Questions for Non-Member Consultants on the Ozone ISA from Dr. Mark Frampton

1. Change in causality determination for short-term cardiovascular effects since the 2013 ISA.

Background: Table ES-1 and section ES.4.1 of the Executive Summary, and Appendix 4, cardiovascular (CV) health effects.

The 2019 ozone ISA has downgraded the causality determination for short-term ozone exposure and cardiovascular effects from "likely" (2013 ISA) to "suggestive". This was due in part to new human clinical studies of CV effects that are inconsistent with the few studies available in 2013, but also to persistent weaknesses in the epidemiological evidence, as reviewed in Appendix 4.1.

Question 1: Please comment on the strengths and weaknesses of the epidemiology literature with regard to CV effects of short-term ozone exposure. Are there key studies that are missing? Are the remaining weaknesses, along with the other new evidence, sufficient to justify the change in causality determination?

2. Metabolic effects, new determination of "likely" for both short- and long-term exposure.

Background: Table ES-1 and section ES.4.1 of the Executive Summary, and Appendix 5, Metabolic Effects.

"Metabolic effects" include effects on body weight, appetite, body composition, caloric intake, diabetes, glucose, insulin, lipid metabolism, stress responses, and thyroid function. Note that "metabolic effects" differ from the issue of metabolic abnormalities as risk factors for other responses. For example, obesity may affect the pulmonary responses to short-term ozone exposures; this should not be considered a "metabolic effect".

This new determination is driven largely by animal toxicology studies, mostly in rodents, and a single human clinical study showing evidence of acute responses in circulating stress hormones.

Question 2: Is there sufficient epidemiological evidence of metabolic effects to justify the "likely" determination for both short- and long-term exposures? Are there additional studies that should be considered?

3. Change in causality determination for total mortality since the 2013 ISA.

Background: Table ES-1 and section ES.4.1 of the Executive Summary, and Appendix 6, Health Effects-Mortality.

The 2019 ozone ISA has downgraded the causality determination for short-term ozone exposure and total mortality from "likely" (2013 ISA) to "suggestive". However, Figure 6-1 on page 6-6, summarizing the epidemiologic studies of short-term total mortality, shows remarkably consistent evidence for an effect. The newer studies are consistent with the findings reviewed in the 2013 ISA.

The rationale for the change is summarized on page 6-20 of the current ISA:

"However, the experimental evidence, specifically from controlled human exposure studies, is not consistent with the studies evaluated in the 2013 Ozone ISA. This contributes additional uncertainty for a biologically plausible mechanism by which short-term ozone exposure could lead to cardiovascular mortality. Lastly, most of the recent studies examined associations between short-term ozone exposure and mortality using ozone data prior to the year 2000, with only Di et al. (2017a) focusing on more recent ozone concentrations."

Although the newer human studies are inconsistent for CV effects, the human studies overall are very consistent for respiratory effects, so there is a plausible pathway for respiratory mortality. In addition, the ISA establishes a new causality category of metabolic effects (see above), with a determination of "likely". Metabolic effects and metabolic syndrome are closely linked with increased risk of CV disease, so this provides a plausible pathway.

Question 3: Please comment on the strengths and weaknesses of the epidemiology literature with regard to short-term ozone exposure and total mortality. Are there key studies that are missing? Does the available evidence justify the change in causality determination for total mortality?

Also please note that, for effects with causal or likely causal determination, the EPA has restricted consideration of epidemiological studies to those in North America (see PECOS Tool, section 6.1.1.1, page 6-3). That was the case for this determination. Are there epidemiological studies of mortality outside of North America that should be considered?