

## **Preliminary Comments on the ISA from Dr. Helen Suh**

### **Comments on Chapters 3 and 7**

#### **Charge Question 3**

*The exposure discussion is re-organized to clarify: a) the connection between particular exposure assessment methods and epidemiologic study designs, and b) the influence of exposure error on health effect associations from epidemiologic studies of specific designs.*

- 1. How explicitly and accurately is epidemiologic study design considered in the discussion of the utility and uncertainties of various exposure assessment methods, the nature of exposure measurement error, and the impact of exposure measurement error on NO<sub>2</sub>-health effect associations? How effective is the discussion in facilitating the evaluation of the strength of inference from epidemiologic studies in Chapters 5 and 6?*
- 2. Section 3.4.4 expands discussion of the relationships of NO<sub>2</sub> with copollutants and traffic noise for various short-term and long-term time periods as well as various exposure parameters (e.g., ambient, personal, indoor). To what extent is this information appropriately characterized and useful for the evaluation of potential confounding in epidemiologic studies in Chapters 5 and 6?*

Chapter 3 provided a comprehensive discussion of exposures to nitrogen oxides, describing key issues related to the characterization of NO<sub>2</sub> exposures and their impact on our interpretation of epidemiological and other health studies. The Chapter is substantially improved over previous versions, with its new organization much better suited to not only describe our understanding of NO<sub>2</sub> exposures and factors affecting them but also to connect this understanding to help interpret epidemiological studies of NO<sub>2</sub>, which it does successfully.

The chapter would benefit from additional relatively minor changes, as listed below.

- The Introduction (Section 3.1) describes the organization of the Chapter as including “methods to estimate personal exposure, current data used to characterize exposure to ambient oxides of nitrogen, exposure-related factors that influence interpretation of epidemiologic models of the health effects of oxides of nitrogen, and considerations for use of exposure metrics in epidemiologic studies of different design.” These terms/phrases differ from section titles; for consistency, it would be helpful for the titles of the subsequent sections to have the same terminology.
- Figure 3-1 is a useful illustration of the variability in NO<sub>2</sub> exposures by location; in the discussion of this figure in the text and as a footnote, it should be mentioned that the data are based on different monitoring methods (in addition to exposure windows). This discussion (and figure footnotes) would be particularly helpful in light of the discussion regarding the method- and exposure window-specific considerations.
- Table 3-1 is a very helpful addition to the Chapter and helps to connect measurement and modeling methods to interpretation of health effect studies. However, the Table may be even more useful with the following changes or considerations:

- The errors and uncertainties section of the table focuses on method bias, but does not address method precision, which also has important implications for epidemiological studies and statistical power.
  - It is not always the case that correlation between concentrations measured at central site monitors and “exposure” decrease with increasing distance, given the influence of roadways on NO<sub>2</sub> monitoring data and exposures. Also, it might be clearer to replace the term “exposure” with “outdoor locations”, since exposure as used in the rest of the chapter can include factors other than outdoor location.
  - Similarly, passive monitors do not always result in positive instrument bias, as negative biases have been demonstrated under stagnant conditions and using manufacturer recommended uptake rates.
  - The term “exposure misclassification” often refers to exposure categories, while the methods included in the table all provide continuous measures of concentration or exposure. As a result, it may be more appropriate to refer to bias (rather than misclassification) in exposure estimation.
- Section 3.2.3 is a comprehensive and well-described review of measurement and modeling methods for NO<sub>2</sub>. In the brief introduction to this section, it states that it will “outline various facets of characterizing NO<sub>2</sub> exposure”, but should instead read “outline various facets of NO<sub>2</sub> measurement and estimation.
  - Section 3.3 would benefit from a short introduction outlining the contents of the section (which tend to be relatively wide-ranging), prior to discussion NO<sub>2</sub> as an Indicator of Source-Based Mixtures. This introduction would help to provide a road-map for the section and to explain the purpose of the discussion, particularly as it relates to Section 3.4.
  - The section on confounding (Section 3.4.4) should be mention that the potential for confounding of NO<sub>2</sub> impacts by co-pollutants can vary by the health endpoint of interest.
  - Page 3-74, line 3-5. The sentence beginning “The next section...” seems out of place. Some clarification or re-wording is needed.
  - Much of the discussion of results for Community Time-Series Studies (Section 3.4.5.1) are based on data from Atlanta. It is not clear that findings from Atlanta are generalizable to other cities in the US, which should be stated, with perhaps pointing to the need for further study in other locations.
  - Section 3.4.4 was useful and appropriately characterized.
  - In addition to the conclusion section at the end of the Chapter, it may be helpful for the reader to include a brief conclusion paragraph after each major Chapter section.

