risk assessments, setting a new NAAQS in the range of 60 to 70 ppb is appropriate, but would provide little margin of safety at its upper end.

In summary, the strengths of the evidence from controlled human exposure and epidemiological studies enumerated in the Criteria Document and its update were substantial, and more than adequate to support the recommended range for the NAAQS

of 60 to 70 ppb. The limitations of the evidence from controlled human exposure and epidemiological studies were well and appropriately stated in the Staff Paper.

2. Recognizing that controlled human exposure studies at 80 ppb 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 60 to 70 ppb?

Results from earlier studies at 80 ppb ozone and above were reviewed in earlier Criteria Documents and were primarily summarized in less detail in the current Criteria Document. Dosimetry of ozone is relevant to extrapolations from higher to lower concentrations. Several articles have pointed out that pulmonary function [1] and other response indicators [2] are related to exposure concentration, ventilation rate and exposure duration, among other variables. The responses at levels below 80 ppb in the Adams and other studies are consistent with predictions using dosimetric and effective dose calculations that were influenced by results obtained at 80 ppb and higher concentrations.

In considering the public health implications of the controlled studies relevant to ozone health effects, CASAC notes that the participants were healthy, non-smoking young adults. Chamber studies of asthmatic and non-asthmatic subjects exposed to ozone at relatively high concentrations showed that the changes in forced expiratory volume in 1 second (FEV_1) and mid-maximal expiratory flow (MMEF) were significantly greater in the subjects with asthma than in those without asthma [3]. For ethical reasons, controlled exposure studies are designed to limit effects to only those that are relatively mild and reversible, including decrements in pulmonary function and evidence of inflammatory changes. One characteristic response to low ozone exposure levels is mucosal neutrophilic cell inflammation probably mediated by phospholipid-derived products and by epithelial cell-derived chemokines and cytokines [4]. This response may be poorly correlated with lung function changes, perhaps because the time course of development for these responses is different from that for changes in FEV_1 or because the mechanism of ozone-induced reduction in lung function may not be related to airway inflammation. In fact, some individuals may exhibit inflammation without significant changes in pulmonary function. However, the data showing elevated levels of inflammatory cytokines, infiltration of inflammatory cells (macrophages and neutrophils) and evidence of oxidative changes provide important components of biological plausibility and advance our understanding of the mechanisms by which ozone affects health. The data also provide mechanistic support for the observed epidemiological associations with regard to exacerbations of asthma at concentrations below 80 ppb. The inflammatory effects are likely to be more serious for individuals with chronic lung diseases. The exposure chamber studies showed that individuals with chronic obstructive pulmonary

disease had significantly greater losses of pulmonary function (19% from their baseline) than did healthy controls when exposed to ozone during light exercise [5]. While these studies are often performed at exposure concentrations higher than typical ambient conditions, they serve to identify disease-relevant mechanisms and underscore the inherent variability of even healthy adult populations with respect to their responses to ozone. It is important that we consider this person-to-person variability in sensitivity to ozone as we examine whether the current or proposed ambient concentration ranges provide an adequate margin of safety for sensitive subpopulations.

McDonnell, W.F., et al. 1997. Prediction of ozone-induced FEV_1 changes. Effects of concentration, duration, and ventilation. *Am J Respir Crit Care Med*. 156(3 Pt 1):715-22.

Mudway, I.S. and F.J. Kelly. 2004. An investigation of inhaled ozone dose and the magnitude of airway inflammation in healthy adults. *Am J Respir Crit Care Med*. 169(10):1089-95.

Kreit, J.W., et al.1989. Ozone-induced changes in pulmonary function and bronchial responsiveness in asthmatics. *J Appl Physiol.* 66(1):217-22.

Bromberg, P.A. and H.S. Koren, 1995. Ozone-induced human respiratory dysfunction and disease. *Toxicol Lett*, 82-83**:**307-16.

Gong, H., Jr., et al. 1997. Responses of older men with and without chronic obstructive pulmonary disease to prolonged ozone exposure. *Arch Environ Health*. 52(1):18-25.

