

2-14-11 Preliminary Individual Comments on the Ozone Reconsideration
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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?

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As noted in the background material included in these charge questions, the available data suggest that there probably is a reasonably “smooth exposure-response curve” going from .080 to .060 ppm. This does not imply that this holds at even lower levels, since that gets into the issue of thresholds. And as with all other aspects of the science, this assumption is weaker at .060 than at .070 ppm.

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

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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 is 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.

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

Additional Comments.

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

Some interested parties have raised the question of the quality of the ozone data used in the epidemiologic studies, saying that there are common situations where the UV absorption measurement method normally used in the ozone monitoring network can significantly over-report ozone concentrations. There is evidence that this can happen, but it is unclear if this a significant factor in the overall ozone exposure-health effect relationship. Additionally, the difference between chamber studies and ambient air exposures with the additional load of strong oxidants not being included in the measurement further reduces the implications of a modest issue with the UV method. It should also be noted that nearly all ambient air measurements of NAAQS pollutants have various biases associated with them, sometimes positive (NO₂, non-trace CO, 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

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of clinical relevance. These results fit well with those from multiple other studies of ozone's effect on lung function at concentrations ≥ 0.080 ppm, which have consistently shown that some individuals are more sensitive to this effect of ozone than others. The selection of a NAAQS for ozone needs to consider an adequate margin of safety to protect the most sensitive subgroup of individuals. Since the scientific evidence was reviewed for the preparation of the 2006 Criteria Document for Ozone, the results of the Adams et al. (2006) study have been carefully reanalyzed (Brown et al., 2008) and actually show a statistically significant group effect. In addition, two other studies have shown statistically significant decrements in 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

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date.

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?*

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

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mortality published prior to 2006 was not considered sufficiently robust by CASAC to serve as the basis for a new NAAQS, EPA estimated effects on mortality in the exposure and risk assessment components of the 2007 Staff Paper. The evidence regarding the ozone exposure-mortality relationship has grown stronger since the publication of the Staff Paper (e.g., Jerrett et al., 2009) and a mortality effect was seen at concentrations below the current standard.

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Schelegle ES, Morales CA, Walby WF, Marion S, Allen RP. 6.6-hour inhalation of ozone concentration from 60 to 87 parts per million in healthy humans. 2009. *Am J Respir Crit Care Med* 180:265-272.

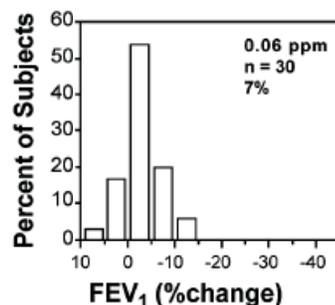
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James Gauderman

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

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results of the 0.06 ppm exposures provide increased confidence and decreased uncertainty about the health effects of ozone exposure at that concentration. Thus it essential that the results of the controlled human exposure studies at 0.060 ppm be taken into consideration for the understanding of the health effects of ozone in the range of 0.070-0.060 ppm.

4. With respect to the information from controlled human exposure studies at 0.060 ppm O₃, what is the scientific importance of the small, group mean 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

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assessments indicate that the number of children and asthmatic children exposed to ozone levels of concern is significant from a public health viewpoint.

8. . EPA's quantitative risk assessment estimated the numbers of occurrences of various ozone related health effects associated with just meeting alternative standard levels down to a standard level of 0.064 ppm. Considering the patterns of change in the estimates of health effects in the risk assessment at the alternative standard levels, and the uncertainties and limitations in the estimates, what is the relative importance from a public health perspective of the estimated reductions in risk, as well as the risk remaining, for alternative standards across the proposed range? Please consider this question in light of the scientific evidence as a whole.

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

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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 ppb 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.

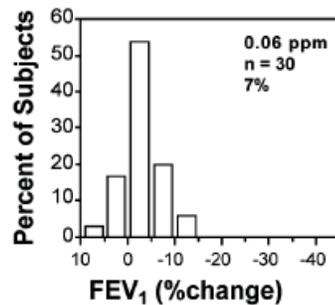
Charge Question #4. With respect to the information from controlled human exposure studies at 0.060 ppm O₃, what is the scientific importance of the small, group mean FEV₁ decrements relative to the findings that 7 to 20% of the subjects experienced FEV₁ decrements $\geq 10\%$? Please consider this question from both a public health and a clinical perspective.

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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.



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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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 essentially 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

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evidence from controlled human exposure studies, mentioned above, inform our understanding of the health effects to healthy adults at exposure levels from 0.060 to 0.070 ppm?

