

Individual Comments on the Ozone Review Panel for the Reconsideration of the 2008 NAAQS.
These are individual panelists' comments that do not represent consensus CASAC advice or EPA
policy. Updated 3-8-11.

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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.

Q 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 FEV1 and inflammatory markers that epidemiological studies can not (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.

Q2. 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 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?

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

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

Q3. How should the results of the controlled human exposure studies at 0.060 ppm O₃, 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?

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.

Q4. 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 FEV1 decrements relative to the findings that 7 to 20% of the subjects experienced FEV1 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 FEV1 decrements indicate some biological response, but the clinical significance of this is unclear especially in light of some studies showing inflammatory responses without FEV1 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.

Q5. 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.

Q6. 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 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

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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.

Q7. 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.

Q8. 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

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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, SO₂ when NO is elevated, sometimes negative (the PM_{2.5} FRM, depending how it is run), sometimes biases between different FRMs for PM₁₀ (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.

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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 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 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 O₃, 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 FEV₁, several subjects experienced decreases $\geq 10\%$, 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

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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 FEV1 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 O₃, 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 $\geq 10\%$? Please consider this question from both a public health and a clinical perspective.*

From a clinical perspective, a 10% decrement in FEV1 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 FEV1) such that a $\geq 10\%$ 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*

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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?

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-

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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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Joe Brain

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 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 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 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.

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3. How should the results of the controlled human exposure studies at 0.060 ppm O₃, 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?

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 PM_{2.5}, 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 O₃, 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 $\geq 10\%$? 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 O₃ lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?

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As the question implies, our 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 reductions 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.

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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.

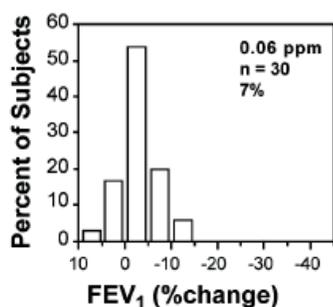
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James Gauderman

Charge Question #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 FEV₁ decrements relative to the findings that 7 to 20% of the subjects experienced FEV₁ decrements $\geq 10\%$? 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 FEV₁ was observed. Specifically, a 2.85% mean O₃-induced decline in FEV₁ was observed following 6.6 hr square wave exposure to 0.060 ppm O₃ 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 FEV₁ 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 FEV₁ effects of 0.06 ppm exposure relative to FA exposure.

Of the 30 study subjects in Adams, 24 showed some evidence for an O₃-induced decline in FEV₁, and 2 of the 30 (7%) experienced a decline greater than 10%. Although the sample size is relatively small, the consistency of effects across O₃ exposure levels, as well as the consistency with effects observed by an earlier independent study (McDonnell, 2002), indicates that the observed deficits in FEV₁ 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 O₃ causes a general shift in the distribution of FEV₁ 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 O₃-induced changes in FEV₁ with exposure to 0.06 ppm.



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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 FEV1 deficits greater than 10% with prolonged exposure to 0.06 ppm O₃. Although most healthy individuals can probably sustain a short-term 10-15% decline in FEV1 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 O₃ exposures over multiple days or weeks. Based on several other controlled exposure studies, we might expect that O₃-induced FEV1 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 FEV1 in an individual with an existing respiratory condition is large enough that it could cause a clinically observable response.

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Rogene Henderson

February 9, 2011

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., doi: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 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 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?

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 O₃, 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?

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

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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 FEV₁ decrements relative to the findings that 7 to 20% of the subjects experienced FEV₁ decrements $\geq 10\%$? 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.

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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.

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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.

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 O₃ 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 O₃ concentrations. There was adequate discussion of the strengths and weaknesses of these 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 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 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?

A characteristic response to low O₃ 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 FEV₁. However these data provide important components of the biological plausibility and advance our understanding of the mechanisms by which O₃ 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 O₃ 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 O₃. It is

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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.

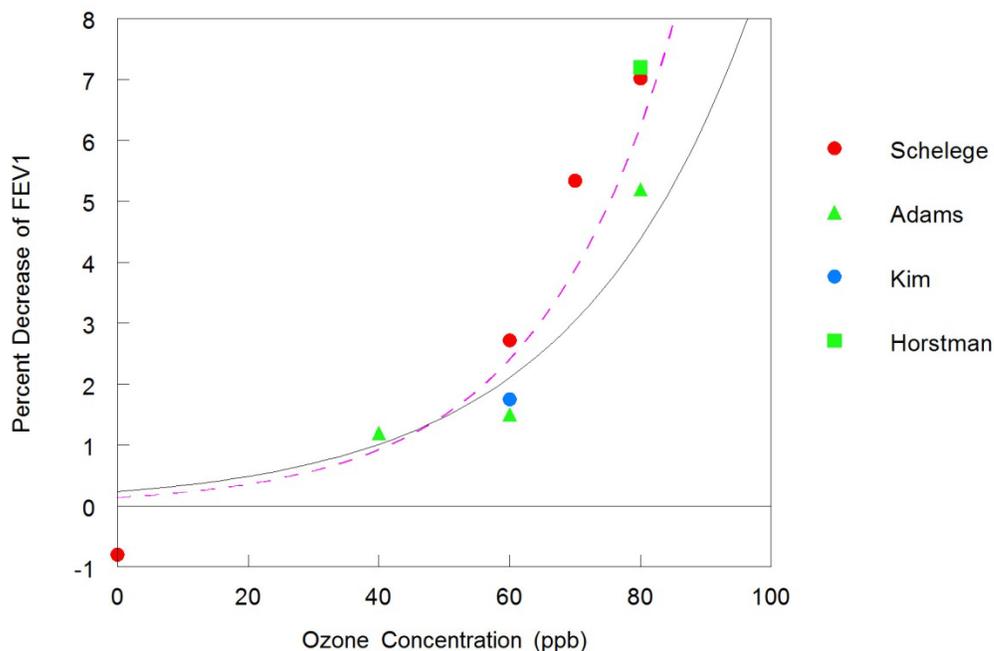
3. How should the results of the controlled human exposure studies at 0.060 ppm O₃, showing effects on FEV1 and respiratory symptoms, in the context of the larger body of evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?

