Oral Testimony Before the CASAC Ozone Review Panel on the Second Draft Ozone ISA

Julie E. Goodman, Ph.D., DABT

January 9, 2012

Thank you for the opportunity to speak today. I am Dr. Julie Goodman from Gradient, and my comments are sponsored by the American Petroleum Institute.

EPA has charged CASAC to provide comments on whether there is sufficient clarity in the presentation of study designs and results in the chapters on integrated health effects of short- and long-term ozone exposure in the Second Draft ISA. In addition, EPA requested guidance on how to improve the interpretation of scientific evidence and on the soundness of the conclusions of these chapters. In our comments on the First Draft ozone ISA, Gradient identified several issues with EPA's approach for evaluating the epidemiology studies of ozone and with the causal determinations based on these evaluations. These issues are still evident in the Second Draft ISA, which does not follow an objective and rigorous weight-of evidence approach for assessing the available data.

Although EPA claims to use a weight-of-evidence approach in the ISA, with consideration of the Bradford Hill "aspects" and weighing of alternative views on controversial issues, there is no evidence that such an approach was used. There is no consistent discussion of strengths and limitations of individual epidemiology studies and, thus, no "weight" is assigned to the studies. Rather, EPA provides summarizing statements that emphasize only the few positive associations for a given outcome, and null results are often discounted or used as positive evidence of a causal relationship without a meta-analysis to confirm whether such an interpretation is correct.

The ISA does not fully consider all of the Bradford Hill aspects in the evaluation of the epidemiology studies. There are no clear statements indicating how evaluations of the various Bradford Hill aspects are to be carried out, how judgments are to be made regarding whether aspects are considered as being met, and how an overall judgment is to be synthesized out of consideration of all of the aspects jointly.

EPA also does not follow through with weighing alternative views on controversial issues. If EPA were truly to weigh alternative views, it would consider the view that it is not ozone, but another

factor, that is causal for the health effects associated with ozone in some of the epidemiology studies. It would then discuss the reasons why this view is less likely to be true than the view that ozone is the causal factor.

Many of these issues have been identified in other EPA assessments by a National Research Council (NRC) committee, such as the lack of methods for evaluating the strengths and limitations of studies, leading to evaluations that appear to give equal weight to all publications. The NRC committee stated that a clearly articulated framework for weighing the evidence is critical for any determination of causation. It recommended that "strengthened, more integrative, and more transparent discussions of weight of evidence are needed" and that "discussions would benefit from more rigorous and systematic coverage of the various determinants of weight of evidence." Although the causality framework and the intended methods of assessment are clearly stated in the beginning of each ISA, the same issues noted by the NRC committee are evident in the implementation of the framework in the First and Second Draft ISA for ozone, and, similarly, were noted in the First Draft ISA by the CASAC lead review panel. EPA should follow the NRC best practices recommendations in a revision of its weight-of-evidence approach. To achieve this, EPA should consider the hypothesis-based weight-of-evidence approach. As discussed in more detail in our written comments, this approach is consistent with the NRC committee's best practices and has been successfully applied in evaluations of potential health effects for several chemicals. It was also cited recently as a model by EPA's Office of Chemical Safety and Pollution Prevention, Endocrine Disruptor Screening Program in its "Weight of Evidence: Evaluating Results of EDSP Tier 1 Screening to Identify the Need for Tier 2 Testing."

In conclusion, the Second Draft ISA for ozone does not follow an objective and rigorous weight-of evidence approach for evaluating the available data from epidemiology studies. Because of this, the ISA cannot be relied upon to support a causal relationship between ozone exposure and health outcomes at exposure levels below the current NAAQS. EPA should follow the NRC recommendations for best practices in risk assessment to ensure its goal of providing credible causal conclusions about ozone-related health effects in the final ISA.

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Sonja Sax, Sc.D.

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Thank you for the opportunity to speak today. I am Dr. Sonja Sax from Gradient, and my comments are sponsored by the American Petroleum Institute.

EPA's charge to the CASAC panel for the integrated health effects sections of the Second Draft ISA is to provide guidance where the interpretation of the scientific evidence may be improved and on the soundness of the conclusions. In EPA's evaluation of the controlled human exposure studies in Chapter 6 of the ISA, EPA did not interpret the data appropriately; therefore, the conclusions related to the controlled exposure studies cannot be relied upon to support a causal relationship between ozone exposure and adverse effects on lung function at exposure levels below the current NAAQS.

In Figure 6-1, EPA provided dose-response curves for data from controlled exposure studies that examined lung function decrements after ozone exposures from 40 to 120 ppb. EPA concluded that a smooth dose-response curve without evidence of a threshold exists in this exposure range, but the fact that a statistical curve without a threshold can be fit to the data does not itself provide evidence for a lack of a threshold. There is evidence that antioxidants can counter the ozone effects on lung function, consistent with a threshold mode of action, and this should inform the fit of dose-response curves. EPA should not choose a non-threshold curve when the mode of action indicates a threshold. In addition, EPA should include the 95% confidence intervals around each point in Figure 6-1 to more accurately reflect the uncertainty and lack of statistical significance at exposures of 40 and 60 ppb.

EPA asserts that the controlled exposure data support an association between a 60 ppb ozone exposure and lung function decrements. However, the group mean change in FEV_1 at 60 ppb was only statistically significant in the study by Kim *et al.* (2011); the results from the other studies showed no effect at this level. Despite this, EPA relied on the statistical approaches used by Brown *et al*. (2008) to reanalyze the data at 60 ppb in the Adams (2006) study, which produced statistically significant results because the majority of the data was selectively omitted from the analysis. While each statistical method has strengths and limitations, several scientifically accepted methods indicate that there is no statistically significant association between exposure to 60 ppb ozone and lung function decrements. EPA needs to

give equal weight to analyses using these methods, as well as to other methods that incorporate all exposure concentrations and time points, such as in a meta-regression.

Regardless of whether the reported lung function decrements at 60 ppb are statistically significant, the more important issue is whether they are adverse effects. The FEV_1 decrements reported at 60 ppb ozone ranged from 1.7 to 3.5% and were not accompanied by an increase in respiratory symptoms. EPA has noted that changes in FEV_1 measurements should exceed 5% to overcome the intra-day variability of FEV_1 in normal subjects. In addition, the decrements were transient, reversible, and of low severity in that they did not interfere with normal activity and would not result in permanent respiratory injury or progressive respiratory dysfunction. Although some individuals had larger decrements, these cannot be fully attributed to ozone because the controlled human exposure studies were designed to assess differences on the group mean level, not changes in a specific individual. Because of this, one cannot determine whether effects in certain individuals, even if large, are in fact representative of a response to ozone exposure.

In closing, EPA's evaluation of the controlled human exposure data is not scientifically appropriate. The lung function effects at 60 ppb ozone in controlled exposure studies are within the range of intra-individual variability in normal subjects and do not meet established criteria for a clinically adverse effect on lung function The lowest ozone concentration associated with both an FEV_1 decrement that is greater than 10% and increased respiratory symptoms is over 80 ppb, as reported in the study by Schelegle *et al*. (2009). Overall the controlled exposure studies do not support a causal relationship between ozone exposure and adverse effects on lung function at exposure levels below the current NAAQS.