Questions for Non-Member Consultants on the Ozone ISA from Dr. Sabine Lange

Epidemiology Study Questions

The EPA states in the ISA preamble that "Traditionally, statistical significance is used to a larger extent to evaluate the findings of controlled human exposure and animal toxicology studies. Understanding that statistical inferences may result in both false positives and false negatives, consideration is given to both trends in data and reproducibility of results. Thus, in drawing judgments regarding causality, the U.S. EPA emphasizes statistically significant findings from experimental studies, but does not limit its focus or consideration to statistically significant results in epidemiologic studies."

1) It has been established that associations found in an epidemiology study can be due to: causation, bias, chance, and/or confounding. **If the concept of statistical significance is not useful in epidemiology studies, then how do the study authors/EPA rule out that chance has caused the observed association?**

Some short-term epidemiology studies use a method that is termed "case-crossover". These studies assess the pollutant concentration on the day of a health effect, and "control" days are those days when a person did not experience that health effect. My understanding is that the intention of this method is to control for intra-individual confounders. These study designs often use days before and after the health event (often matched to day of the week) as control days.

2) **Am I correct in understanding that the intention of ozone case-crossover studies is to compare the ozone concentrations on a day when a health effect occurred for a person, to the ozone concentrations on a day when that health effect did not occur for that person?**

3) If so, then it would be important that some other factor (not related to ozone) did not prevent the health event from occurring on a control day. These studies often use days before and after the health event as control days, but for mortality studies (such as Di et al., 2017), how can a day after death be used as a control day? It doesn't matter what the ozone concentrations are after a person's death, that person would not be able to respond to that concentration. **How should we interpret case-crossover studies that use control days after the event (particularly mortality) occurred?**

Experimental Study and Dose Concordance Questions

4) **What is the importance of dose-concordance in establishing the biological likelihood of ozone-mediated effects occurring at relevant exposure concentrations in humans?** Particularly in the context of known dose information about ozone: total inhaled dose includes concentration, exposure time, and exercise duration; Hatch et al., (2013) have shown that humans and rats that are exposed to ozone at rest achieve similar alveolar ozone doses, and that humans exercising at 5-times a resting ventilation rate achieved an ~ 5-times higher alveolar ozone dose; and that ozone concentrations are 2-10 times lower indoors where people spend most of their time.

5) **Is there evidence that the animal models used to assess ozone effects (largely rats, mice, and non-human primates) are more, less, or similarly sensitive to ozone-mediated adverse effects compared to humans, at approximately equal inhaled doses?**

Causality Question

In this ISA I did not find population studies that considered causal pathways when assessing the association between ozone and health endpoints. It has been shown that the type of interaction between variables (e.g. confounding, colliding, mediating) can impact the results of regression analyses if these variables are controlled for in the regression equation.

6) **In the absence of a causality diagram to direct the choice of variables to control in an epidemiological study, how can we judge whether a study has appropriately controlled for confounders, and has not inappropriately controlled for colliders (which can open up pathways between variables that otherwise would not be connected) or mediators (and thereby controlled away the effect)?**

References

Di, Q., Dai, L., Wang, Y., Zanobetti, A., Choirat, C., Schwartz, J.D., Dominici, F., 2017. Association of Short-term Exposure to Air Pollution With Mortality in Older Adults. Jama 318, 2446. https://doi.org/10.1001/jama.2017.17923

Hatch, G.E., Mckee, J., Brown, J., Mcdonnell, W., Seal, E., Soukup, J., Slade, R., Crissman, K., Devlin, R., 2013. Biomarkers of dose and effect of inhaled ozone in resting versus exercising human subjects: Comparison with resting rats. Biomark. Insights 8, 53–67. https://doi.org/10.4137/BMI.S11102