UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

March 30, 2011

EPA-CASAC-11-004

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C.20460

Subject: Clean Air Scientific Advisory Committee (CASAC) Response to Charge Questions on the Reconsideration of the 2008 Ozone National Ambient Air Quality Standards

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, two drafts of the Criteria Document, 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 of 60 to 70 ppb (Henderson, 2006, 2007 and 2008). 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 (Henderson, 2008).

[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.

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 (Samet, 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* (Environmental Protection Agency, 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 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. Supporting evidence can be found in the attached responses to charge questions.

- The evidence available on dose-response for effects of ozone shows associations extending to levels within the range of concentrations 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 $\geq$ 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 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 do not exceed the NAAQS concentration of 75 ppb.

- Large segments of the population fall 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.

Public Comments

There were 57 public comments presented during the teleconferences on February 18, 2011 and March 3, 2011. As always, we welcome public input into our deliberations. Some commenters 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. Some raised questions about the evidence showing effects at the lower end of the concentration range in the U.S. Other public comments addressed 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 concerned the possibility of deferring any change in the 2008 standard until the newer evidence has been considered. The uncertainties involved in establishing "policy relevant background" for this naturally occurring as well as internationally-transported pollutant also received comments.

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, CASAC consensus responses to the charge questions and this letter are based on the literature considered in the last ozone NAAQS review.

Conclusion

Again, we reaffirm our unanimous recommendation expressed in former CASAC Chairperson Henderson's 2008 letter to former Administrator Johnson, 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.

Sincerely,

/signed/

Dr. Jonathan M. Samet
Chair
Clean Air Scientific Advisory Committee

Enclosures

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names of commercial products does not constitute a recommendation for use. CASAC reports are posted on the EPA website at http://www.epa.gov/CASAC.

U.S. Environmental Protection Agency
Clean Air Scientific Advisory Committee
Ozone Review Panel for the Reconsideration of the 2008 NAAQS

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CASAC Consensus 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 of participants with a wider range of susceptibility. 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) over which the ratio of ozone to other photochemical oxidants is unlikely to change, reducing the ozone NAAQS 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 correlations 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 index the near-ground exposure of most individuals in the population.

Taken together, results of 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. “Clinically relevant” effects are decrements >10%, a decrease in lung function considered clinically relevant by the American Thoracic Society. 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 the evidence is 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.

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.

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 (McDonnell, et. al., 1997) and other response indicators (Mudway and Kelly 2004) 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 reductions 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 (Kreit et. al., 1989). 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 (Bromberg and Koren, 1995). 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 (Gong et. al., 1997). 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.

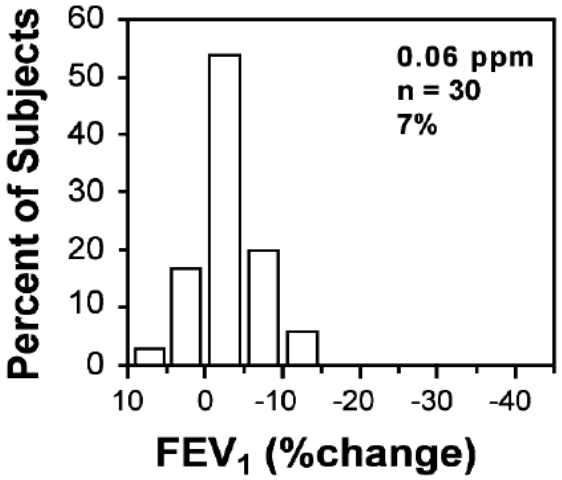
3. **How should the results of the controlled human exposure studies at 60 ppb O_3, showing effects on FEV_1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults 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 et. al., 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 a 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 (American Thoracic Society, 2000). 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 (McDonnell et. al., 1997). The results of the Adams et al. study also have been carefully reanalyzed by EPA investigators (Brown, et. al., 2007), and this reanalysis showed a statistically significant group effect on FEV_1 after 60 ppb ozone exposure.

In addition to FEV_1, Adams et. al. also assessed respiratory symptoms. While no statistically significant difference in symptoms was detected for a square-wave exposure to 60 ppb ozone for 6.6 hours compared to filtered air, there was a statistically significant increase in symptoms after a triangular exposure to ozone that averaged 60 ppb over 6.6 hours.

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). 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), supports the validity of the observed deficits in FEV_1 at 60 ppb from the Adams study. In other words, the evidence suggests that prolonged exposure to 60 ppb ozone causes a general shift in the distribution of FEV_1 towards lower values. 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).

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 can lead to 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 lead to 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.”

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 80ppb 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 rangeand some examples are given below. 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 that 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.

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 (included here) in the January 19, 2010 Proposed Rule (75 Federal Register 11, p. 2978) 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. It is important to note that use of a benchmark level of concern assumes that exposures below the benchmark are not harmful to anyone. 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. Public health significance is directly addressed by the risk assessment for selected endpoints (see responses to charge question #8) and can only be partially assessed based on exposure alone. 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 not particularly 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 about health impacts going from 80 down to 60 ppb. Part of this uncertainty relates to the scant human clinical data that were available for consideration at exposure concentrations below 80 ppb, and the data available are largely 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 at 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 by lowering the benchmark level of concern translates directly into increased numbers of 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 who will experience health effects 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 benchmark levels of concern across the different standards being considered? (The response to charge question #8 directly addresses the question of public health significance based on quantitative risk assessment.) 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 and below the benchmark level of concern of 60 ppb. Indeed, the concept of a benchmark level of concern is inconsistent with the concept of no threshold. It should be understood that use of Table 1 to make inferences about the public health significance of various standards involves assuming there is a threshold at the benchmark level of concern. Making use ofTable 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 fraction will be sensitive. Therefore, at the posed lowest concentration of concern (60 ppb), a further reduction in the standard from 70 ppb is estimated to have a small public health impact. However, the absence of a threshold means that levels below 60 ppb are also of concern. Consequently, this and any other analysis that assumes a level of concern of 60 ppb is an underestimate of the true public health impact.

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 $\geq$ 13 l-min/m^2.

[2] Estimates are the aggregate results based on 12 combined statistical areas (Atlanta, Boston, Chicago, Cleveland, Detroit, Houston, Los Angeles, New York, Philadelphia, Sacramento, St. Louis, and Washington, D.C.). 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.

As indicated in our previous comments, CASAC had a number of concerns relating to the mortality estimates in the ozone risk assessment, and did not consider those mortality estimates sufficiently robust to serve as the sole basis for establishing a new NAAQS. However, based primarily on the morbidity effects in the risk assessment components of the 2007 Staff Paper, CASAC previously and unanimously concluded 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 from the January 19, 2010 Proposed Rule (75 Federal Register 11, p. 2983) 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.

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 $\geq$ 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, D.C.) 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.

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Individual Panelist Comments
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Mr. George Allen

Caveat: With regard to the range of ozone concentrations under consideration, these comments assume the form of the NAAQS will remain unchanged from what was promulgated in the 2008 rule. Any change in the form (daily average duration, percentile, multi-year averaging) will change the effects of a standard even if the numerical value (e.g., .060 to .070 ppm) remains the same.

