

## **Preliminary Comments on the ISA from Dr. Douglas W. Dockery**

### **Comments on Chapters 5 and 6 – Integrated Health Effects of Short-term and Long-term Exposure to Oxides of Nitrogen**

1. *To more transparently characterize the weight of evidence for health effects, discussions are organized by specific outcome groups. Please comment on the extent to which individual endpoints are appropriately placed into specific outcome groups.*

The organization of this ISA to truly integrate evidence across disciplines is a major improvement. With regard to the health effects chapters, bringing the evidence from toxicology, clinical studies, and epidemiology to bear on specific outcomes is much more in keeping with how we should be evaluating the scientific evidence. When these three approaches are considered separately, it is difficult for the reader to bridge to other chapters and to see how these independent approaches inform (or contradict) each other. This integrative approach presents the entire spectrum of information to the reader. When presented in separate chapters, there is the temptation to pay much more attention to the evidence from one approach, and only skim the other chapters. Moreover, in the approach specific presentation, there is a tendency to deconstruct the evidence from individual studies, rather than integrating across studies and approaches.

Beyond the health chapters, I also see more integration with the other chapters. I see the Chemistry and Ambient Concentration (Chapter 2), Exposures (Chapter 3), and Dosimetry (Chapter 4) chapter as being more informative regarding health effects, and in this sense integrative also. Overall, I endorse and encourage this integrative organization.

2. *Please comment on the extent to which the results from the meta-analysis of controlled human exposure studies of airway responsiveness in individuals with asthma, are clearly described, appropriately interpreted, and informative to the evaluation of NO<sub>2</sub>-induced increases in airway responsiveness.*

I found the meta-analysis of controlled human exposure studies interesting and the data presented very informative. It is very appropriate to combine these studies in a meta-analysis. Given that this meta-analysis has been published, I agree that much of the detail is no longer needed in the ISA.

With regard to the lack of a dose response in these data, I am not convinced that we would expect to see a dose response in these data. The combined data are for 116 NO<sub>2</sub> exposures among 72 individuals. Thus most individuals have only one exposure, which makes it hard to see individual dose response. Moreover, for these asthmatics, I would expect each to have a threshold for their individual response. Given a large enough sample, the distribution of individual response would show a continuous dose response. These controlled exposure studies are not measuring that threshold however, and 72 subjects is a small number to define a distribution.

Specific comments:

Page 5-21, Tables 5.2 and 5.3: Would be informative to include actual P-values rather than “n.s.” if available.

Page 5-26, Tables 5.4, 5.5, 5.6: In describing table, it would be informative to specify that null is 0.50 (correct?). Also, please specify P-value rather than “n.s.” In comparing “Exposure with Exercise” to “Exposure at Rest,” should we compare to each other rather than to null? That is, is fraction responding with “exposure with exercise” significantly different from those with “exposure at rest”?

Page 5-29, Figures 5.1 and 5.2: Very informative. Could we see similar presentation for “exposure with exercise”?

Figure 5-2: What % of individuals had doubling?  $19/66 = 23\%$

3. *To what extent is available information on health effects related to personal and indoor NO<sub>2</sub> adequately considered in conclusions?*

Chapter 3 (Exposure Assessment) provides a very thoughtful and thorough examination of the state of knowledge regarding NO<sub>2</sub> exposures. Most importantly, Chapter 3 puts this information in context for evaluating the approaches and implications of these approaches for epidemiologic inference. Chapter 3 therefore provides an excellent base for evaluating exposure assessment methods used in the epidemiologic studies. This cross-chapter integration is a major strength of this revised ISA.

The epidemiologic studies in Chapter 5 and 6 are evaluated in the context of the NO<sub>2</sub> exposure estimate approaches. Whenever possible, epidemiologic associations are compared stratified by the exposure assessment approaches. NO<sub>2</sub> exposure assessment is a rapidly evolving. This evaluation of the effect of alternative NO<sub>2</sub> exposure assessment approaches is a major strength of this ISA.

4. *Critical evaluation of potential confounding by traffic-related exposures in epidemiologic studies?*

This ISA appropriately and consistently evaluates the potential for confounding by co-pollutants or other traffic related exposures. The ISA makes it clear that the failure to consider these potential traffic related co-pollutants or confounders is a weakness in almost all of the existing epidemiologic studies. This is not to say that these studies are not informative. Most importantly, the ISA appropriately integrates information across studies and approaches to evaluate the likelihood that such confounding is likely to be important in these studies.

5. *To what extent are the strengths, sources of bias, and uncertainties in the integrated evidence base adequately considered in forming causal determinations?*

I can understand the need to provide guidelines for each of the three approaches - controlled human exposure, animal toxicology, and epidemiology, as in Section 5.1.2 and Table 5-1. As stated one would hope “to improve standards of reporting and ensure that data ... can be fully evaluated.” Indeed, it is helpful in integrating information across approaches to have some understanding basic concepts of study design, subject/model selection, exposure assessment, outcome assessment, and statistical analytic approaches. Nevertheless, one should not expect such lists to substitute for experience and expertise in each of these fields of study.

Thus the criteria for evaluating epidemiologic studies (such as STROBE guidelines), should not be considered as defining study quality. These are guidelines representing common best practice. However, such guidelines are backward looking and would downweight innovative designs and analyses, or even deem them inappropriate based on historical practice. For example, time series or case-crossover studies would be classified as uninformative in NAAQS reviews in the 1990’s using earlier sets of guidelines, whereas they have been shown to be robust, reproducible, and highly informative. Moreover, proscriptive guidelines are inconsistent with the integrative approach being used in this evaluation. Rather guidelines encourage a deconstructive evaluation of individual studies, that is checking off which study characteristics are not met within the list of positive characteristics.

There is no indication in the ISA that these guidelines are being used as criteria for acceptable studies. However, we should be on guard to ensure these do not become checklists in some sense.

Page 5-11: Not clear why confounding in epidemiologic studies is specifically highlighted by a separate Section.