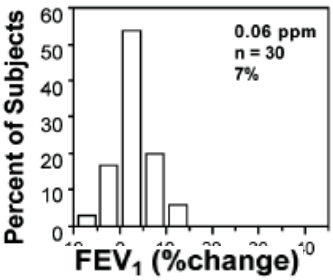
3. How should the results of the controlled human exposure studies at 60 ppb O_3, showing effects on FEV_1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 60 to 70 ppb?

The results of only one controlled human exposure study of the effect of ozone at concentrations <80 ppb were available for the committee to consider (Adams, 2006). This study was well-designed and conducted with appropriate methods. The authors reported a statistically significant group mean decrement in FEV_1 of 4.7% after 6.6-hour exposure to 80 ppb as compared to the response to filtered air (a 1.35% increase in FEV_1). They also reported group mean decrement in FEV_1 of 1.5% after 6.6-hour exposure to 60 ppb ozone that was not significantly different from the response to filtered air. However, eight of the 30 subjects in the Adams et al. study experienced decrements in FEV_1 >5% and two had decrements >10%, a decrease in lung function considered clinically relevant by the American Thoracic Society. The results of the Adams et al. study fit well with those from multiple other studies of the effect of ozone on lung

function at concentrations ≥80 ppb, which have consistently shown that some individuals are more sensitive to this effect of ozone than others.

As discussed at length in the Criteria Document and Staff Paper, there is no evidence for a threshold below which ozone does not affect lung function. The magnitude of the effect of ozone diminishes with decreasing concentration, but does not reach the comparison level associated with exposure to ozone-free filtered air. Furthermore, there is a great degree of variability of response magnitude among the healthy individuals studied, with some having clinically relevant responses, even at 60 ppb.

4. **With respect to the information from controlled human exposure studies at 60 ppb O_3, what is the scientific importance of the small, group mean FEV_1 decrements relative to the findings that 7 to 20% of the subjects experienced FEV_1 decrements ≥ 10%? Please consider this question from both a public health and a clinical perspective.**



The inset plot of the Adams data (Adams 2006), derived from Figure 8-2 of Volume I of "Air Quality Criteria for Ozone and Related Photochemical Oxidants, 2006", shows an approximately normal distribution in the ozone-induced decrements in FEV_1 with exposure to 0.060 ppm (60 ppb). Although the mean decrement is less than 3% and would not be considered clinically important, the shift to the right in this distribution pushes a fraction of subjects (7%) into the region of clinical importance (>10% decrement). The consistency of effects across ozone exposure levels within the Adams study, as well as the consistency with effects observed in an earlier independent study (McDonnell et al. 1991) indicates that the observed deficits in FEV_1 at 60 ppb from the Adams study are not likely to be spurious. In other words, prolonged exposure to 60 ppb ozone probably causes a general shift in the distribution of FEV_1 towards lower values.

All of the Adams study subjects were healthy adult volunteers. From a public health standpoint, these results suggest that a large number of individuals in the general population (that are otherwise healthy) are likely to experience FEV_1 deficits greater than 10% with prolonged exposure to 60 ppb ozone.

A 10% decrement in FEV_1 is often associated with respiratory symptoms, especially in individuals with pre-existing pulmonary or cardiac disease. For example, people with chronic obstructive pulmonary disease have decreased ventilatory reserve (i.e., decreased baseline FEV_1) such that a ≥10% decrement could be associated with moderate to severe respiratory symptoms. The exposure and risk assessment conducted for the last review of the ozone NAAQS clearly document that a substantial proportion of the U.S. population is exposed to levels of ozone at the various alternative standards considered. This means

that even if a NAAQS of 60 ppb were to be adopted, some sensitive individuals could still be exposed to concentrations that could cause them to have a clinically relevant decrement in lung function.

The experimental study results in healthy subjects essentially preclude extension of these studies to groups that may be more sensitive because of the ethics of carrying out clinical studies in diseased individuals. Thus, without having specific studies among asthmatics and children at these levels of exposure, it is prudent, in spite of the uncertainty, that EPA select an exposure level below the current standard (closer to the 60 ppb level) to "protect public health with an adequate margin of safety, including the need to protect susceptible populations."

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(2):127-136.

McDonnell, W.F., H.R. Kehrl, S. Abdul-Salaam, P.J. Ives, L.J. L.J. Folinsbee, R.B. Devlin, et al. 1991. Respiratory response of humans exposed to low levels of ozone for 6.6 hours. *Arch Environ Health* 46(3):145-150.