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?*

As with nearly all other pollutants, the exposure-response relationship is stronger and more scientifically robust as you go to higher concentrations. This holds for both controlled human exposures and epidemiological studies. Both approaches have their limitations, especially toward the lower end of the proposed range. The controlled exposure studies usually do not include sensitive and vulnerable populations (SVP) as subjects; this makes it more difficult to extrapolate results to the SVP that the NAAQS is intended to protect. The bias here is to underestimate the effects of a given concentration on SVP. These types of studies do allow detailed assessment of physiological markers such as FEV_1 and inflammatory markers that epidemiological studies cannot (usually) assess. Epidemiological studies do include SVP, although they are usually not constrained to this group. These studies have much greater exposure mis-classification than controlled exposure studies, and potential confounding from other pollutants and uncontrolled variables; these factors would usually bias effect results toward the null. However, since the ambient ozone measurements used in epidemiological studies are reasonably specific to ozone, they are actually an indicator of strong oxidants in the air, and thus the health effects may be larger than if the exposure were only to ozone. This is different than the ozone concentrations used in controlled exposure studies where other strong oxidants are presumably not present; thus these studies may underestimate the reported ozone health effects relative to epidemiological studies. Another potential difference between controlled exposure and epidemiological studies is the reaction products from ozone once it gets indoors (Weschler, Atmospheric Environment 38 (2004) 5715–5716); these include a wide range of gas-phase respiratory irritants and ultra-fine particles.

2. *Recognizing that controlled human exposure studies at 0.080 ppm O3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV_1, how should the results of these studies inform our understanding the health effects to healthy adults at exposures levels from 0.060 to 0.070 ppm?*

As noted in the background material included in these charge questions, the available data suggest that there probably is a reasonably "smooth exposure-response curve" going from .080 to .060 ppm. This does not imply that this holds at even lower levels, since that gets into the issue

of thresholds. And as with all other aspects of the science, this assumption is weaker at .060 than at .070 ppm.

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

These studies support the concept of a reasonably smooth exposure-response curve down to these levels as opposed to a health effect threshold near .060 ppm.

4. *With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean FEV_1 decrements relative to the findings that 7 to 20% of the subjects experienced FEV_1 decrements $\geq$ 10%? Please consider this question from both a public health and a clinical perspective.*

For healthy adult subjects in controlled human exposure studies, these FEV_1 decrements indicate some biological response, but the clinical significance of this is unclear especially in light of some studies showing inflammatory responses without FEV_1 decrements. From a public health perspective, where SVP would be expected to have an enhanced response to exposures to these concentrations, these results may have more importance. Ideally, controlled human exposure studies would be conducted at these levels using SVP, but that has risks of adverse outcomes in the study subjects, making such studies difficult to do.

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?*

The results of controlled human exposure studies conducted on healthy adults provide a "best case" (least health effect) scenario relative to SVP. Epidemiological studies that focus on SVP would be expected to show greater health effects for a given concentration, but are subject to the confounding factors noted above. The best approach may be a "weight of evidence" scenario that assesses the consistency (or lack thereof) across these very different approaches to quantifying ozone health effects.

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?*

As noted previously, the uncertainty (or confidence if you wish) of any exposure study decreases as the exposure concentrations decrease. For epidemiological studies, the effects of confounders are likely to be larger at .060 than .070 ppm. However, it's a reasonable assumption that this factor would bias observed health effects toward the null, not strengthen them.

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm 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?*

There is little doubt that reduced exposure, both in size of SVP exposed and the concentrations they are exposed to, has some public health benefit as you go from .070 to .060 ppm. However, it is difficult to quantify the changes in public health benefits across this range of concentrations. There will always be some remaining exposures with health effects across the proposed range in SVP.

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 0.064 ppm. 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.*

This is really a policy question, not a science question. There is likely some risk (i.e., not 0) for SVP even at the low end of the proposed range. This is not unique to ozone; some residual risk is present for every NAAQS pollutant, since none of them (except maybe CO) have a clear effect threshold. The quantitative risk assessment does not provide a bright line; it only provides guidance to the best estimate of risk at the various ranges considered. The science can only take the process so far, and after that it becomes a policy judgment that weighs the estimated (and more uncertain at the lower end of the range) health benefits against the difficulty of implementing effective control strategies to meet any given NAAQS.

Additional Comments.

Although the reconsideration of the 2008 ozone NAAQS is constrained to the literature available during that NAAQS review process, it is worth noting that more recent studies over the last 4-5 years support and perhaps strengthen the scientific justification for an ozone NAAQS in the range of .060 to .070 ppm.

Some interested parties have raised the question of the quality of the ozone data used in the epidemiologic studies, saying that there are common situations where the UV absorption measurement method normally used in the ozone monitoring network can significantly over-report ozone concentrations. There is evidence that this can happen, but it is unclear if this a significant factor in the overall ozone exposure-health effect relationship. Additionally, the

difference between chamber studies and ambient air exposures with the additional load of strong oxidants not being included in the measurement further reduces the implications of a modest issue with the UV method. It should also be noted that nearly all ambient air measurements of NAAQS pollutants have various biases associated with them, sometimes positive (NO2, non-trace CO, SO_2 when NO is elevated, sometimes negative (the $PM_{2.5}$ FRM, depending how it is run), sometimes biases between different FRMs for PM_{10} (the SSI Hi-Vol "war" in the 1980's), and sometimes just very goofy (the Hi-Vol FRM for lead). Some of these biases are as large or larger than the likely positive bias from the UV ozone method. In this context, I am not concerned with the reported biases in the UV method. However, since there may be effective ways to reduce the biases in this method, EPA may want to consider additional specifications for the testing of UV ozone analyzers in the Federal Equivalent Method (FEM) regulations to assess this issue.

Dr. John Balmes

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?*

Taken together, the evidence from controlled human and epidemiological studies strongly supports the selection of a new primary ozone standard that is well below the 1997 standard of 0.08 ppm over an 8-hour averaging time. There is scientific certainty that 6.6-hour exposures to concentrations ≥0.08 ppm with intermittent exercise cause clinically relevant decrements of lung function in young, healthy volunteers. The results of multiple epidemiological studies also show that children and adults with asthma are at increased risk of acute exacerbations of this disease on or shortly after days when ozone concentrations are elevated above background but remain below 0.08 ppm. Given the need to protect public health with an adequate margin of safety and the results of EPA's exposure and risk assessments, setting a new NAAQS in the range of 0.060 to 0.070 is appropriate.

2. *Recognizing that controlled human exposure studies at 0.080 ppm O_3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV1, how should the results of these studies inform our understanding the health effects to healthy adults at exposures levels from 0.060 to 0.070 ppm?*

The results of studies that show that exposure to ozone at 0.080 ppm and above causes airway inflammation, increased permeability, and increased responsiveness provide mechanistic support for the observed epidemiological associations with regard to exacerbations of asthma at concentrations below 0.080 ppm. The mechanism of ozone-induced decrements in lung function may not be related to airway inflammation.

3. *How should the results of the controlled human exposure studies at 0.060 ppm O_3, showing effects on FEV1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?*

At the time of the last EPA review of the evidence on the health effects of ozone, only the study of Adams et al. (2006) provided data on exposures at concentrations ≤0.080 ppm. Although that study as published reported a non-significant group decrease (~3%) in FEV_1, several subjects experienced decreases ≥10%, which have been previously determined to be of clinical relevance. These results fit well with those from multiple other studies of ozone's effect on lung function at concentrations ≥0.080 ppm, which have consistently shown that some individuals are more sensitive to this effect of ozone than others. The selection of a NAAQS for ozone needs to consider an adequate margin of safety to protect the most sensitive subgroup of individuals.

Since the scientific evidence was reviewed for the preparation of the 2006 Criteria Document for Ozone, the results of the Adams et al. (2006) study have been carefully reanalyzed (Brown et al., 2008) and actually show a statistically significant group effect. In addition, two other studies have shown statistically significant decrements in FEV_1 after 6.6-hour exposures to 0.070 ppm (Schelgele et al., 2009) and 0.060 ppm (Kim et al., 2011), respectively.

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

From a clinical perspective, 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. From a public health perspective, 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 0.060 ppm were to be selected, some sensitive individuals could still be exposed to concentrations that could cause them to have a clinically relevant decrement in lung function.

