

Comments: Kent E. Pinkerton

Agency Charge Question 3. To what extent is the discussion and integration of evidence from the animal toxicology and controlled human exposure studies and epidemiologic studies technically sound, appropriately balanced, and clearly communicated? What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of NO₂-related health effects?

General Comments:

The organization of the ISA document for Oxides of Nitrogen – Health Criteria is excellent. The document is greatly improved over the last version. The content, flow, presentation and logic of materials are well done. The addition of new publications from the scientific literature since 1993 is thorough and impressive. The majority of papers cited in the document are highly relevant from an environmental perspective, although some toxicology documents which provide biologic plausibility exposure concentrations that are well above ambient conditions (greater than or equal to 5 ppm). The addition of new human clinical and epidemiologic studies to this second draft of the ISA is highly impressive and far exceeds new animal toxicology studies. However, some new toxicology studies are included to demonstrate effects as low as 0.04 ppm. Human studies also provide strong evidence for health effects at NO₂ levels in the 0.02-0.03 ppm. In summary, the second draft of the ISA document represents an excellent compilation and reasonable interpretation of new research findings that should greatly aid in formulating decisions for setting the next criteria standard for oxides of nitrogen. I feel the conclusions drawn in the ISA document provide strength, consistency, coherence and plausibility for NO₂-related health effects.

Minor Comments:

- 1) P 2-35, line 15 Will increased use of biomass fuels lead to an increase in NO₂ concentration in the future?
- 2) P2-40: this section provides an excellent detailed description on the relationship of personal exposures to ambient concentrations.
- 3) P 2-50 Is there a reason for no section labeled as 2.5.7?
- 4) P 3-6: Excellent table to summarize the proposed mechanisms whereby NO₂ exacerbates airway symptoms.
- 5) P3-12: Figure 3.1.1: It would be helpful to more completely label the y axis. Perhaps “observed response” could be added. At first examination the meaning of the symbols + and – was not clear. Does + mean increased or adverse response; does – mean no change from control or a reduction of response from control
- 6) P3-18: Figure 3.1.2: Same comments as for Figure 3.1.1., although the text referring to this figure clarifies the meaning of + and – for the y-axis.
- 7) P3-25: Excellent comparison of NO₂ concentrations leading to increased airway responsiveness in healthy and asthmatic humans and animals.

- 8) The intervention study of Pilotto et al (2004) provides striking evidence for health effects among asthmatic children for NO₂ concentrations at extremely low levels. The only concern for the interpretation of this study remains the possibility that ultrafine particles, rather than NO₂ may be driving this effect.
- 9) There appears to be strong evidence of NO₂ effects on physician-diagnosed asthmatic children (Pilotto et al., 2004). Although it may be difficult to completely rule out the effects of ultrafine particles, multi-pollutant models continue to demonstrate NO₂ when adjusting for other pollutants such as CO, O₃ and PM.
- 10) P 3-50, line 29: the term “not sensitive” in this sentence is unclear. Does this mean co-pollutant regression analysis does not work or that other co-pollutants do not confound NO₂ effects?
- 11) Excellent studies are included throughout the document to demonstrate positive associations between ambient NO₂ concentrations and health effects among young children and older adults (65+ years).
- 12) There continues to be a concern relative to confounding of co-pollutants, as well as NO₂ being a surrogate for other pollutants. However, there appears to be consistent data throughout more recent publications to suggest NO₂ can elicit health effects at current ambient levels.
- 13) Susceptible populations are clearly an important group to consider for NO₂ health effects. The Southern California Children’s Health Study clearly points to NO₂-related changes with reduction in lung growth function in children.
- 14) Excellent summary and integration of scientific evidence for all aspects of health effects of NO₂ throughout the document.