5. The evidence, including that summarized above, indicates that susceptible populations may have greater responses than healthy people. In light of this evidence, how can we appropriately use the results of controlled human exposure studies conducted on healthy adults, as well as the epidemiological studies of susceptible groups, to inform a judgment on the effects of ozone exposure on susceptible populations?

As discussed above, the findings from clinical studies of healthy volunteers may underestimate the risks in groups considered potentially susceptible. In the controlled human exposure studies carried out at concentrations of 80-ppb ozone and below, a percentage of healthy subjects have lung function changes much higher than the average response (e.g., FEV_1 changes > 10 %). While FEV_1 changes > 10% may not prevent healthy individuals from pursuing their normal daily activities, individuals with compromised lungs, such as persons with asthma, may incur significant health impacts with reductions of this magnitude. As CASAC has commented in the past to EPA, evidence is accumulating that persons with asthma, the elderly, and particularly children, are more sensitive and experience larger decrements in lung function due to ozone exposure than do healthy adult volunteers.

In addition, epidemiological studies considered in the last review showed adverse effects of ozone on various health endpoints (e.g., emergency department visits and increased hospital admissions for respiratory illness) at relatively low exposure levels. These findings and the results of the clinical studies suggest the possibility of ozone effects

down to the lower end of the 60-70 ppb range. CASAC concluded at the last review that the lower range of consideration for revision of the NAAQS should be 60 ppb ozone, acknowledging inherently that margin of safety considerations would be better met at 60 ppb than at 70 ppb ozone. Moreover, since the relative strength of the evidence is weaker at lower ozone concentrations (see # 6 below for comments on the epidemiological evidence), a range of 60 to 70 ppb ozone allows the Administrator to place her judgment on the weight that any uncertainties and limitations in the science play in selecting an exposure level protective of public health with some margin of safety.

6. To what extent does your confidence that the effects observed in epidemiological studies are attributable specifically to O_3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?

While epidemiological studies are inherently more uncertain as exposures and risk estimates decrease (due to the greater potential for biases to dominate small effect estimates), specific evidence in the literature does not suggest that our confidence on the specific attribution of the estimated effects of ozone on health outcomes differs over the proposed range of 60-70 ppb. In framing our answer to this question, we note that the range covered is quite narrow and we would not anticipate major differences in the characteristics of the pollution mixture across this range.

Several distinct classes of epidemiological studies are relevant in this range. For instance, mortality effects for ozone have been found in time-series studies in communities where mean ambient concentrations are well below the proposed range (e.g., Vedal et al 2003). Exercise-induced decrements in lung function, known to be causally related to ozone in controlled exposure studies, have been observed in field studies of healthy volunteers. For instance, in a cross-sectional study, Korrick et al. (1998) found hikers on Mount Washington experienced significant decreases in FEV_1 after prolonged exercise on days when ozone averaged 40 ppb (range 21 to 74 ppb). The magnitude of these decrements increased as mean ozone levels increased and it was nearly fourfold higher for persons with asthma than for persons without asthma. Panel studies of campers are yet another class of field studies that have shown effects on children's lung function are associated with ambient ozone. For example, in a panel of healthy children, Spektor et al. (1988) showed significant reductions in FEV_1 associated with one-hour average ambient ozone, even when restricted to days with ozone below 60 ppb. Similarly, in panels of children with moderate to severe asthma attending summer camp, Thurston et al. (1997) reported not only respiratory function changes, but also more clinically significant responses, including increases in physician prescribed rescue medication and respiratory symptoms. In yet another class of epidemiological studies, health care utilization for asthma has been shown to decrease when ozone concentrations decreased. For example, Friedman et al (2001) found that during the Summer Olympic Games in Atlanta in 1996 there was significantly decreased use of pediatric care for asthma that correlated best with a reduction in peak ozone concentrations. In this study, the relative risk of asthma events

increased stepwise at cumulative ozone concentrations 60 to 89 ppb and 90 ppb or more compared with ozone concentrations of less than 60 ppb. The reduction of the adverse effects on asthma in this study was dependent on reduction of ozone exposures to levels below 60 ppb.

