

Preliminary ISA Comments from Dr. Jack Harkema

Comments on the Executive Summary

General Comments:

The changes made to the first draft of the executive and integrative summaries (ES and IS, respectively) have markedly improved the document. Much of the technical language in the first draft has been removed from the ES improving the readability for the general public. In addition, there is more integration and less summary of the IS in the ES, making the two sections more distinctive and with less redundancy. The limited number of references and references only to specific sections, figures or tables are also appropriate.

The summary of major findings at the end of the ES, however, is too wordy and could be more concisely crafted. Key findings related to the determination of causality could be further condensed (less findings and shorter text for each finding; delete subpoints).

There still remains some inconsistencies between the ES and IS in the justification of causal determinations that need to be reconciled (see below under the IS review).

Specific comments:

Figure ES-1. This mode of action figure could be improved by indicating what key events or outcomes (health effects) that are the result of short- or long-term exposure. This should be articulated in the text as well.

lxxxii. lines 22-24. The statement, *The key evidence for an independent effect of NO₂ are the controlled human exposure findings for NO₂-induced increases in airway responsiveness ...*, appears to contradict the statement in the IS, *NO₂-related decreases in lung function are observed in epidemiologic but not in controlled human exposure studies* (p.I-19, line 23-24).

lxxxii. lines 24-27. These two sentences do not make good pathobiological sense and should be revised. NO₂ reaction with antioxidants in lining fluid is thought to be a good thing (protection for the airway epithelium), but depletion of antioxidants and generation of reactive oxygen/nitrogen species could be detrimental (adverse effect) resulting in cell injury, airway dysfunction, and altered immunity.

lxxxv. lines 22. Authors need to clarify what they mean by *at low concentrations*.

Comments on Chapter 1 - Integrative Summary

General Comments

In general, the revised chapter better synthesizes the key findings for each topic area and integrates the important information across the ISA to inform policy-relevant issues.

The authors due a good job of justifying their recommendations for no causality change in specific areas, but some of the areas where they are recommending changes to the causality determination their rationale appears weak and needs more justification (e.g., respiratory effects associated with short-term exposure to NO₂; see specific comments below).

Specific Comments:

1-16. lines 1-2. Modes of action are proposed pathways that lead to an adverse health outcome(s) and are based on identified pathological key events. A mode of action helps to *explain* exposure/effect relationships but it does not *support* the relationship. The introductory paragraph for respiratory health effects is not well constructed and in some areas confusing. For example, if asthma exacerbation is the primary response to short-term exposure than the effects of NO₂ should be on the conducting airways and not on alveolar region of the lung (NO₂ uptake in the distal region of the lung is irrelevant and probably inconsequential) for this respiratory effect. It would be better to highlight what is known about NO₂-induced lung pathology that results in airway dysfunction related to asthma.

1-17 Figure 1-2. This expanded mode of action figure does illustrate key events and outcomes but their relationship to short- or long-term exposures are not illustrated.

1-17. line 5. Change *describe* to *suggest*. A mode of action pathway identifies potential key events in the development of potential health effects, but it is not definitive, like a discovered mechanism.

1-19. 28-37. The closing paragraph of this section suggests that no new data has been generated since the last review and that the justification for a causal relationship between short-term NO₂ exposure and respiratory effects is based on a better assessment/evaluation made by the authors. It is not clear how the authors arrived at this new insight. It appears to belittle any new scientific discoveries in this area since the last review that added to the weight of evidence. This closing paragraph should be more in line with the introductory paragraph of this section and the ES.

1-29-30. The potential confounding exposure factor of diesel engine exhaust particles (a known carcinogen) should be addressed in this section, especially since the authors are suggesting a change in the causal determination for NO₂ exposure and lung cancer.