Vedal. May19, 2011

Charge Question 2: *The framework for causal determination and judging the overall weight of evidence is presented in Chapter 1. Is this framework appropriately applied for this O3 ISA? How might the application of the framework be improved for O3 effects?*

1. Causation.

Causes do not need to be "significant" (1-14. line 1); the term is also ambiguous. So, this definition in essence relies on the term "effectual" (as in effectual relationship) to define causality. Not a very informative (as in "cause and effect," therefore a little circular) or useful definition. Couching the definition of causality in counterfactual terms, as alluded to in line 5, is arguably the most informative. This incorporates the notion of "all else being equal" and is most readily operationalized, reflecting what is attempted in both experimental (e.g., control exposures) and observational (e.g., control of confounding) studies.

2. Confounding and effect modification.

The concepts of confounding and effect modification are more clearly expressed in this ISA. Including a discussion of multiple pollutants in this context (1-16, lines 8-13) is appropriate, but it needs to be made clear that what is being developed here is the notion that ozone effects might be confounded by effects of other pollutants, which is not clear from the discussion.

The discussion of effect modification should define it (e.g., differences in the effect of exposure [ozone] by differences in another factor) before launching into a discussion of how it differs from confounding. Also, temperature is presented as a potential effect-modifier, but it might be valuable (and less confusing) to contrast how temperature is also (and more importantly) a potential confounder. Essentially, effect modification refines our understanding of the effect of an exposure while confounding addresses whether an effect is actually present, or what the size of that effect is, if present.

The discussion of measurement error (1-17, para 3) should refer to ISA Chapter 4, especially 4.5.1 "Exposure Measurement Error" and 4.6. The discussion here in this context (confounding) is merely confusing. The point should be that measurement error that differs in degree across pollutants complicates interpretation of individual pollutant effect estimates in multi-pollutant regression models – effects of pollutants that are measured with less error can dominate effects of other pollutants, even though their effects may in fact be weaker.

3. Causality determination and weighing evidence.

The Hill "criteria" are listed in Table 1-2. Coherence also refers to findings across epidemiological study designs, not just between epidemiological, toxicological and other experimental studies. It is noteworthy that presence of exceptions to each of the "criteria," except temporality, is still consistent with causality (Rothman).

The weighing of evidence to come up with a causality grade is reasonable. This worked reasonably well in the context of PM. I like the inclusion of a "not likely to be a causal relationship" category in this version – it maintains symmetry.

I'm not sure that studies with concentrations "within an order or two of ambient" (1-22, line 5) concentrations are relevant for causality determination. This would imply that for, say, an ozone concentration of 0.070 ppm, findings from studies of 7.000 ppm would be relevant. I doubt that.

4. Effects on human populations.

The shape of the exposure-response relationship is influenced by the degree of measurement error, as touched on (1-23, line 8). Specifically, measurement error at lower concentrations can obscure a threshold and make it appear that a linear relationship extends to lower concentrations (Brauer M et al. Exposure misclassification and threshold concentrations in time series analyses of air pollution health effects. *Risk Anal* 2002; 22: 1183-1193). This could potentially be a particularly important issue for pollutants such as ozone that exhibit large degrees of measurement error.

I am happy to see a discussion of publication bias included in this ISA (1-23) and the reference to Ioannidis, 2008. The observation that publication bias in the case of ozone may not be so important (1-23, line 27) is contradicted by the work of Bell showing substantial difference in ozone effect estimates from meta-analyses of published studies and multi-city study effect estimates.

The discussion of susceptibility indicates that the term here will be used in a general sense to include both susceptibility and vulnerability, terms that include both disease risk factors and factors that increase exposure (1-23, line 36) and therefore risk.

5. Adversity.

The discussion of adversity is appropriate to include here. There is no discussion, however, of the types of endpoints that are more problematic in a discussion of adversity, such as markers of inflammation or oxidative stress, for example.

<u>Specific</u>.

1-13, line 15. It is not clear that the type of important evidence would vary by pollutant – It would vary if this were based on the availability of evidence for different pollutants, but I would think the important evidence should be pretty much the same, given findings across multiple lines in inquiry.

1-15, line 35. While this is true, clinical studies also have the potential of overestimating effects when exposures used (concentration or intensity) are seldom experienced in the real world.

1-16, lines 29-31. Drop this unless you intend to be inclusive, since effect modifiers can be found in many other settings than these in air pollution epi studies.

1-16, line 33. Some approaches to controlling confounding are very satisfactory. I think what may be intended here is that approaches to controlling co-pollutant confounding are not very satisfactory.

Charge Question 5.
Chapter 4 describes human exposures to O3. Is the evidence relating human exposure to ambient O3 and errors associated with exposure assessment presented clearly, succinctly, and accurately? Do the characterizations of temporal and spatial variability of O3 in urban areas provide support for better understanding and interpreting epidemiologic studies discussed later?

4-21, lines 1-5. This makes it seem that exposure measurement issues are not so important for ozone, whereas they are probably more acute for ozone than for any other pollutant.