Our confidence that the effects from epidemiological studies are attributable to ozone is also bolstered by the recognition that the endpoints of concern do not change at the lower levels of the proposed range. While it may be difficult to disentangle the effect of a single pollutant in epidemiological studies, the evidence regarding ozone-related health effects from epidemiological studies is consistent with the evidence from controlled exposure studies that involve ozone alone. Indeed, evidence from observational studies of individuals exercising outdoors indicates ozone may have even stronger lung function effects than those estimated in controlled exposure studies, suggesting the possibility that a mixture of photochemical oxidants may be more toxic than ozone alone. Finally, whether or not the effects attributed to ozone in epidemiological studies are specific to ozone vs. the entire photochemical oxidant pollutant mixture, it is likely that reductions in population exposures to ozone will result in fewer adverse health effects. Our confidence in this statement does not change at the lower levels of the proposed range.

References Cited:

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Korrick, S.A. L. M. Neas, D.W. Dockery, D.R. Gold, G.A. Allen, L.B. Hill, K.D. Kimball, B.A. Rosner, F.E. Speizer. 1998. Effects of ozone and other pollutants on the pulmonary function of adult hikers. *Environmental Health Perspectives* 106: 93-99.

Spektor, D.M., M. Lippmann, P. J. Lioy, G.D. Thurston, K. Citak, D.J. James, N. Bock, F.E. Speizer, and C. Hayes. 1998. Effects of ambient ozone on respiratory function in active normal children. *American Review of Respiratory Disease* 137:313-320.

Thurston, G.D., M. Lippmann, M.B. Scott, J.M. Fine. 1997. Summertime haze air pollution and children with asthma. *American Journal of Respiratory and Critical Care Medicine* 155:654-660.

Vedal, S, M. Brauer, R. White, J. Petkau . 2003. Air pollution and daily mortality in a city with low levels of pollution. *Environmental Health Perspectives* 111:45-51.

7. **EPA's exposure assessment quantified the number of all children and asthmatic children likely to be exposed to specific benchmark levels of ozone, including in**

particular 60 and 70 ppb. Considering the patterns of change in the estimates of exposures of concern at and above the 60 and 70 ppb benchmark levels, and the uncertainties and limitations in the estimates, what is the relative importance from a public health perspective of the estimated reductions in exposures of concern, as well as the exposures remaining, for alternative standards across the proposed range?

The first issue is the estimated change in exposures for alternative standards across the proposed range of 60 to 70 ppb. Table 1 in the Proposed Rules (p. 2978 in the *Federal Register*, January 19, 2010; included here) presents the modeled number and percentage of children with exposure (defined as at least one 8-hr average exposure per year with moderate or greater level of exercise) at each of three ozone benchmark levels of concern (80, 70 and 60 ppb) for ozone standards ranging from the old standard of 84 ppb to a lowest standard of 64 ppb, for the 12 urban areas in aggregate. Since no estimates are presented down to the lower end of the proposed range, i.e., 60 ppb, we cannot directly answer the question for the entire proposed range of the standard, based on these model estimates. However, at least for levels of concern of 70 ppb or greater, because the number and percent exposed is either zero or exceedingly small when meeting a standard of 64 ppb, depending on the year, it can be inferred that even fewer would be exposed if a standard of 60 ppb was met. For a level of concern of 60 ppb, for the year with the lowest concentrations that were considered (2004), essentially no exposures were estimated to occur when meeting the standard of 64 ppb, whereas for the year with the higher concentrations that were considered (2002), it was estimated that around 5% of children would be exposed, implying that even fewer would be exposed if a standard of 60 ppb was met. Some individual city estimates of exposure were lower while others were higher than these aggregate estimates. Based on earlier uncertainty and sensitivity analyses carried out by EPA, and relative to uncertainty in health effect estimates, the extent of uncertainty in these exposure estimates is acceptable.