Because these results represent a continuum of effects and it is unlikely that there is a threshold I would argue that the results are informative and suggest that EPA in carrying out its obligation must suggest a standard in the range indicated. I would argue that because there is no threshold that the data are consistent with the lower end of the range being more protective than the upper end.

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 addition pollutants coming into play rather than simply more variability in response cannot be determined. The few cities in which there are essentially no alternative pollutants to consider or where seasonal selection has been used to minimize alternative pollutants still show similar effects, and thus the likely cause of the uncertainty relates to greater

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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 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.

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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.

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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.*

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

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threshold in ozone-mediated impacts. As a result, even with uncertainty in the benchmark exposures, it is likely that a significant fraction of asthmatic children will remain exposed to ozone exposures above the benchmark level.

8. *EPA's quantitative risk assessment estimated the numbers of occurrences of various ozone related health effects associated with just meeting alternative standard levels down to a standard level of 0.064 ppm. Considering the patterns of change in the estimates of health effects in the risk assessment at the alternative standard levels, and the uncertainties and limitations in the estimates, what is the relative importance from a public health perspective of the estimated reductions in risk, as well as the risk remaining, for alternative standards across the proposed range? Please consider this question in light of the scientific evidence as a whole.*

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

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Dr. James Ultman

Charge question 1:

Strengths:

1. Objective, accurate and precise measurements of exposure pattern and response endpoints.
2. Minimize confounding influence of particulate matter, other oxidants and other copollutants on subject response.
3. Large database of forced expired response to constant ozone exposure with intermittent exercise using fairly consistent protocols within labs and between labs.
4. Newest studies are designed for more realistic exposure levels and concentration patterns.

Weaknesses:

1. Ethical limitations testing subjects that have severe respiratory and/or cardiovascular disease.
2. Usually not designed to model different exercise levels or multiple daily exposures.
3. Large majority of studies on ozone concentrations at or above 0.08 ppm and on constant exposure patterns.
4. Are usually not specifically designed or analyzed to examine the health effect of ozone exposure relative to a an exposure that emulates a policy-relevant background.

Charge question 2:

Results from numerous studies indicate that exposure to 0.08ppm ozone and greater induces decrements in FEV₁ and also elevates various markers of inflammation. Because lung function decrements and airway inflammation occur by different mechanisms, they are not directly related to one another. Thus, it is not feasible to use the results of inflammation at 0.08 ppm and above to inform our understanding of health effects at lower concentrations.

There is one recent study(1)that reported a significant increase in neutrophil counts in the sputum of healthy subjects during the day following a 0.06 ppm, 6.6 hour, ozone exposure. Whether or not this observation can be confirmed in another study remains to be seen. Even with this scientific uncertainty, the possibility of a clinically consequential airway inflammation must be kept in mind when specifying a “margin of safety” in the ozone standard.

Charge question 3:

Data from two clinical studies, show that exposure to 0.06ppm ozone causes a significant pre-to-post exposure decrement in FEV₁ relative to that in clean air. The reanalysis of

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Adams 2006 study by Brown(2) indicates that a 6.6 hr exposure to a square-wave or variable ozone concentration pattern and intermittent exercise results in a 3% decrease in FEV₁ with 2/30 subjects exhibiting a decrement greater than 10%. For a constant 0.06 ppm exposure, Kim *et et al.*(2) reported a 2% decrease in the group mean FEV₁ with 3/59 subjects exhibiting a decrement greater than 10%. In a third study (3), the group mean FEV₁ decrement during a 0.06 ppm variable ozone exposure pattern was not statistically different from that observed during clean air exposure. Nevertheless, 6/31 subjects had FEV₁ decrements that were greater than 10% relative to clean air.

Thus, the evidence for a clinically relevant decrement in lung function among a subpopulation of subjects is coherent among these studies even though statistical comparisons of the group means are equivocal. Although it is doubtful that children, asthmatics and other susceptible populations would achieve the high workloads employed in these studies (MV=20 L/m/m² body surface for adults), some vulnerable populations such as outdoor laborers could would.

Charge question 4:

From a clinical perspective, the observation of decrements in FEV₁>10% is an important indicator of a possible health effect in a limited number of patients. From a public health perspective, the group mean effect of long exposures at high workloads on mechanical lung function is minimal.

1. Kim, C., *et. Al.*(2011). Lung function and inflammatory responses in healthy young adults exposed to 0.06 ppm ozone for 6.6 hours. *Am J Resp Crit Care Med.* (on-line).
2. Brown,J.S. (2007) The effects of ozone on lung function at 0.06ppm in healthy adults. Ozone NAAQS Review Docket (OAR-2005-0172).
3. Schelegle *et al* (2009). 6.6-Hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans. *Am J Resp Crit Care Med.* 180:265-272.