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?*

Controlled human exposure studies have shown that individuals with asthma have enhanced responses to ozone, in terms of both airway inflammation and lung function decrements with exercise. Epidemiological studies have shown that such individuals are at increased risk of exacerbations of their disease on or shortly after days with elevated ambient ozone concentrations. Taken together, the results of these studies provide strong evidence that people with asthma are a subgroup of the population with increased susceptibility to ozone. Given the effects on lung function that have been documented in healthy adults exposed to ozone at concentrations ≤0.080 ppm, a NAAQS with a margin of safety is necessary to protect the susceptible population of children and adults with asthma. Older individuals with pre-existing lung and heart disease, who have not been adequately investigated in controlled human exposure studies, as well as young children who cannot participate in such studies, may also be more susceptible than the healthy young adults who have been studied to date.

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 the effects of ozone cannot be easily isolated from the effects of other pollutants in

epidemiological studies, health care utilization for asthma has been shown to decrease when ozone concentrations are decreased. For example, when traffic density was decreased 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 (Friedman et al., 2001). In this study, the relative risk of asthma events increased stepwise at cumulative ozone concentrations 0.060 to 0.089 ppm and 0.090 ppm or more compared with ozone concentrations of less than 0.060 ppm. The reduction of the adverse effects on asthma in this study was dependent on reduction of ozone exposures to levels below 60 ppb.

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm 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 cumulative evidence to date on the ozone exposure-lung function response relationship strongly suggests that it is linear with no threshold, at least through 0.060 ppm. Therefore, it is reasonable to assume a similar exposure-response relationship for exacerbations of asthma. Considering the patterns of change in the estimates of exposures at alternative standards, as well as the uncertainties and limitations of the estimates, it is likely that susceptible individuals would still be adversely affected at a NAAQS of 0.060 ppm, although the number of such individuals would be substantially lower than at higher alternate 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 0.064 ppm. 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.*

In addition to what I have stated in my responses to the previous seven questions, it is also important to consider the effect of reductions in exposures to ozone on mortality with the alternate standards. Although the evidence from epidemiological studies of ozone-related mortality published prior to 2006 was not considered sufficiently robust by CASAC to serve as the basis for a new NAAQS, EPA estimated effects on mortality in the exposure and risk assessment components of the 2007 Staff Paper. The evidence regarding the ozone exposure-mortality relationship has grown stronger since the publication of the Staff Paper (e.g., Jerrett et al., 2009) and a mortality effect was seen at concentrations below the current standard.

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Dr. Joe Brain

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 quality of the controlled human exposures to ozone is extremely good. Established investigators at distinguished institutions did their best to measure pulmonary function changes. There are even some bronchoalveolar lavage data. In general, there are more data here than for many other regulated and unregulated pollutants. At the same time, there are limitations worth considering. They are primarily carried out in healthy, young, non-smoking volunteers. Data for susceptible populations are modest at best. It should also be noticed that most of the studies involve exercise as a necessary component to reveal responses to ozone. Of course, many Americans exercise, so that's not irrelevant. But it is important to keep in mind that higher levels of ventilation, and especially switching from nose to mouth breathing, have a substantial effect on ozone responses. Finally, the issue of adaptation has generally not been addressed. On the one hand, when humans are chronically exposed to steady-state levels of ozone, they may adapt, and their responses may be diminished. On the other hand, if they have not seen these levels of ozone recently, responses may be greater. There is also a considerable amount of epidemiologic data as well. This has the advantage of more diverse subjects, but typically less invasive responses – primarily limited to pulmonary function studies. As noted elsewhere, in contrast to chamber studies where exposures are limited to ozone, epidemiologic studies inevitably involve a mixture of pollutants. Identifying changes relating to ozone only may be difficult or impossible.

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

The database reviewed and summarized is consistent with past evaluations, but emphasizes the fact that responses to ozone can be seen within the proposed range of 0.06-0.07 ppm, especially when exercise is included.

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

The data mentioned above, especially inflammation, are important. If responses to ozone were completely limited to reversible pulmonary function changes, we would be less concerned.

However, chronic inflammation and the presence of increased neutrophils and neutrophil elastase raise concerns. Chronic inflammation and resulting increased levels of reactive oxygen species (ROS) may result in cumulative irreversible damage. These changes raise concerns about increases in morbidity and mortality caused by chronic exposure to ozone.
Unfortunately, the number of studies at 0.06 ppm of ozone are more limited than those at higher concentrations of ozone. Like other pollutants, our confidence about the magnitude of health effects increases as we go to higher levels. However, the limited studies that do exist at 0.06 ppm ozone demonstrate that there are responses among some individuals. Like PM2.5, there is the absence of a clearly defined threshold. Instead, we can always find a susceptible group that responds to lower and lower levels.

4. *With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean 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.*

We must not only look at average responses to a given pollutant exposure. We need to take into consideration the entire distribution of responses, particularly that of outliers. We must protect even a minority of exposed subjects, if they experience significant declines in pulmonary function. The existence of susceptible subgroups will usually drive standard setting.

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 indicated above, the presence of susceptible populations and the magnitude of their increased responsiveness is a key factor in regulation setting. As the question suggests, an advantage of epidemiologic studies is that they usually encompass a wider range of populations including older, younger, and sicker individuals. In contrast, the chamber studies typically exclude these much more susceptible populations. Asthmatics have been studied to a certain extent. However, it is also true that epidemiologic studies generally don't utilize exercise to the same degree as chamber studies for ozone. Moreover, the sickest individuals probably spend less time out of doors where ozone levels are highest. The answer to question five is that both chamber studies and epidemiologic studies need to be considered and integrated.

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?*

As the question implies, out confidence in attributing the effects observed in epidemiologic studies to ozone alone is usually limited and decreases with progressively lower levels of ozone. As the question implies, ozone never exists by itself in outside air. There are other sources of oxidant injury, as well as other pollutants known to produce some of the same effects, such as decreases in pulmonary function. Ozone concentrations/exposures throughout the day definitely

have a "signature" because of the important role of sunlight in generating ozone from other gaseous pollutants. Then the time course of some acute responses may be helpful in identifying the role of ozone *per se*. More generally, however, this dilemma suggests that we should be thinking more and more about the aggregate effects of different types of air pollution, such as those that collectively produce oxidant injury.

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm benchmark levels, and the uncertainties and limitations in the estimates, what is the relative importance from a public health perspective of the estimated eductions in exposures of concern, as well as the exposures remaining, for alternative standards across the proposed range?*

As indicated before, focusing on susceptible individuals is appropriate. Children represent a familiar and important susceptible class. Even at rest. their ventilation per kilogram is higher than that of adults. Moreover, they tend to be much more active and more likely to be exercising. Moreover, if there are chronic, cumulative changes produced by ozone, there is a longer period of lifespan ahead for children where these effects may become manifest. The existing data and these considerations of children and other susceptible groups suggest that continued reduction of ozone exposures will produce public health benefits. Of course, attention to other sources of oxidant injury from other air pollutants should be emphasized as well.

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 0.064 ppm. 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.*

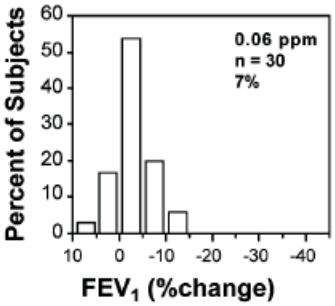
I believe that each year brings additional scientific evidence documenting the importance of ozone exposures, both acute and chronic, at progressively lower levels. Maintaining or perhaps lowering the ozone standard will reduce the numbers of people who suffer from ozone-induced adverse health effects. I also agree with the suggestion that even tighter regulatory standards will not eliminate ozone-induced changes entirely – especially in the most susceptible groups. Because of variations in susceptibility and exposure, no threshold for ozone effects is likely. Moreover, there is no plausible scenario to reduce ozone levels to zero, given the multiplicity of industrial and natural sources.

