Responses to CASAC Questions on the Ozone PA from Consultant Dr. Duncan Thomas

Questions from Dr. Sabine Lange:

Air Quality

Not my area of expertise.

Epidemiology

1) *Is an epidemiology study with higher statistical power (sample size) innately more protected against problems of confounding, error, and bias, than an epidemiology study with lower statistical power (sample size)?*

   Response: No. Sources of selection, information, and confounding biases could potentially affect any study, irrespective of sample size (or power). That said, very large studies conducted by highly experienced investigators generally make every effort to address such problems in the design and analysis and would discuss these issues in their publications. Also, studies of individual-level data may have access to more information to address bias than meta-analyses or aggregate-level studies.

2) *In section 3.3.3 (Exposure Concentrations Associated with Effects) and section 3.3.4 (Uncertainties in the Health Effects Evidence), the EPA notes that the epidemiology studies are generally assessing the associations between ambient ozone and specific health outcomes and are not investigating the details of the exposure circumstances eliciting these effects (e.g. pg 3-40 and pg 3-43). Do you think that this statement is correct? If so, is this statement generally true of air pollution epidemiology studies, or is it peculiarly specific to ozone? If it is not specific to ozone, then should this caveat always be considered when evaluating exposure concentrations associated with these types of epidemiology studies?*

   Response: The two statements cited are generally correct and apply broadly to air pollution epidemiology studies, not just ozone. Most epidemiologic studies are based on measurements of ambient pollution levels, which are readily available. For some pollutants, indoor sources or penetration from outdoor sources, local variation in pollutant concentrations, time-activity patterns, etc., can be important sources of inter-individual variation, which some studies have attempted to quantify by, for example, personal monitoring, microenvironmental measurements, exposure modeling, GPS or accelerometer instruments, etc., but such studies are expensive and may be infeasible for large-scale epidemiologic studies. Since the statements queried do apply to ozone studies, I don't see than any particular caveats are needed to point out the generality of this issue.

Exposure-Response Modeling

3) *In section 3.4.4 (Key Uncertainties) of this PA, the EPA notes that "In recognition of the lack of data for some at risk groups and the potential for such groups, such as children with asthma, to experience lung function decrements at lower exposures than healthy adults, both models generate nonzero predictions for 7-hour concentrations below the 6.6-hour concentrations investigated in the controlled human exposure studies." Is assuming a lack of threshold in an*

exposure-response relationship a standard method for considering potential at-risk populations that may not have been characterized in an exposure-response assessment?

Response: As I pointed out in earlier rounds of questions, the exact shape of a dose-response relationship at low doses, including the existence or not of a threshold, is difficult if not impossible to determine from feasible-sized epidemiologic studies. Hence, the default analysis model generally assumes low-dose linearity (or log-linearity depending on the form of the outcome variable); see for example the classic paper by Crump, Hoel, Langley, and Peto (1976) I previously cited. This would be true for either main effects in the whole population or for effect modification in potentially sensitive subpopulations, to the extent that the necessary data on individuals are available. The question of effects below the current standard is particularly important, and especially for highly sensitive groups; to the extent that such data exist, any demonstrable low-dose associations should be considered in revising the standard, whether or not the assumption of low-dose linearity or thresholds can be tested.

4) *The EPA also notes in this section that there is a lack of information about the factors that make people more susceptible to ozone-related effects, and that the risk assessment could therefore be underestimating the risk. However, the exposure-response model used to estimate the risk of lung function decrements uses those people in the health population with a greater response to ozone than the mean response (i.e. that fraction of the people in controlled human exposure studies who had FEV1 responses >10%, 15%, or 20%). Does this method already include consideration for more susceptible people in the population?*

Response: This question appears to relate more to controlled human exposure studies than to epidemiologic studies but does seem to be a reasonable approach for getting a handle on inter-individual variability in susceptibility in that context. Obviously, the slope of an exposure-response relationship in the general population will underestimate risk for more sensitive individuals, or more importantly, for identifiable subgroups. Of course, there are other characteristics than lung function (e.g., genetic variants, age/gender, baseline health status, etc.) that could influence sensitivity of ozone or other pollutants. To the extent that the necessary data are available, most epidemiologic studies have reported variation across quantifiable subgroups, and given EPA's mandate to provide adequate protection to such groups as well as to the entire population should be taken into consideration in revising standards.

Questions from Dr. James Boylan

Chapter 2 – Air Quality

Not my area of expertise.

Chapter 3 – Review of the Primary Standard

- *Is the discussion on Exposure and Risk Conceptual Model and Assessment Approach (Section 3.4.1) accurate and complete? If not, what additional information needs to be included?*

- *Is the discussion on Population Exposure and Risk Estimates for Air Quality Just Meeting the Current Standard (Section 3.4.2) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Population Exposure and Risk Estimates for Additional Air Quality Scenarios (Section 3.4.3) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Key Uncertainties (Section 3.4.4) accurate and complete? If not, what additional information needs to be included?*
- *Is the discussion on Public Health Implications (Section 3.4.5) accurate and complete? If not, what additional information needs to be included?*

> **Response:** I found the passages that I read to be accurate and complete, to the best of my knowledge.

Appendix 3C – Air Quality Data Used in Population Exposure and Risk Analyses

Not my area of expertise.

Questions from Dr. Corey Masuca

None of these are in my area of expertise.