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Comments on the Executive Summary

The summary adequately presents the purpose of the ISA, the scope and methods that were used. The summary of source and exposure-related information is given in great detail and could possibly be shortened by limiting the discussion to what is different from what was reported in the 2008 ISA. On the other hand, the discussion of the basis for strengthening the causal determination for the evaluated health effect categories does relate to new information and perhaps could be expanded since this is the going to greatly influence discussion of any proposed changes to the current NAAQS.

Comments on Chapter 3: Dosimetry and Modes of Action

- a. The discussion of the unlikelihood of NO₂ penetrating through lung lining fluid does not address the heterogeneous nature of the chemical composition and thickness of the lining fluid as a function of location in the respiratory tract. The lining fluid in conducting airways is thicker and of different composition from that in alveolar spaces. The lining fluid in the alveolar region is thinner (on the order of 0.2 μm)[1], is rich in surfactants and plays a role in the innate defenses of the lung. The models estimate that NO₂ can penetrate 0.6 μm so NO₂ might be able to penetrate to cell surfaces. The information in Table 3-1 might be expanded to separately discuss the chemistry of airway and alveolar lining fluids in the context of what fraction of inhaled NO₂ penetrates to those regions.
- b. To the extent that NO₂ dosimetry models predict penetration of NO₂ to the alveolar region given the relatively small volume of alveolar lining fluid there might some utility to examining potential cross species effects on innate immunity functions mediated by the constituents of alveolar lining fluid.
- c. The discussion of endogenous NO and NO₂ should mention the possibility that endogenous production may be great enough in small selected spatial regions of the respiratory tract that the local anti-oxidant capacity is exhausted and thus exogenous oxidant insults could overbalance the system and increase the likelihood of an adverse effect.
- d. There are some specific issues that could be mentioned with regard to populations such as individuals with acute respiratory distress syndrome that could be more sensitive to NO₂ reactions with lung lining surfactants.

1. Ng AW, Bidani A, Heming TA: **Innate host defense of the lung: effects of lung-lining fluid pH.** *Lung* 2004, **182**(5):297-317.