The second issue relates to the public health significance of reductions in exposure for the range of standards from 70 to 60 ppb. Some of the public health significance is addressed by the risk assessment for selected endpoints (see responses to charge question #8). For endpoints for which it was not possible to carry out a quantitative risk assessment (e.g., pulmonary inflammation and bronchial hyper-responsiveness), public health significance is gauged in light of the toxicologic, human clinical and epidemiological findings. Toxicologic data (i.e., animal experimental data) are largely not helpful in this regard. In the absence of demonstrable effects in human clinical studies (in normal individuals or those with mild disease) on other than lung function decrements for exposure concentrations less than 80 ppb, we can only infer effects at lower concentrations and in the more severely diseased. Findings from epidemiological studies are less causally conclusive, but indicate effects at substantially lower concentrations than were used in the experimental studies. The benchmark levels in Table 1 correspond to greater degrees of uncertainty going from 80 down to 60 ppb. Part

of this uncertainty relates to the precious little human clinical data that were available for consideration at exposure concentrations below 80 ppb, and what exists is essentially limited to effects on lung function. Uncertainty also comes from the reliance on epidemiological (non-experimental) findings at the lower concentrations. Therefore, while (in Table 1) the predicted number exposed increases for every level of the standard as the benchmark level of concern is reduced, the public health impact of this increase in number exposed becomes less certain. One could argue that since there is no clear threshold for ozone effects, increases in the number exposed translates directly into increases in health effects. This ignores not just increasing uncertainty, but also the fact that "exposure" at the decreasing benchmark levels results in an increasingly smaller percentage of people affected at the decreasing levels of exposure. These latter percentages are difficult to estimate for endpoints other than, perhaps, acute lung function changes. Consequently, the public health significance is difficult to gauge for these other endpoints.

What then can be said about the public health significance of exposures at the different levels of concern across the different standards being considered? It is prudent to assume that for at least some segments of the population, adverse effects (in addition to acute lung function effects) occur at levels below 80 ppb and, making use of epidemiologic observations, that there is no obvious threshold ,with effects occurring even at the benchmark level of concern of 60 ppb. At some concentration the number of individuals affected must be exceedingly small, even though the number of days with these lower ozone concentrations is relatively large. From Table 1, in the year with the higher ozone concentrations (2002), less than 20% of children will experience at least one day at an exposure of concern of 60 ppb at a standard of 70 ppb, and only a small fraction of these children will be expected to experience an effect on these other health endpoints (e.g., pulmonary inflammation and bronchial hyperresponsiveness). At a standard of 64 ppb, approximately 5% of children will be exposed, of whom only a small fraction will be sensitive. Therefore, at the lowest concentration of concern (60 ppb), a further reduction in the standard from 70 ppb would be expected to reduce an already relatively small public health impact to an even smaller impact.

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TABLE 1—NUMBER AND PERCENT OF ALL AND ASTHMATIC SCHOOL AGE CHILDREN IN 12 URBAN AREAS ESTIMATED TO EXPERIENCE 8-HOUR OZONE EXPOSURES ABOVE 0.080, 0.070, AND 0.060 PPM WHILE AT MODERATE OR GREATER EXERTION, ONE OR MORE TIMES PER SEASON, AND THE NUMBER OF OCCURRENCES ASSOCIATED WITH JUST MEETING ALTERNATIVE 8-HOUR STANDARDS BASED ON ADJUSTING 2002 AND 2004 AIR QUALITY DATA[1][2]

Benchmark levels of exposures of concern (ppm)	8–Hour air quality standards [3] (ppm)	All children, ages 5–18 Aggregate for 12 urban areas Number of children exposed (% of all) [% reduction from 0.084 ppm standard]		Asthmatic children, ages 5–18 Aggregate for 12 urban areas Number of children exposed (% of group) [% reduction from 0.084 ppm standard]	
		2002	2004	2002	2004
0.080	0.084	700,000 (4%)	30,000 (0%)	110,000 (4%)	0 (0%)
	0.080	290,000 (2%) [70%]	10,000 (0%) [67%]	50,000 (2%) [54%]	0 (0%)
	0.074	60,000 (0%) [91%]	0 (0%) [100%]	10,000 (0%) [91%]	0 (0%)
	0.070	10,000 (0%) [98%]	0 (0%) [100%]	0 (0%) [100%]	0 (0%)
	0.064	0 (0%) [100%]	0 (0%) [100%]	0 (0%) [100%]	0 (0%)
0.070	0.084	3,340,000 (18%)	260,000 (1%)	520,000 (20%)	40,000 (1%)
	0.080	2,160,000 (12%) [35%]	100,000 (1%) [62%]	330,000 (13%) [36%]	10,000 (0%) [75%]
	0.074	770,000 (4%) [77%]	20,000 (0%) [92%]	120,000 (5%) [77%]	0 (0%) [100%]
	0.070	270,000 (1%) [92%]	0 (0%) [100%]	50,000 (2%) [90%]	0 (0%) [100%]
	0.064	30,000 (0.2%) [99%]	0 (0%) [100%]	10,000 (0.2%) [98%]	0 (0%) [100%]
0.060	0.084	7,970,000 (44%)	1,800,000 (10%)	1,210,000 (47%)	270,000 (11%)
	0.080	6,730,000 (37%) [16%]	1,050,000 (6%) [42%]	1,020,000 (40%) [16%]	150,000 (6%) [44%]
	0.074	4,550,000 (25%) [43%]	350,000 (2%) [80%]	700,000 (27%) [42%]	50,000 (2%) [81%]
	0.070	3,000,000 (16%) [62%]	110,000 (1%) [94%]	460,000 (18%) [62%]	10,000 (1%) [96%]
	0.064	950,000 (5%) [88%]	10,000 (0%) [99%]	150,000 (6%) [88%]	0 (0%) [100%]