Dr. James Gauderman

4. *With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean 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.*

In the re-analysis of Adams (2006) study of 30 subjects by EPA (Brown, 2007), a small but statistically significant decline in FEV_1 was observed. Specifically, a 2.85% mean O_3-induced decline in FEV_1 was observed following 6.6 hr square wave exposure to 0.060 ppm O_3 compared to 6.6 hr filtered air (FA) exposure. The statistical analysis by EPA was based on a straightforward paired comparison, and they conservatively used a nonparametric sign test to obtain a p-value of 0.002 for the 0.06 ppm vs. FA comparison. Alternative, more powerful analytic methods using either a Wilcoxon signed-rank test or a paired t-test yielded even lower p-values in the EPA analysis. The EPA comparison remained significant after a Bonferroni correction for multiple comparisons. The original analysis of the data by Adams did not find a significant difference in FEV_1 between the 0.06 and FA exposure conditions. However, that analysis was based on a Scheffe correction for multiple comparisons, which is known to have very low power for the type of pairwise comparisons conducted by Adams compared to other well-known methods for multiple-testing correction (Kirk, 1982). Thus, from my understanding of the statistical analyses that have been conducted, I would argue that the analysis by EPA should be preferred to that of Adams for the specific comparison of the FEV_1 effects of 0.06 ppm exposure relative to FA exposure.

Of the 30 study subjects in Adams, 24 showed some evidence for an O_3-induced decline in FEV_1, and 2 of the 30 (7%) experienced a decline greater than 10%. Although the sample size is relatively small, the consistency of effects across O_3 exposure levels, as well as the consistency with effects observed by an earlier independent study (McDonnell, 2002), indicates that the observed deficits in FEV_1 at the 0.060 ppm from the Adams study are not spurious. In other words, it is likely that prolonged exposure to 0.06 ppm O_3 causes a general shift in the distribution of FEV_1 towards lower values. The following plot of the Adams data, derived from Figure 8-2 of Volume I of the "Air Quality Criteria for Ozone and Related Photochemical Oxidants, 2006" document, shows an approximate normal distribution in the O_3-induced changes in FEV_1 with exposure to 0.06 ppm.



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 into the region that becomes

clinically interesting (>10%). All of the Adams study subjects were healthy 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 0.06 ppm O_3. Although most healthy individuals can probably sustain a short-term 10-15% decline in FEV_1 with little or no noticeable effect, it is not clear how they might be affected in the longer term if they experience repeated lung function deficits due to 0.06 ppm or greater O_3 exposures over multiple days or weeks. Based on several other controlled exposure studies, we might expect that O_3-induced FEV_1 deficits in subjects with an existing respiratory condition (e.g. asthma) would be shifted even further to the right compared to the above figure. A 10-15% (or greater) pollution-related deficit in FEV_1 in an individual with an existing respiratory condition is large enough that it could cause a clinically observable response.

Dr. Rogene Henderson

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?*

I reviewed the previous correspondence between CASAC and the Agency as well as the Federal Register notice of the reconsideration of the 2008 primary NAAQS for ozone and found that the evidence from controlled human exposures and epidemiological studies, as well as the results of the exposure and risk assessments, fully supported the selection of the primary ozone standard in the range of 0.060 to 0.070 ppm to protect public health with a margin of safety. Human exposure studies provide the most direct evidence of the health effects on humans and the studies clearly show that adverse effects occur in some healthy adults after exposure for 6.6 hr to 0.060 ppm ozone. This finding has recently been confirmed in clinical studies in 59 healthy young adults exposed to 0.060 ppm ozone for 6.6 hours (Kim et al., dol:10.1164/rccm.201011-18130C, Lung function and inflammatory responses in healthy young adults exposed to 0.060 ppm ozone for 6.6 hours.) Asthmatic persons are known to be more sensitive to ozone than are healthy persons. Therefore, to provide some margin of safety, the standard must take into consideration these sensitive subpopulations.

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

These additional health-effect endpoints should definitely be taken into account in setting the standards to the extent that information is available. The recent publication by Kim et al. (2011) provides information on both types of endpoints endpoints.

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

The results of human controlled exposures to 0.080, 0.070 and 0.060 form a continuum of levels of effect that must all be considered in setting a standard with a margin of safety. The results of the 0.06 ppm exposures provide increased confidence and decreased uncertainty about the health effects of ozone exposure at that concentration. Thus it essential that the results of the controlled human exposure studies at 0.060 ppm be taken into consideration for the understanding of the health effects of ozone in the range of 0.070-0.060 ppm.

4. With respect to the information from controlled human exposure studies at 0.060 ppm O3, 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.

I am not a clinician, so will not comment on that aspect. From a public health viewpoint, I think the effect is significant. The Clean Air Act requires that a margin of safety be taken into account, and from a public health viewpoint, the 0.060 level does induce adverse health effects in a portion of the healthy community and those effects are likely to be greater in the asthmatic population.

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.

The epidemiology data showing increased use of medication, school absences, and hospital admissions is one way to evaluate the response of sensitive populations to ozone. The controlled human exposures gives you a ceiling level which is higher than the level that would be protective of sensitive populations.

6. To what extent does your confidence that the effects observed in epidemiological studies are attributable specifically to O3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?

For any pollutant, as one goes down the dose-response curve to lower levels of exposure, confidence in the effects seen decrease and uncertainties increase. However, the effects of ozone exposure can best be considered as a continuum, with decreasing incidence or severity with decreasing exposure. However, the endpoints of concern remain the same, providing some confidence that the effects are due mainly to ozone.

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm 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 exposure assessments were reasonable and made with the best data available. The assessments indicate that the number of children and asthmatic children exposed to ozone levels of concern is significant from a public health viewpoint.

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 0.064 ppm. 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 CASAC took into account the uncertainties associated with assessing the risks to low levels of ozone and concluded that in a range of 0.060 to 0.070 ppm exposures, one could have confidence in the observed effects. I am still in agreement with that conclusion.

Dr. Philip K. Hopke

The charge questions provided to the ozone panel revolve primarily around the toxicological and epidemiological evidence for the adverse health effects of exposure to ozone and other oxidants. One critical aspect that I believe is generally lost in the discussion is the presence of other photochemical oxidants. Thus, if we are looking at controlled exposures to ozone alone, we will be underestimating the effects of the total collection of oxidants in the ambient atmosphere. Epidemiology would take these other oxidants into account to some greater or lesser extent with respect to the covariance of the other ambient oxidants with ozone. However, central monitors particularly monitors typically placed in downwind locations in urban areas to avoid significant titration effects of motor vehicle emissions, may not be an adequate measure of population exposure across that urban area.

We also have to recognize the full extent of the change made with the promulgation of the 2008 ozone NAAQS. By changing the reported precision of the measurements, we have effectively lowered the standard from 84 ppb to 75.4 ppm and not from 80 to 75 ppb. This difference is a relatively large reduction whose effects have not yet been fully felt. Given that there is another review underway and this review is not supposed to take new literature into account, my recommendation would be that the standard not be lowered any further than 70.0 ppb, the upper end of the range judged as likely to be protective of public health, and reexamine all of the body of information available as part of the current round of review. Then a better informed judgment can be rendered.

Dr. Michael T. Kleinman

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?

a. Controlled Human Exposure:
   Controlled human studies to O_3 were, in large part, conducted with volunteers that were relatively young, in good physical condition and were non-smokers. The proposed range of 0.060 to 0.070 ppm was identified after a thorough and intensive review of the available studies and was an important part of the data used to identify that range (Horstman et al., 1990, Adams, 2003b, a, 2006). However that data did not stand alone and was view in context with population studies that showed significant effects at and perhaps below the selected range and mechanistic studies that provided evidence of biological plausibility.
b. Epidemiological Studies: Epidemiological studies and panel studies with sensitive populations, e.g. asthmatic adolescents) have demonstrated significant effects at exposures that were within, and sometimes below, the proposed range of O_3 concentrations. There was adequate discussion of the strengths and weaknesses of this study in the ISA and risk documents that were previously reviewed.
c. Advice: Given the points in a and b above, and the fact that subsequent studies (Schelegle et al., 2009, Kim et al., 2011) did not negate the previous conclusions, there is not adequate reason to alter the Panel's prior advice to the Administrator.

