

## **Ozone NAAQS Comments to CASAC, 9-10 January 2012**

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Good morning/afternoon, I am Bruce Copley, an epidemiologist from ExxonMobil Biomedical Sciences, Inc. I will comment on two areas of concern: (1) the EPA's 'cumulative weight of the evidence methodology' in general, and (2) the Agency's application of this methodology for long-term, or chronic, ambient ozone exposure and respiratory mortality.

The EPA's weight of evidence scale is as follows: Causal, Likely to Be Causal, Suggestive of a Causal Relationship, Inadequate to Infer a Causal Relationship, and Not Likely to Be Causal. This framework is imbalanced, as 3 of the 5 designations indicate or suggest causality with no analogue for designating non-causal evidence. The middle, or third, category is not neutral as is commonly seen in Likert Scales; rather, it is designated as "Suggestive". Moreover, the most certain designation of non-causality is phrased in a manner that allows for the possibility of a causal association. This weight of evidence scale has not received scientific peer review for use in observational studies. Scientific peer review is required for studies to be considered by EPA in NAAQS determinations. Likewise, we believe this new weight of evidence framework should also be peer reviewed.

I will now address the EPA's criteria for those designations. The basis for Causal is more compatible with a Likely to Be Causal classification under a more objectively scientific paradigm. The Agency's acceptance that "chance, bias, and confounding [can] be ruled out with reasonable confidence" in observational studies is not defensible, particularly in light of the observed weak statistical associations.<sup>1</sup> Consider the relative risk of 1.04 for respiratory mortality in Jerrett et al (2009), arguably the most influential paper on chronic ozone mortality. As in many other chronic air pollution studies, the role of chance is reduced owing to the large

sample size. However, there are many opportunities for uncontrolled bias and confounding to render that relative risk unreliable. The effect of confounding by PM alone in this study and many others is almost certainly greater than the effects of ozone exposure. Likewise for the ever-present exposure misclassification which, for ozone, can be substantial.<sup>2,3</sup> Unexplained regional heterogeneity of effect in Jerrett et al further adds to concerns about reliability.

The Agency offers examples of support for earning the Causal designation, as follows: *a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information)*. Controlled human exposure studies cannot replicate real-world chronic exposure. Consequently, observational studies with their attendant weak statistical associations are relied on to examine health endpoints. It seems entirely plausible that a constellation of factors other than ambient ozone exposure—but somehow associated with such exposure—could have generated those small relative risks. The potential for an alternative causal agent is high given that stationary ambient monitor measurements are a poor surrogate for individual and population average exposure for use in epidemiology studies.<sup>4-7</sup>

The remaining Causal designation criterion is *Evidence includes replicated and consistent high-quality studies by multiple investigators*. True replication is essentially non-existent in observational air pollution epidemiology. Even studies of the same population, e.g., the American Cancer Society (ACS) cohort, update the data or use analytical tools that differ from those of previous studies. Additionally, I submit that studies which lack individual-level exposure data and cannot adequately control confounding—characteristics of those studies now being considered for chronic mortality—cannot establish causality. True, some studies are stronger than others, but relativism should be not be used as a substitute for reliability when assessing weight of evidence.

Chronic mortality is a new health endpoint that EPA proposes to quantify in their Risk and Exposure Assessment and Regulatory Impact Analysis for the 2013 ozone NAAQS. The Agency has determined that the evidence for a mortality effect is ‘Suggestive of a Causal Relationship’. Here are the criteria for this designation:

*Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent. This allows for the possibility that one so-called high quality study that contradicts findings from several other studies could raise the designation from Inadequate to Infer a Causal Relationship to Suggestive.*

In short, the EPA’s causal weighting paradigm and its associated criteria is of questionable validity with a bias towards designations that exaggerate the certainty of causal inference. In addition, there is insufficient evidence for the Suggestive designation for the ozone-mortality relation.

Thank you once again for allowing me the opportunity to present these concerns to you.

### **References**

- <sup>1</sup>Taubes, G and Mann, C.; (1995). Epidemiology faces its limits. *Science* 269, 164-169.
- <sup>2</sup>Rhomberg, L.R., Chandalia, J.K, Long, C.M, and Goodman, J.E. (2011). Measurement error in environmental epidemiology and the shape of the exposure-response curve. *Critical Reviews in Toxicology* 41 (8), 651-671.
- <sup>3</sup>Brauer M., Brumm, J, Vedal, S, and Petkau, A.J. (2002). Exposure misclassification and threshold concentrations in time series analyses of air pollution and health effects. *Risk Analysis* 22 (6), 1183-1193.
- <sup>4</sup>Koutrakis P. (2005). Characterization of particulate and gas exposures of sensitive subpoulation living in Baltimore and Boston. Health Effects Institute Report 131.
- <sup>5</sup>Sarnat *et al.* (2001). Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? *Environmental Health Perspectives* Vol. 109, 1053-1060.
- <sup>6</sup>Sarnat *et al.* (2005). Ambient gas concentrations and personal particulate matter exposures. Implications for studying the health effects of particles. *Epidemiology* 16 No.3, 385-395.
- <sup>7</sup>Sarnat *et al.* (2006). Factors affecting the association between ambient concentrations and personal exposure to particles and gases. *Environ. Health Perspect* 114(5):649-654.