[1] Moderate or greater exertion is defined as having an 8-hour average equivalent ventilation rate ≥ 13 l-min/m2. [2] Estimates are the aggregate results based on 12 combined statistical areas (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los An-geles, New York, Philadelphia, Sacramento, St. Louis, and Washington, DC). Estimates are for the ozone season which is all year in Houston, Los Angeles and Sacramento and March or April to September or October for the remaining urban areas. [3] All standards summarized here have the same form as the 8-hour standard established in 1997 which is specified as the 3-year average of the annual 4th highest daily maximum 8-hour average concentrations must be at or below the concentration level specified. As described in the 2007 Staff Paper (EPA, 2007b, section 4.5.8), recent O_3 air quality distributions have been statistically adjusted to simulate just meeting the 0.084 ppm standard and selected alternative standards. These simulations do not represent predictions of when, whether, or how areas might meet the specified standards.

8. EPA's quantitative risk assessment estimated the numbers of occurrences of various ozone-related health effects associated with just meeting alternative standard levels down to a standard level of 64 ppb. Considering the patterns of change in the estimates of health effects in the risk assessment at the alternative standard levels, and the uncertainties and limitations in the estimates, what is the relative importance from a public health perspective of the estimated reductions in risk, as well as the risk remaining, for alternative standards across the proposed range? Please consider this question in light of the scientific evidence as a whole.

The evidence from epidemiological studies of ozone-related mortality published prior to 2006 was not considered sufficiently robust by CASAC to serve as the sole basis for establishing a new NAAQS. However, based upon EPA estimates of effects on morbidity and mortality in the risk assessment components of the 2007 Staff Paper, CASAC previously and unanimously concluded, based primarily on the effects on morbidity, that "Beneficial effects in terms of reduction of adverse health effects were calculated to occur at the lowest concentration considered (i.e., 0.064 ppm)." (Henderson, 10/24/06, p.4).

Table 2 in the 2007 Staff Paper and reproduced in the Federal Register as part of this Proposed Rules material (Vol. 75, No. 11/Tuesday, January 19, 2010) is provided below, as background for addressing this charge question. With regard to protecting the public health, the numbers of children aged 5-18 who would suffer at least a once per year drop in their pulmonary function of a potentially clinically relevant amount with 6-hour ambient air ozone concentrations at 74 - 64 ppb is estimated to be between 340,000 and 180,000 in the worse case vs 130,000 and 70,000 in the best case scenarios (as estimated from 15 urban sites). Among children with asthma over this same exposure range, potentially important decreases in pulmonary function would occur in 5% to 1.5% of all children with asthma (estimated from 5 urban sites). It is not clear that 2002 is the "worse case" or that 2004 is the "best case," but these two scenarios provide bounds. Since estimates were not presented down to the lower end of the proposed range, i.e., 60 ppb, we cannot, based on the model results available, answer the charge question for the entire proposed range of the standard,. However, the available estimates, which represent a substantial fraction of at-risk children, would represent a significant public health impact. Reduction of the NAAQS to 60 ppb would further reduce the number of people affected.