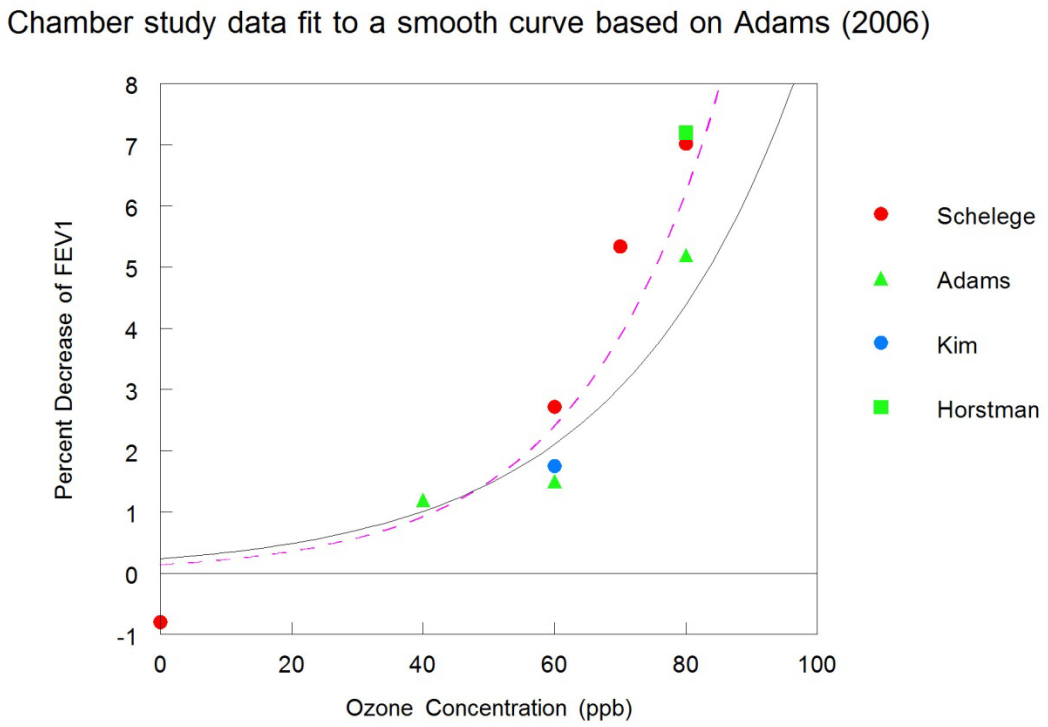
2. Recognizing that controlled human exposure studies at 0.080 ppm O_3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV_1, how should the results of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

A characteristic response to low O_3 levels is mucosal neutrophilic inflammation probably mediated by phospholipid-derived products and by epithelial cell-derived chemokines and cytokines (Bromberg and Koren, 1995). This response may be poorly correlated with lung function changes because the time course of development for these responses is different from that for changes in FEV_1. However these data provide important components of the biological plausibility and advance our understanding of the mechanisms by which O_3 affects health. It should be noted that inflammatory effects are likely to be more serious for individuals with chronic lung diseases. This is consistent with the exposure chamber study findings 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 O_3 during light exercise (Gong et al., 1997). While these studies are often performed at exposure concentrations higher than typical ambient conditions, they serve to identify disease-relevant mechanisms and also to underscore the inherent variability of even healthy populations with respect to their responses to O_3. It is important that we consider this variability as we examine

whether the current or proposed ambient concentration ranges provide an adequate margin of safety for sensitive individuals in the population.

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

As stated in the charge document, "The controlled human exposure studies at 0.060 ppm O_3 are limited, with only two published studies (Adams 2003a and 2006) available from one investigator. However, the Adams studies are well-designed and employed an exposure protocol that was consistent with earlier studies (Horstman *et al.,* 1990; McDonnell *et al.*, 1991). At the 0.080 ppm level, the subjects did not appear to be more responsive to O_3 than subjects in previous studies, as the observed response was similar to that of previous studies (Horstman et al., 1990, Mcdonnell et al., 1991, Adams, 2003b, a, 2006). Although of much smaller magnitude, the temporal pattern of the 0.060 ppm response was generally consistent with the temporal patterns of response to higher concentrations of O_3 in this and other studies. These findings are not unexpected because the previously observed group mean FEV_1 responses to 0.080 ppm were in the range of 6–9% suggesting that exposure to lower concentrations of O_3 would result in smaller, but real group mean FEV_1 decrements, *i.e.*, the responses to 0.060 ppm O_3 are consistent with the presence of a smooth exposure-response curve with responses that do not end abruptly below 0.080 ppm (75 FR 2950)". A graph showing an exponential fit (R^2=0.87) to the group mean changes in FEV_1 from the Adams et al. (2006) study only are shown as the solid line in context with data from more recent studies demonstrates that the previous conclusions remain valid. The dashed linen is an exponential fit (R^2=0.85) to all the data.



4. With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean 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 human exposure studies used relatively small populations of healthy, non-smoking young individuals. The within group variability of this preselected relatively homogeneous population might underestimate that of the population at large. The 7-20 percent of individuals with changes in pulmonary function that would be considered to be clinically relevant (i.e. 10%) should have great weight in the evaluation of potential public health risk, especially for the less homogeneous population at large.

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?

There are very few controlled human studies that have been conducted with susceptible groups . The Gong, et al. (1997) study showed that for some outcomes individuals with COPD were considerably more susceptible to O_3 effects than were healthy individuals, when results were

expressed in terms of changes from their respective baseline levels. Individuals with COPD have diminished respiratory reserves and are likely to have less capacity to compensate for adverse environmental effects. This might be intensified when such individuals are under some stress, such as the light exercise imposed during the Gong et al. (1997) study. Thus one should consider that even though the potential benefits accruing from reducing O_3 exposures below the current standard might be considered small based on responses of healthy subjects, there might still be important benefits for individuals with compromised lungs and hearts.

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?

It has been very difficult to apportion effects in epidemiological studies between O_3 and co-pollutants. However some studies that examined multiple pollutant models (i.e. O_3 and particulate matter) have shown independent effects of O_3. There might be a seasonal characteristic since the strongest associations between O_3 and health outcomes occur in the warm season months. The uncertainties at lower concentrations are greater. However the epidemiological studies are consistent with the controlled human studies which do not suffer from multiple pollutant interactions. Thus reducing O_3 concentrations will be expected to reduce adverse effects, especially in more susceptible members of the population.

*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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm 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 exposures of concern are at levels at which controlled studies found significant pulmonary function changes in health adults. Asthmatic children and others with pre-existing heart and lung diseases are likely to be more susceptible to effects of O_3 than are healthy young adults. Some epidemiological studies have identified effects at or below those levels. The panel's previous deliberations and the EPA assessments were based on an intensive search of the scientific literature at the time (2005 and earlier). The conclusions drawn remain valid and are, in fact, substantiated by more recent studies. The reduction of ozone exposures is important from the public health perspective.

*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 0.064 ppm. 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 previous deliberations of this panel concluded "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)." The potential benefits accrued to literally thousands of individuals when combined improvements with respect to mortality and morbidity were considered. This is important from the public health standpoint. (Also see previous points).

