Answers to Charge Questions Given to the Ozone Review Panel in Regard to the Reconsideration of the 2008 NAAQS

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

The quality of the controlled human exposures to ozone is extremely good. Established investigators at distinguished institutions did their best to measure pulmonary function changes. There are even some bronchoalveolar lavage data. In general, there are more data here than for many other regulated and unregulated pollutants.

At the same time, there are limitations worth considering. They are primarily carried out in healthy, young, non-smoking volunteers. Data for susceptible populations are modest at best. It should also be noticed that most of the studies involve exercise as a necessary component to reveal responses to ozone. Of course, many Americans exercise, so that's not irrelevant. But it is important to keep in mind that higher levels of ventilation, and especially switching from nose to mouth breathing, have a substantial effect on ozone responses. Finally, the issue of adaptation has generally not been addressed. On the one hand, when humans are chronically exposed to steady-state levels of ozone, they may adapt, and their responses may be diminished. On the other hand, if they have not seen these levels of ozone recently, responses may be greater.

There is also a considerable amount of epidemiologic data as well. This has the advantage of more diverse subjects, but typically less invasive responses – primarily limited to pulmonary function studies. As noted elsewhere, in contrast to chamber studies where exposures are limited to ozone, epidemiologic studies inevitably involve a mixture of pollutants. Identifying changes relating to ozone only may be difficult or impossible.

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

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

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

The data mentioned above, especially inflammation, are important. If responses to ozone were completely limited to reversible pulmonary function changes, we would be less concerned. However, chronic inflammation and the presence of increased neutrophils and neutrophil elastase raise concerns. Chronic inflammation and resulting increased levels of reactive oxygen species (ROS) may result in cumulative irreversible damage. These changes raise concerns about increases in morbidity and mortality caused by chronic exposure to ozone.

Unfortunately, the number of studies at 0.06 ppm of ozone are more limited than those at higher concentrations of ozone. Like other pollutants, our confidence about the magnitude of health effects increases as we go to higher levels. However, the limited studies that do exist at 0.06 ppm ozone demonstrate that there are responses among some individuals. Like PM2.5, there is the absence of a clearly defined threshold. Instead, we can always find a susceptible group that responds to lower and lower levels.

4. With respect to the information from controlled human exposure studies at 0.060 ppm O_3, what is the scientific importance of the small, group mean FEV_1 decrements relative to the findings that 7 to 20% of the subjects experienced FEV_1 decrements $\geq$ 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 O_3 lessen or otherwise change, if at all, at the lower levels in the proposed range as compared to the higher levels?

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

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

7. EPA's exposure assessment quantified the number of all children and asthmatic children likely to be exposed to specific benchmark levels of ozone, including in particular 0.060 and 0.070 ppm. Considering the patterns of change in the estimates of exposures of concern at and above the 0.060 and 0.070 ppm benchmark levels, and the uncertainties and limitations in the estimates, what is the relative importance from a public health perspective of the estimated eductions in exposures of concern, as well as the exposures remaining, for alternative standards across the proposed range?

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

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

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