

## **Preliminary Comments on the Policy Assessment from Dr. Michael Kleinman**

### **Chapter 3 – Consideration of the Evidence for NO<sub>2</sub>-Related Health Effects:**

Chapter 3 summarizes key aspects of the health effects evidence that are particularly relevant to considering the adequacy of the current primary standards and describes staff's consideration of this evidence to inform preliminary conclusions regarding the adequacy of the current standards.

*1. To what extent does Chapter 3 capture and appropriately characterize the key aspects of the evidence assessed and integrated in the ISA?*

Chapter 3 provides an excellent overview of the evidence summarized in the ISA. The discussion of the Brown (2015) meta-analysis was provided in clear detail and was used to, in part, substantiate the increased causality category for Respiratory effects from 'sufficient to infer a causal relationship' to 'Causal relationship.' It might be useful to consider that another recent meta-analysis (Shah et al., 2015) which used lags and reported a significant acute effect of NO<sub>2</sub> on morbidity and mortality from stroke, with regard to causality for cardiovascular disease. The Shah study examined 238 articles and found 103 suitable for inclusion in their analysis. They found that NO<sub>2</sub> was the most commonly measured gaseous pollutant and that NO<sub>2</sub> exposure showed a consistent association with both ischemic and hemorrhagic stroke (1.024 (95% confidence interval 1.010 to 1.038, I<sup>2</sup> =56%) and 1.024 (1.003 to 1.045; I<sup>2</sup> =42%). Associations persisted when data were stratified by outcome, age, and study design. (See Figure 1 on next page).

*2. To what extent is staff's consideration of the evidence from epidemiologic and controlled human exposure studies, including important uncertainties, technically sound and clearly communicated? What are the Panel's views on staff's interpretation of the health evidence for short-term (section 3.2) and long-term (section 3.3) NO<sub>2</sub> exposures for the purpose of evaluating the adequacy of the current standards?*

In general the epidemiologic and controlled human exposure studies are clearly presented as are many of the important uncertainties and caveats. One additional caveat that might be considered is that the subject pool for controlled human exposures are, for ethical reasons, not selected from among the most susceptible individuals, even when the subjects are drawn from among those with respiratory or cardiologic diseases. Thus it might be fair to say that dose-response relationships derived from these studies might underestimate risks for the most sensitive subjects in the population. Another caveat is that exposures are almost always to atmospheres that are much less complex than ambient air and might not fully represent interactions with co-pollutants that could alter the dose, dose distribution and potential toxicity of NO<sub>2</sub> when present in mixtures with other pollutants. For example, in the atmosphere NO<sub>2</sub> and O<sub>3</sub> could react together to form nitric acid vapor which could enhance irritant effects but few, if any studies of this mixture have been performed.

Specific Comment:

P 3-24 do not indicate *excess* NO<sub>2</sub>-associated...?

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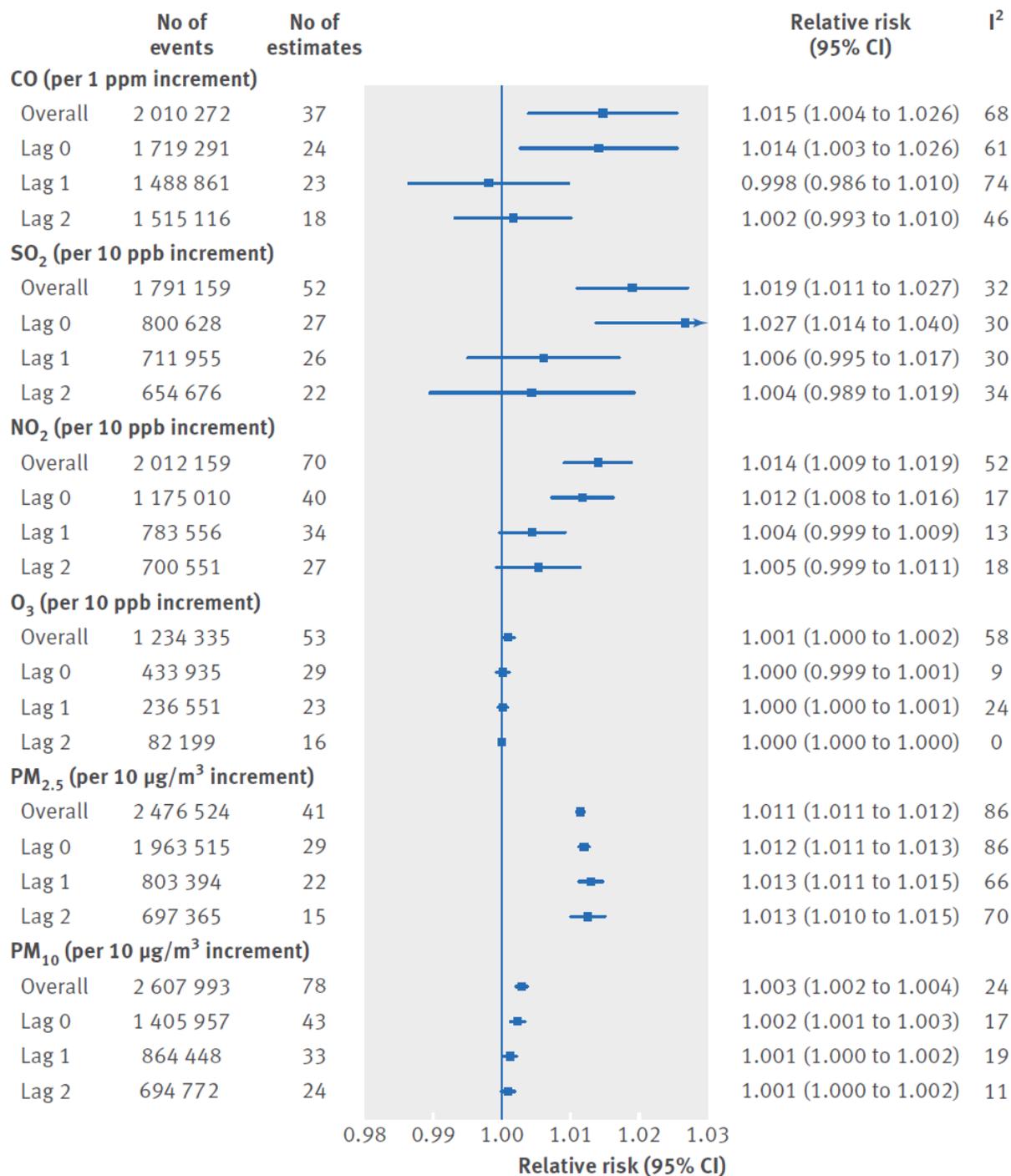


Fig 1 | Association between gaseous and particulate air pollutants and admission for stroke or mortality from stroke stratified by time lag (days)

Shah, A. S. V., Lee, K. K., McAllister, D. A., Hunter, A., Nair, H., Whiteley, W., Langrish, J. P., Newby, D. E., and Mills, N. L. (2015). Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ*, 350:h1295 (doi:10.1136/bmj.h1295).