As discussed at length in the Criteria Document and Staff Paper, there is no evidence of a threshold, i.e., the magnitude of the effects measured in clinical studies diminishes with decreasing ozone concentration, but does not reach the functional level associated with exposure to ozone-free clean air. Furthermore, there is a great degree of variability of response magnitude among the individuals studied, with some having clinically-relevant responses, even at 60 ppb, and more of them with such responses at higher concentrations. Importantly, these clinical studies were carried out in normal healthy adults, and even in these volunteers from 7-20% had clinically relevant changes in pulmonary function or symptoms. These findings suggest that comparable ozone exposures to more sensitive

people could lead to more adverse health effects in the substantial proportion of the population with lung disease. .

Thus, considering the available evidence and the findings of the exposure and risk assessment, a substantial number of susceptible individuals are at risk and the degree of protection afforded to them would increase as the NAAQS is lowered. The evidence available suggests that an adequate margin of safety cannot be achieved for all and that a level should be set that reduces the at-risk population to a minimally acceptable number, with a reasonable degree of certainty. The unanimous recommendation of CASAC, given in Chairperson Henderson's 2008 letter to the Administrator was to set the NAAQS within the range of 60 to 70 ppb. In that range, CASAC found that the evidence was sufficiently certain to be confident of public health benefits and additional protection for susceptible groups. We are still in agreement with that conclusion.

TABLE 2—NUMBER AND PERCENT OF ALL AND ASTHMATIC SCHOOL AGE CHILDREN IN SEVERAL URBAN AREAS ESTIMATED TO EXPERIENCE MODERATE OR GREATER LUNG FUNCTION RESPONSES ONE OR MORE TIMES PER SEASON ASSOCIATED WITH 8-HOUR OZONE EXPOSURES ASSOCIATED WITH JUST MEETING ALTERNATIVE 8-HOUR STANDARDS BASED ON ADJUSTING 2002 AND 2004 AIR QUALITY DATA [1 2]

8-Hour air quality standards [3]	All children, ages 5–18 $FEV_1 \geq 15$ percent Aggregate for 12 urban areas Number of children affected (% of all) [% reduction from 0.084 ppm standard]		Asthmatic Children, ages 5–18 $FEV_1 \geq 10$ percent Aggregate for 5 urban areas Number of children affected (% of group) [% reduction from 0.084 ppm standard]	
	2002	2004	2002	2004
0.084 ppm (Standard set in 1997).	610,000 (3.3%)	230,000 (1.2%)	130,000 (7.8%)	70,000 (4.2%)
0.080 ppm	490,000 (2.7%) [20% reduction]	180,000 (1.0%) [22% reduction]	NA [4]	NA
0.074 ppm	340,000 (1.9%) [44% reduction]	130,000 (0.7%) [43% reduction]	90,000 (5.0%) [31% reduction]	40,000 (2.7%) [43% reduction]
0.070 ppm	260,000 (1.5%) [57% reduction]	100,000 (0.5%) [57% reduction]	NA	NA
0.064 ppm	180,000 (1.0%) [70% reduction]	70,000 (0.4%) [70% reduction]	50,000 (3.0%) [62% reduction]	20,000 (1.5%) [71% reduction]

[1] Associated with exposures while engaged in moderate or greater exertion, which is defined as having an 8-hour average equivalent ventilation rate ≥ 13 l-min/m^2.

[2] Estimates are the aggregate central tendency results based on either 12 urban areas (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los Angeles, New York, Philadelphia, Sacramento, St. Louis, and Washington, DC) or 5 urban areas (Atlanta, Chicago, Houston, Los Angeles, New York). Estimates are for the O_3 season which is all year in Houston, Los Angeles and Sacramento and March or April to September or October for the remaining urban areas.

[3] All standards summarized here have the same form as the 8-hour standard set in 1997, which is specified as the 3-year average of the annual 4th highest daily maximum 8-hour average concentrations. As described in the 2007 Staff Paper (section 4.5.8), recent O_3 air quality distributions have been statistically adjusted to simulate just meeting the 0.084 ppm standard set in 1997 and selected alternative standards. These simulations do not represent predictions of when, whether, or how areas might meet the specified standards

[4] NA (not available) indicates that EPA did not develop risk estimates for these scenarios for the asthmatic school age children population.