Preliminary Comments on the Policy Assessment from Dr. Douglas W. Dockery

Chapter 5 – Preliminary Conclusions on Adequacy of the Current Primary NO2 Standards:

1. *What are the Panel's views on staff's preliminary conclusions regarding adequacy of the current standards and on the public health policy judgments that support those preliminary conclusions? Does the discussion provide an appropriate and sufficient rationale to support staff's preliminary conclusion that it is appropriate to consider retaining the current standards, without revision, in this review?*

The PA provides a clear synthesis of the basis for the determination of a "causal" relationship between short-term NO_2 exposure and respiratory effects, specifically asthma exacerbation. There is growing epidemiologic evidence for this relationship, but the correlation between NO_2 and other traffic-related co-pollutants in real world settings makes it impossible to separate the specific effect of NO_2 in existing epidemiologic studies. Thus the available controlled short-term NO_2 exposure studies of asthmatic subjects provides confirming experimental evidence of the specific effect of NO_2. The Brown (2009) meta-analysis provides an important synthesis of the effects on a recognized clinical indicator, halving of provocative dose. While these controlled exposure studies are at concentrations above the standard or commonly observed NO_2 concentrations in the US, and they do not show an exposure response, they provide experimental confirmation of clinical asthma exacerbation in asthmatic subjects. Note, that while the subjects in these studies were asthmatics, there is a range of response in the population even among asthmatics, and these study participants were no doubt not the most sensitive.

The evidence for a "suggestive" relationship of short-term NO_2 exposure and triggering of acute cardiovascular events in epidemiologic studies is growing. However, this body of epidemiologic evidence lacks confirmation by understanding of mechanisms and by experimental studies. Thus the PA appropriately has not characterized this relationship as "causal" yet, but informative further studies could quickly change that evaluation.

- Given the body of evidence in the ISA, I would agree that there is not a basis for modifying the level or averaging time of the short-term NO_2 standard.

The PA also provides a clear synthesis of the evidence for the determination that there is "likely to be a causal relationship" between long-term NO_2 exposures and respiratory effects, that is development of asthma in children. The development of improved home-specific estimates of exposures to NO_2 and correlated traffic-related co-pollutants has led to multiple epidemiologic studies showing such associations in children. Mechanistic studies in animals support this evidence, but extrapolating from these animal models to children is tenuous. Thus the characterization remains "likely" until more informative animal models are found.

Similarly there is developing epidemiologic evidence of associations of long-term exposures to NO_2 and other traffic-related co-pollutants with incidence of a number of health outcomes including total mortality, cardiovascular disease, diabetes, birth outcomes, and cancer. However, this body of epidemiologic evidence is weaker, and lacks confirmation of specific links to NO_2 by mechanistic or experimental studies.

- Given the body of evidence in the ISA, I would agree that there is not a basis for modifying the level or averaging time of the long-term NO_2 standard.

2. What are the Panel's views on the areas for additional research that are identified in Chapter 5? Are there additional areas that should be highlighted?

The PA describes the need for future research and data collection in three areas. Let me comment on each in turn.

Interpretation of Epidemiologic Evidence

With the development of improved exposure assessment methods for traffic related pollution, the epidemiologic body of evidence for health effects of these exposures is growing rapidly, both for short-term and long-term exposures. In addition, a much wider array of health outcomes is being investigated, including no only respiratory, but also cardiovascular, cardio-metabolic, birth outcomes, cancer, and others not considered in the ISA. The correlation of NO_2 with other traffic-related co-pollutants will continue to be problematic in these studies. This is a constraint on epidemiologic studies by the nature of exposures in the real world, and will not be solved by improved analytic methods.

We can examine the specific effects in epidemiologic studies if we can find populations or situations in which NO_2 exposures are not predominately from traffic sources. (A historical example would be the epidemiologic studies of ambient nitrogen dioxide exposures from TNT and fertilizer production in Chattanooga in the 1970's.) In that sense, examination of the epidemiologic evidence from studies of indoor NO_2 exposures could be informative.

The other option would be to examine ambient exposures with varying levels and correlations of NO_2 with other traffic-related co-pollutants. As noted, the multi-city studies of short-term effects have been very informative. Combining data across the US and Canada, where we see substantial differences in ambient NO_2 exposures should be considered. The body of epidemiologic evidence for NO_2 and traffic related co-pollutants is growing even faster in Europe. The focus on US and Canadian studies is missing this body of evidence, but more importantly missing the opportunity to examine the contrasts in the mixtures of NO_2 with other traffic-related pollutants across populations in the US, Canada, and Europe.

Data Collection and Methods Development

The PA highlights the value of the near-road monitoring network for improving NO_2 exposure for health effects assessment. Improved exposure models which will be informed by near-road monitoring of traffic-related air pollution will improve epidemiologic studies and risk assessment. However, current epidemiologic studies have used short term monitoring programs to develop such city-specific models. The residential or population oriented monitoring network will remain the essential part of long-term epidemiologic studies.

As noted above, the advances in the epidemiology of NO_2 exposures will come from multi-city or multi-location with contrasting mixtures of NO_2 and other traffic-related co-pollutants. Thus effort to provide comparable data across a wider range of different climatic zones in North America, and different cities in the developed world more broadly would be more informative.

Again as noted above, development of low-cost sensors to characterize the short-term exposures to NO_2 and co-pollutants indoors would also be informative for advancing the epidemiology.

Airways Responsiveness in Controlled Human Exposure Studies

The controlled human NO_2 exposure studies conducted in the 1980's and 1990's, and recently synthesized in meta-analyses, were critical to identifying NO_2 as having a "causal relationship" with asthma exacerbation. While sensitive subjects (asthmatics) were studied, they were not the most sensitive. The value contributed by these studies was not in identifying a safe level, or in showing (or not showing) exposure response. Rather it was in demonstrating experimentally a clinically relevant response to specifically NO_2. There is value in further examination of this NO_2-asthma exacerbation pathway, however, I would suggest that there is more value in examining pathways for other health outcomes.

As noted earlier, given the improved exposure assessment methods, the body of epidemiologic studies reporting associations of NO_2 with cardiovascular disease, cardio-metabolic disease, birth outcomes, and cancer is growing rapidly. Indeed, in terms of total public health impact, these health outcomes are likely much larger than asthmatic exacerbation. The weakness in the evidence for a causal association is the specific link to NO_2. Controlled human NO_2 exposure studies would be most informative, but are unlikely to be feasible for most of these outcomes. However, controlled animal NO_2 exposure and other mechanistic studies would be particularly informative for the next NO_2 NAAQS review.