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Dr. Morton Lippmann

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 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 0.060 to 0.070 ppm. The limitations of the evidence from controlled human exposure and epidemiological studies were well and appropriately stated in the Staff Paper. These limitations have subsequently been substantially reduced since CASAC's last commentary of April 7, 2008 (EPA-CASAC-08-009) concerning the "Final rule" by the findings in peer-reviewed papers that have provided further evidence of the risks of inhaled ozone to normal individuals (Brown et al. 2008, (which was included in the final docket and can be officially cited in our CASAC letter); as well as newer work, which we cannot officially cite, i.e., Schelegle et al. 2009; Kim et al. in press), and in recent work on children and adults with asthma at concentrations well below 0.080 ppm (Lin et al. 2008; Moore et al. 2008; Islam et al. 2009; Silverman and Ito 2010).

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

These results demonstrate that there are subclinical responses to ozone inhalation that contribute to the physiological responses that are more readily measured in studies focused on clinically-relevant indices. They also provide results that provide a mechanistic basis for the functional effects and increased morbidity and mortality.

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

As discussed at length in the Criteria Document and Staff Paper, there is no evidence of a threshold, i.e., the magnitude of the effect 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 0.060 ppm, and more of them with such responses at higher concentrations. Since the numbers of subjects exposed in the each of the controlled chamber studies at each concentration have been small, extrapolation to the much larger general population indicates that a very large number of individuals would have substantial responses, even though they would constitute only about 10% of the population.

Schelege et al. (2009) show that FEV_1 decrements >20% can occur at 0.060 as well as at 0.070 and 0.080 ppm.

4. *With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean 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.*

See my response to #3 above.

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?*

Epidemiological studies generally show responses comparable to those observed in controlled human exposure studies conducted on healthy adults, but at lower ozone concentrations. This is partly due to the presence of less healthy, i.e., more susceptible people in the general population, but also due, at least in part, to the influence of prior days' exposures, and to evidence that ambient air containing other pollutants that can exacerbate the responses. Thus, the chamber studies underestimate population responses that are known to be associated with ozone exposures. A margin-of-safety is needed to compensate for the understatement of effect from the chamber exposure studies.

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?*

I do <u>not</u> have confidence that the effects observed in epidemiological studies are attributable specifically to O_3, as noted above. However, the effects are characteristic of those produced by ozone, and not associated with other pollutants in the ambient air, at least at the levels found there. Thus reduction of the adverse health effects is dependent on reduction of ozone exposures. It is highly informative that associations of effects with O_3 ambient concentrations at 0.060 ppm and below were seen in adults and children engaged in recreational exercise programs. 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 0.040 ppm (range 0.021 to 0.074 ppm). 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 were 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 0.060 ppm. 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.

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm 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?*

Since the most reasonable assumption concerning the ozone exposure response relationship is linear with no threshold, it is important to reduce ozone exposures by reducing the NAAQS in order to reduce the adverse health effects. However, it must be kept in mind that reductions of the NAAQS to either 0.060 or 0.070 will only reduce the numbers of people with adverse health effects, and will not eliminate such effects.

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 0.064 ppm. 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.*

See my response to #3 above.

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Dr. Fred Miller

Charge Question 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?*

Response -- In many ways, the lowest exposure level of 0.06 ppm showing some symptom changes and statistically significant lung function changes in healthy subjects in an EPA analysis conducted for the last O3 NAAQS review represented a greatest lower bound on the ozone concentration of public health concern. In all of the controlled human exposure studies at 0.08-ppm ozone and below, a reasonable 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 still allow healthy individuals to go about their normal daily activities, individuals with compromised lungs, such as asthmatics, incur significant health impacts with such lung function changes. As CASAC has noted in the past to the Agency, evidence is accumulating that persons with asthma, and particularly children, are more sensitive and experience larger decrements in lung function due to O_3 exposure than do healthy volunteers.

This, coupled with the fact that a number of epidemiology studies discussed in the last review were showing O_3-related effects on various health endpoints (e.g., emergency department visits, increased hospital emissions, and mortality increases) at relatively low exposure levels leads one to conclude that O_3 may cause effects even below 0.06 ppm. Since strengthening such a conclusion would need additional data from new studies, the CASAC concluded at the last review that the lower range of consideration for revision of the NAAQS should be 0.060 ppm O_3. By doing so, the CASAC felt that margin of safety considerations would better be met than at 0.070 ppm O_3. Moreover, since the relative strength of the science is weaker as one lowers the O_3 concentration under consideration, a range of 0.060 to 0.070 ppm O_3 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.

Dr. Lianne Sheppard

Individual comments:
I still fully agree with the advice provided by CASAC in its letters of October 24, 2006 (EPA-CASAC-07-001), March 26, 2007 (EPA-CASAC-07-002), and February 10, 2010 (EPA-CASAC-10-007). My opinion has been strengthened by the experience I have gained since 2008 through my continued involvement in air pollution and health research; this has contributed to my updated understanding of the evidence available in the 2008 review.

Dr. Frank Speizer

Preliminary Comments

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?*

Although the two Adams studies represent the only reported work at levels of exposure below 0.080 ppm of Ozone what has been pointed out and what is highly significant is that first the studies were done in normals and second that some 7-20% of the subjects experienced what I would consider very significant lung function decreases (> 10%) and or moderate respiratory symptoms. These findings essential preclude, because of the ethics of carrying out clinical studies in diseased individuals, from extending these studies to what are likely to be an even more sensitive groups. Thus, without having specific studies among asthmatics and children at these levels of exposure it is most prudent that, in spite of the uncertainty—more later on this issue—that EPA is justified to select an exposure level below the 0.080pppm (and I would say closer to the 0.060 ppm level) to "protect public health with an adequate margin of safety, including the need to protect susceptible populations…"

2. *Recognizing that controlled human exposure studies at 0.080 ppm O3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV_1, how should the results of these studies inform our understanding the health effects to healthy adults at exposures levels from 0.060 to 0.070 ppm?*

Given the evidence of pathophysiologic changes in smaller airways with exposures at 0.08 ppm as well as the occurrence of pulmonary function changes in a substantial number of normal subjects, the only mechanism that would change these finding in diseased subjects if there were some way that the diseased airways, perhaps because of the presence of excess mucus, would be "protected" from the potential oxidative effects of ozone. This seems highly unlikely in that disease subjects studied at 0.08 ppm and higher seem to respond **more than** normals and thus would not likely be protected more at the lower levels to which normals have responded. Clearly, these experiments have not been done and one might argue that thus there is uncertainty; however, as indicated above such experiments might be considered unethical.

3. *How should the results of the controlled human exposure studies at 0.060 ppm O3, showing effects on FEV_1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?*

Because these results represent a continuum of effects and it is unlikely that there is a threshold I would argue that the results are informative and suggest that EPA in carrying out its obligation must suggest a standard in the range indicated. I would argue that because there is no threshold

that the data are consistent with the lower end of the range being more protective than the upper end.

4. *With respect to the information from controlled human exposure studies at 0.060 ppm O3, 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.*

Please see answer to Charge Question 1 and 3. These small numbers of up to one-fifth of normals of the studied populations having changes in lung function or symptoms of this magnitude strongly suggests that the susceptible population would respond even greater and could reach clinically significant responses that might result in emergency room visits and or hospitalizations.

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?*

It would be difficult to make an actual estimate of the difference in impact that might occur between 7-20% of normals responding and even a similar if not greater number of diseased subjects who might have similar size responses. It would be reasonable to assume that the responses certainly would not be less frequent and are likely to be of greater magnitude or at least large enough to increase the likelihood that symptomatic responses would need to be treated. Given the substantial number of potentially at risk adults in the population and the distributions of possible exposures even at the lower level of the bounded exposures it would be prudent to argue that there will be some individuals remaining at risk. The judgment is how large a population is the Administrator willing to tolerate as being still at risk, not whether she can protect the entire population of potentially susceptible individuals.