## **Charge Question 7**

*Chapter 7 is revised to address the CASAC Oxides of Nitrogen Panel’s recommendation to provide a more integrated analysis of the weight of evidence for potential at-risk populations and lifestages and to expand the discussion of populations with proximity to roadways and risk of NO<sub>2</sub>-related health effects due to multiple co-occurring factors.*

1. *The enhanced integrated analysis of at-risk populations and lifestages includes moving individual study results to tables and focusing the discussion on the synthesis of the health effects evidence as well as available information on exposure and dosimetry. Please comment on the effectiveness of the integrated analysis and the extent to which the strengths and limitations of the evidence are*

*explicitly and consistently described in communicating the rationale for conclusions about at-risk populations and lifestyles.*

The Chapter is well-written, -organized, and -reasoned, providing a solid scientifically-based rationale for its conclusions. The movement of study results to tables was a welcome change and allowed for a streamlined and as a result, more useful and thoughtful Chapter. The Chapter would benefit further from greater reference to topics and issues raised in earlier ISA chapters.

Other comments include:

- No data are provided for COPD in Table 7-2. It may make sense to remove the row for COPD and instead include COPD in the footnote and note that it is comprised of chronic bronchitis and emphysema. Else, it gives a false impression that no individuals have COPD within the US population.
  - While not relevant for many potential at-risk sub-groups with pre-existing diseases, it is likely important to include a discussion of exposure-related issues for people with asthma (even though it is included later in the section discussing children). For example, both children and adults with asthma may have different time/activity patterns as compared to other groups or may stay indoors on days with high air pollution levels, possibly reducing the ability of studies based on central site NO<sub>2</sub> concentrations to detect NO<sub>2</sub>-related health impacts.
  - The lack of evidence showing different time-activity patterns for older as compared to younger ages, the limited evidence from controlled human exposure studies, and the well-documented impacts of PM<sub>2.5</sub> and ozone on hospital admissions and other health endpoints in older adults suggests the possibility of confounding of NO<sub>2</sub>-impacts in older adults by PM<sub>2.5</sub>, ozone, or other correlated co-pollutants. Some discussion of this possibility should be provided.
2. *A new section (Section 7.5.6) describes what information is available on differences in NO<sub>2</sub> exposure or risk of NO<sub>2</sub>-related health effects for populations with proximity to roadways. To what extent does the added discussion accurately reflect the available information?*

This new section focusing on populations living near roadways and spending time near traffic is appropriate and is important addition to this Chapter. It is well-written, but needs greater background/review at the beginning of the section to link roadway proximity or time spent in traffic to elevated NO<sub>2</sub> concentrations. For example, the paragraph on page 7-52, lines 1-5 states that high NO<sub>2</sub> concentrations are found within 20 m of roads, while the following paragraph (as well as other paragraphs, such as on page 7-55, lines 10-26) presents data for population living within 100-250 m from roadways. As a result, these paragraphs are spatially inconsistent and together with the subsequent paragraph (page 7-53, lines 6-19) suggest that most of the US population is not exposed to elevated NO<sub>2</sub> exposures from busy roadways.