As stated in the charge document, "The controlled human exposure studies at 0.060 ppm O₃ 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 O₃ 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 O₃ in this and other studies. These findings are not unexpected because the previously observed group mean FEV1 responses to 0.080 ppm were in the range of 6–9% suggesting that exposure to lower concentrations of O₃ would result in smaller, but real group mean FEV1 decrements, *i.e.*, the responses to 0.060 ppm O₃ 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 FEV1 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 line is an exponential fit ($R^2=0.85$) to all the data.

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Chamber study data fit to a smooth curve based on Adams (2006)



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 FEV₁ decrements relative to the findings that 7 to 20% of the subjects experienced FEV₁ decrements $\geq 10\%$? 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 O₃ effects than were healthy individuals, when results were expressed in terms of changes from their respective baseline levels. Individuals with COPD have

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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 O₃ 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 O₃ 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 O₃ and co-pollutants. However some studies that examined multiple pollutant models (i.e. O₃ and particulate matter) have shown independent effects of O₃. There might be a seasonal characteristic since the strongest associations between O₃ 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 O₃ 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 O₃ 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

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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).

Adams WC (2003a) Comparison of chamber and face mask 6.6-hour exposure to 0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. *Inhal Toxicol* 15:265-281.

Adams WC (2003b) Relation of pulmonary responses induced by 6.6-h exposures to 0.08 ppm ozone and 2-h exposures to 0.30 ppm ozone via chamber and face-mask inhalation. *Inhal Toxicol* 15:745-759.

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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; Schelegle et al. 2009; Kim et al. in press), and in 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 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 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?*

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 O₃, 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?*

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

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individuals would have substantial responses, even though they would constitute only about 10% of the population. Schelege et al. (2009) show that FEV1 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 O₃, 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 \geq 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 O₃ lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?*

I do not have confidence that the effects observed in epidemiological studies are attributable specifically to O₃, 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.

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

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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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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., FEV1 changes > 10 %). While FEV1 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 O₃ exposure than do healthy volunteers.

This, coupled with the fact that a number of epidemiology studies discussed in the last review were showing O₃-related effects on various health endpoints (e.g., emergency department visits, increased hospital admissions, and mortality increases) at relatively low exposure levels leads one to conclude that O₃ 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 O₃. By doing so, the CASAC felt that margin of safety considerations would better be met than at 0.070 ppm O₃. Moreover, since the relative strength of the science is weaker as one lowers the O₃ concentration under consideration, a range of 0.060 to 0.070 ppm O₃ 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.

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Lianne Sheppard

February 11, 2011

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.

Preliminary thoughts on a draft response to Charge Question 6 (for CASAC discussion):

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?

Possible points for CASAC's response:

- The endpoints of concern do not change at the lower levels of the proposed range.
- Many of the epidemiological studies had mean exposures well below the proposed range of 0.070 ppm to 0.060 ppm and found ozone-related health effects. These include time series studies, field studies, and panel studies. The strengths and weaknesses of these studies do not differ appreciably in the proposed range.
- The epidemiological evidence does not suggest a threshold exists for mean concentrations within or above the proposed range.
- While it is always difficult to tease out the effects of a single pollutant in epidemiological studies, there is evidence regarding ozone-related health effects from epidemiological studies that is consistent with the evidence from controlled exposure studies. This holds for the entire proposed range.
- While the effects attributed to ozone in epidemiological studies may not be specific to ozone, 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 in the proposed range.

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Frank Speizer

Feb 8, 2011

Charge Question 1. What is your advice on the overall strengths and limitations of the evidence from controlled human exposure and epidemiological studies and the results of the exposure and risk assessments, in the context of EPA's selection of a standard level within the proposed range that would be requisite to protect public health with an adequate margin of safety, including the need to protect susceptible populations, such as children and people with asthma?

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...”

Charge Question 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 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?

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.

Charge Question 3. How should the results of the controlled human exposure studies at 0.060 ppm O₃, 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?

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

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

Charge Question 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 FEV1 decrements relative to the findings that 7 to 20% of the subjects experienced FEV1 decrements \geq 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.

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?

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.

Charge Question 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 additional 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 uncertainty relates to greater variability rather than confounding by additional pollutants and thus the effects noted seem attributable to ozone pollution.

*Charge Question 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*

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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.

Charge Question 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 DATA^{1 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.

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 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?*

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 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?*

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 FEV₁ decrements relative to the*

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findings that 7 to 20% of the subjects experienced FEV1 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 FEV1 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

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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.

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James Ultman

Charge question 1:

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

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 sponges 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.

Charge question 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 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?

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 FEV₁ are probably not directly related to biological endpoints such as eosinophilia. Thus, although significant FEV₁ 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.

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Charge question 3:

How should the results of the controlled human exposure studies at 0.060 ppm O₃, 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?

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 FEV₁ 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 FEV₁ with 2/30 exhibiting a decrement greater than 10%. In susceptible subjects, we expect that the FEV₁ 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 FEV₁ responses can occur in moderately exercising subjects at 0.06 ppm ozone exposure.

Charge question 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 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.

Though it only occurs in 7-20% of the subjects, the observation of decrements in FEV₁>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.

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?

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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.

Charge question 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.

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

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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.

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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.

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