6. *To what extent does your confidence that the effects observed in epidemiological studies are attributable specifically to O3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?*

Clearly there is greater uncertainty at the lower bound of the range of exposure; however, whether this is due to the mixture of addition pollutants coming into play rather than simply more variability in response cannot be determined. The few cities in which there are essentially no alternative pollutants to consider or where seasonal selection has been used to minimize alternative pollutants still show similar effects, and thus the likely cause of the uncertainly relates to greater variability rather than confounding by additional pollutants and thus the effects noted seem attributable to ozone pollution.

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at*

and above the 0.060 and 0.070 ppm 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?

As indicated in the discussion across the 12 urban areas the assessment are considerably larger for the benchmark level of 0.60 ppm compared to the 0.070 ppm benchmark. However, they also note that the pattern of exposure is similar for all children and asthmatic school age children. The Administrator also stated that she must consider the public health impact in cities receiving considerably less protection associated with air quality just meeting the same standard. This is a difficult criteria to meet with a single standard. Thus it becomes prudent to weigh the impact of the exposure against the cost of meeting that standard. The science is clear that there will be children as risk at any reasonable standard chosen. Thus the public health consideration is how big a population the Administrator is willing to leave at risk.

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 0.064 ppm. 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.*

From the Fed Reg TABLE 3—NUMBER AND PERCENT OF ALL AND ASTHMATIC SCHOOL AGE CHILDREN IN 12 URBAN AREAS ESTIMATED TO EXPERIENCE 8-HOUR OZONE EXPOSURES ABOVE 0.060 AND 0.070 PPM WHILE AT MODERATE OR GREATER EXERTION,ONE OR MORE TIMES PER SEASON ASSOCIATED WITH JUST MEETING ALTERNATIVE 8-HOUR STANDARDS BASED ON ADJUSTING 2002 AND 2004 AIR QUALITY DATA1 2
This table not reproduced here suggests a wide range of at risk children dependent upon the choice of levels of exposure. Unfortunately, it is not clear that 2002 is the "worse case" or 2004 is the "best case". Nevertheless, with regard to protecting the public health the range of all children aged 5-18 between 0.064-0.074 is between 4.5 million and 950, 000 in the worse case vs 350,000 and 10,000 in the best case, with proportionately lower numbers for asthmatic children. Clearly truth must lay somewhere in between. Even these lower numbers represent a substantial fraction of at risk children. Given the evidence of the pathophysiology, the clinical studies data in normals and the likelihood that symptomatic subjects will respond to a greater degree, and the fact that there is no evidence for a threshold of effects, the prudent decision is to set a standard that is as protective of the public health with a margin of safety as mandated by law.

Dr. Helen Suh

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 scientific evidence from controlled human exposure and epidemiological studies and from the exposure and risk assessments supports a primary ozone standard (with a margin of safety) between 0.060 to 0.070 ppm. The controlled human exposure studies by Adams (2002, 2006) show statistically significant changes in lung function from a 6.6 hour exposure to 0.060 ppm ozone. While these studies were limited in number, they were well designed and results were consistent with those from previous studies, thus lending credibility to their findings. Of particular interest is the fact that a small but important fraction of the study subjects experienced lung function decrements greater than 10% at exposures to 0.060 ppm ozone. These findings suggest that the impacts of ozone exposures at these levels may be significant for individuals with pre-existing respiratory conditions and must be considered to ensure adequate margin of safety for sensitive subpopulations.

2. *Recognizing that controlled human exposure studies at 0.080 ppm O3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV_1, how should the results of these studies inform our understanding the health effects to healthy adults at exposures levels from 0.060 to 0.070 ppm?*

   It is reasonable to consider findings of sub-clinical adverse impacts, such as increased inflammation and airway responsiveness, when considering adverse health impacts to healthy adults at exposures levels from 0.060 to 0.070 ppm. These findings are certainly pertinent to margin of safety considerations.

3. *How should the results of the controlled human exposure studies at 0.060 ppm O3, showing effects on FEV_1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?*

   These results provide important evidence that exposures to 0.060 ppm of ozone are harmful and are consistent with previous observations of no safe level for ozone exposures. Findings from Adams studies (2002, 2006) must be considered, at the least as being central to margin of safety determinations.

4. *With respect to the information from controlled human exposure studies at 0.060 ppm O3, 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 $\geq$ 10%? Please consider this question from both a public health and a clinical perspective.*

For individuals with pre-existing respiratory disease, a 10% decrement in FEV_1 is significant.

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.*

   Although the sample sizes are small, the variability in the response observed for healthy adults in the controlled human studies can inform judgments on the effects of ozone in susceptible populations. For example, the 7-20% of healthy adults who were found to have large ozone-mediated responses in controlled exposure studies may provide an indication of the fraction of individuals in the general population who may also be large responders. Ozone-mediated response may comprise an even greater percentage of the susceptible population.

6. *To what extent does your confidence that the effects observed in epidemiological studies are attributable specifically to O3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?*

   The uncertainty in the epidemiological findings at low ozone levels is certainly greater than that at high ozone levels, with greater confidence about the existence of health effects at the upper end and less confidence at lower O3 levels. Confounding by other pollutants is certainly of concern. However, ozone mediated impacts have been observed for a variety of endpoints, including those such as school absences that have not been related to particulate matter (PM), perhaps the most important potential confounder. Further, ozone-mediated impacts have been demonstrated in a number of locations, with varying correlations between ozone and PM. Finally, additional support for epidemiological findings is provided by results from controlled exposure studies.

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm 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 exposure assessment shows considerable temporal and spatial variability in exposure estimates, which is expected and which has important implications in determinations about adequate margin of safety. Given results from health studies, it is reasonable to assume no threshold in ozone-mediated impacts. As a result, even with uncertainty in the benchmark exposures, it is likely that a significant fraction of asthmatic children will remain exposed to ozone exposures above the benchmark level.

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 0.064 ppm. 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 quantitative risk assessment showed public health significant reductions in risk in going from a 0.074 ppm to a 0.064 ppm standard. As acknowledged by the Administrator, reductions in risk may be even greater, as the risk assessment examined only a fraction of the observed health outcomes, with many unexamined health outcomes posing greater risks for sensitive subgroups. These limitations may outweigh, or at the least counteract, any concerns regarding uncertainty in the risk estimates.

Dr. James Ultman

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?*

Clinical Studies. Has several strengths including accurate and precise administration of exposure gas mixtures and patterns of exposure. The methods of measuring lung function and biological responses are also accurate, and precise, and are generally standardized between different laboratories. The medical and physiological states of the subjects are well-defined. Weaknesses include the use of ozone exposure levels that are usually 0.08 ppm or above. Only two studies (Adams 2002,2006) were conducted in the range 0.06-0.07 ppm ozone being considered for the new standard. Also, due to ethical concerns, the large majority of all clinical studies are performed on healthy or young subjects or subjects with mild respiratory disease. Moreover, only a handful clinical studies elucidate the role of copollutants in the exposure gas mixture, and sponses are observable only when exercise is superimposed on exposure.
Epidemiological Studies. A major strength is data that are drawn from large and diverse populations that include people of all ages and all states of health. Another strength is the use of morbidity endpoints (e.g., hospital admissions from asthma exacerbation) that directly elucidate the clinical importance of the exposure. Although a strength of these studies is exposure to real world gas mixtures, this results in a major problem in separating out the effect of ozone alone from its other copollutants; this can result in an overestimation of the ozone health effect. Another weakness is the need to utilize exposure data from above-ground monitoring sites; this can also cause an overestimation of the health effect.

2. *Recognizing that controlled human exposure studies at 0.080 ppm O3 and above have provided evidence of other health effects, including inflammation and increased airway responsiveness which may occur through different physiological mechanisms than the reduction in FEV_1, how should the results of these studies inform our understanding the health effects to healthy adults at exposures levels from 0.060 to 0.070 ppm?*

Results from numerous studies indicate that exposure to 0.08ppm ozone and greater induces decrements in pulmonary function and also elevates various biological responses such as airway inflammation. Because lung function decrements and airway inflammation occur by different mechanisms and do not necessarily appear together in the same subject or occur in the same time-frame in a given subject, functional endpoints such as FEV_1 are probably not directly related to biological endpoints such as eosinophilia. Thus, although significant FEV_1 decrements at ozone exposure levels of 0.04 and 0.06 ppm were documented in the literature up to 2008 (Adams 2002, 2006), one cannot conclude that the same would be true of airway inflammation.

3. *How should the results of the controlled human exposure studies at 0.060 ppm O3, showing effects on FEV_1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?*

Data from two clinical studies on healthy young subjects (Adams 2002,2006), provides evidence that 0.06 ppm ozone causes a pre-to-post exposure decrement in FEV_1 relative to that in clean air. The reanalysis of Adams 2006 study by Brown(2), in particular, indicates that a 6.6 hr exposure to a square-wave or variable ozone concentration pattern with intermittent exercise results in a 3% decrease in FEV_1 with 2/30 exhibiting a decrement greater than 10%. In susceptible subjects, we expect that the FEV_1 decrement under the same exercise and exposure conditions would be even greater, possibly reaching a clinically significant level.
An exposure-response curve was developed in the Staff Paper of January 2007 using several different scenarios regarding the nature of the function (figure 5-3). The results indicate that Adam's subject-averaged data at 0.04 and 0.06 ppm ozone exposure fit very well with data obtained at higher ozone exposure levels in his lab (California) as well as in EPA's clinical laboratory (Chapel Hill). The distribution of responses among subjects at ozone levels at 0.08 ppm and above also appears to be similar between the two labs (table 5-3). This coherence of a substantial amount data at 0.08 ppm and above, together with the plausibility of the exposure-response curve that passes through the more limited data at 0.06 and 0.04 ppm gives us confidence that clinically importance FEV_1 responses can occur in moderately exercising subjects at 0.06 ppm ozone exposure.

4. *With respect to the information from controlled human exposure studies at 0.060 ppm O3, 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.*

Though it only occurs in 7-20% of the subjects, the observation of decrements in FEV_1>10% at 0.06 ppm ozone exposure is an important indicator of a possible health effect in sensitive individuals. The probabilistic exposure-response curve in the staff paper of January 2007 (Fig. 5-4) further supports the expectation that, even in a "healthy" population, there will be some individuals whose lung function is adversely affected by a single 8 hour exposure that includes intermittent moderate exercise.

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?*

In this connection, it is useful to consider the exposure-dose-response paradigm. While exposure refers to inhaled concentration, dose is closely related to the product of minute ventilation with inhaled concentration. Importantly, increasing the level of physical activity increases minute ventilation. This, in turn, can increase the severity of pulmonary function or biological responses without changing exposure concentration.

In natural settings, susceptible people (e.g.,asthmatics or the aged) may avoid or even be incapable of the hour-long bouts of moderate exercise that are produced by healthy subjects during clinical studies. Thus, at comparable ozone exposure levels, respiratory dose to

susceptible individuals would be smaller than the dose to healthy exercising individuals. However, susceptible people will (by definition) react with a greater response to a given inhaled dose of ozone. Because of these counteracting effects, the exposure-response behavior found for healthy subjects in clinical studies(e.g., Fig. 5-4, Staff paper, January 2007) is a reasonable basis for estimating the exposure-response of susceptible populations.

6. *To what extent does your confidence that the effects observed in epidemiological studies are attributable specifically to O3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?*

As concentration levels are reduced, uncertainties in personal exposure as well endpoints attributed to ozone alone would generally increase.

Dr. Sverre Vedal

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 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm 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 0.060 to 0.070 ppm. Table 1 in the Proposed Rules (p. 2978 in the *Federal Register* January 19, 2010) presents 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 (0.080, 0.070 and 0.060 ppm) for ozone standards ranging from the old standard of 0.084 to a lowest standard of 0.064 ppm, for the 12 urban areas in aggregate. Since no estimates are presented down to the lower end of the proposed range, i.e., 0.060 ppm, 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 0.070 or greater, because the number and percent exposed is either zero or exceedingly small when meeting a standard of 0.064, depending on the year, it can be inferred that even fewer are exposed were a standard of 0.060 to be met. For a level of concern of 0.060, for the year with the lowest concentrations (2004), no exposures are estimated to occur when meeting the standard of 0.064, whereas for the year with the higher concentrations (2002), it is estimated that around 5% of children will be exposed, implying that even fewer will be exposed were a standard of 0.060 to be 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, 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 0.070 to 0.060. 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, we must infer public health significance 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 normals or those with mild disease) on other than lung function decrements for exposure concentrations less than 0.080 ppm, we are left inferring effects at lower concentrations and in the more severely diseased. Findings from epidemiological studies are less certain, 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 0.080 down to 0.060. Part of this uncertainty relates to the precious little human clinical data at exposure concentrations below 0.080, and what exists is essentially limited to effects on lung function. Another part of the uncertainty relates to 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. So, 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? 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 0.080, and, making use of epidemiologic observations, that there is no obvious threshold for these effects with effects occurring even at the benchmark level of 0.060. At some concentration the number of individuals affected must be exceedingly small, although, because the number of days with lower benchmark levels is greater than with higher levels, a feature not captured by the exposure estimates in Table 1, the opportunities for exposure throughout the year are greater at the lower benchmark levels. This explains the observation from the risk assessment that the majority of adverse effects are due to exposures occurring at relatively lower concentrations.

Dr. Barbara Zielinska

The charge questions provided to the CASAC Ozone Panel members concern only adverse health effects of exposure to ozone. Since I am an atmospheric chemist I do not feel qualified to answer these questions. However, I would like to comment on another important aspect of NAAQS for ozone reconsideration, namely the uncertainties associated with establishing an appropriate policy relevant background (PRB). Since PRB is not directly measured, EPA relies on modeling to establish the range of PRB. In the 2006 Criteria Document and 2007 Staff Paper, which served as a basis for the setting of the ozone 2008 NAAQS, EPA relied on a global model (GEOS-Chem) with emphasis on a particular GEOS-Chem PRB simulation for the year 2001 (Fiore et al., 2003). The resulting modeled PRB range was reported to be 15- 35 ppb, depending on location and month. The newer versions of the GEOS-Chem model that are currently being used are greatly improved over the version used by Fiore et al (2003) for the 2001 simulation. They predict higher PRB levels and are more consistent with observational analysis. In addition, Parrish et al. (2009) found that ozone from Asia entering the US west coast increased at a rate of 3-5 ppb during the past decade.

During the 2005 -2007 CASAC Ozone Panel deliberations, the uncertainties and inconsistencies of this model (Fiore et al., 2003) were discussed. The model did not agree with observations that indicated higher background ozone levels (often exceeding 50 ppb), and evidence of stratospheric intrusion events during the winter and spring seasons. Since EPA's ozone risk estimates are sensitive to the assumed PRB level, it is important to recognize and reflect these model uncertainties in the risk analysis. In the CASAC letter of February 19, 2010, the Panel noted that as levels for ozone standards move closer to "background" levels, new issues may arise with implementation as background levels vary throughout the country and advised EPA to carefully consider these issues in the next ozone review cycle (letter from CASAC chair, Dr. Jonathan M. Samet, EPA-CASAC-10-007, February 19, 2010).

It must be acknowledged that the most recent information relevant to the PRB level was not available prior to 2006 and thus cannot be considered in the current reconsideration of the ozone NAAQS. Given the importance of this issue, the next periodic ozone NAAQS review cycle should take into account the newer information available on a background level of ozone, as well as newer health related research results.

References:

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