Dr. Ronald E. Wyzga

Charge Questions for Chapters 4 and 5:

a. *To what extent do the discussions in this chapter accurately reflect the body of evidence from epidemiologic, controlled human exposure and toxicological studies?*

The information provided is mixed. In some cases it is extensive and helpful in reaching a concluison. In other cases, the information provided needs to be augmented. It is not always clear when and which co-pollutants were considered in analyses. Some portions of the description do not differentiate among co-pollutants. The statistical significance of results is often not indicated, and summary statements such as "positive but imprecise" are not helpful. See specific comments below.

c. *Please comment on the adequacy of the discussion of the strengths and limitations of the evidence in the text and tables within Chapters 4 and 5 and in the evaluation of the evidence in the causal determinations.*

It varies thoughout the chapters. In some cases the inout for the evidence is comprehensive and allows one to make a reasonable judgment; in other cases it is not. See specific comments below.

d. *What are the views of the panel on the integration of epidemiologic, controlled human exposure, and toxicological evidence, in particular, on the balance of emphasis placed on each source of evidence? Please comment on the adequacy with which issues related to exposure assessment and mode of action are integrated in the health effects discussion. Please provide recommendations on information in other chapters of the ISA that would be useful to integrate with the health effects discussions in these chapters.*

Again the integration differs according to the health endpoint considers. See specific comments below. In general, there is limited discussion of the relationship between personal and ambient exposures and how these differences could impact the results.

e. *Please comment on the appropriateness of using experimental and epidemiologic evidence for morbidity effects to inform the biological plausibility of total mortality associated with short-term (Section 4.4) and long-term (Section 5.5) NO2 exposure and in turn, to inform causal determinations.*

This is clearly appropriate.

f. *Section 4.2.2 discusses the effect of short-term NO2 exposure on airways responsiveness. This section focuses primarily on an EPA meta-analysis developed for this ISA of airway responsiveness data for individuals with asthma and secondarily on the potential of various factors to affect airways hyperresponsiveness independently or in conjunction with NO2 exposure in controlled human exposure studies. This material presently is unpublished and we ask the Panel to provide the peer review for the analysis, in particular, to comment on the appropriateness of the methodology utilized for the meta-analysis, the conclusions reached based this analysis, and its use in the draft ISA. With regard to factors potentially affecting airways responsiveness, please comment on the adequacy of this discussion. Are there other modifying factors that should be considered?*

   I for one would like to see this information presented in a paper format before making any judgments about suitability for publication.

g. *The 2008 ISA for Oxides of Nitrogen stated that one of the largest uncertainties was the potential for health effects observed in association with NO2 exposure to be confounded by correlated copollutants. To what extent has evidence that informs independent effects of NO2 been adequately discussed in Chapters 4 and 5 and appropriately interpreted as reducing uncertainty (for example, evaluation of copollutant model results)? Has the current draft ISA appropriately considered recent epidemiologic findings regarding potential copollutant confounding in causal determinations? Please provide comments specifically for respiratory effects, cardiovascular effects, and total mortality of short-term NO2 exposure.*

   The consideration of co-pollutants varies considerably throughout the document. See specific comments below. It is clear that some co-pollutants are more relevant than others in that their concentrations in ambient air are correlated with those of NO2 and there is some evidence suggesting that these co-pollutants are also associated with the health effect under consideration. Ideally one would have the resources to examine all competing co-pollutants, not only in each study, but also in terms of evaluating their roles in impacting the health effects studied. For example, is there greater evidence associating some cardiovascular endpoint with EC than NO2? The other issue that is laregely ignored is the role of NO2 in a complex air pollution mixture. Unfortunately the exisiting framework for considering NAAQS precludes or greatly limits this consideration.

h. *To what extent is the causal framework transparently applied to evidence for each of the health effect categories evaluated to form causal determinations? How consistently was the causal framework applied across the health effect categories? Do the text and tables in the summaries and causal determinations clearly communicate how the evidence was considered to form causal determinations?*

I do not believe that it is consistent. I was particularly troubled with its application to reproductive effects. Perhaps better guidance from the Agency on the extent of evidence required to make a causal inference could help here.

i. What are the views of the panel regarding the clarity and effectiveness of figures and tables in conveying information about the consistency of evidence for a given health endpoint? In particular, was the use of the tables and figures in both the text and online in the HERO database effective in providing additional information on the studies evaluated? Are there tables and figures in the ISA that would be more appropriate to include as a resource in the HERO database?

The value of the information in Tables and Figures varied considerably. I felt that more attention should be given to the influence of co-pollutants on analytical results.

Specific comments:

Executive Summary: I assume that changes in the document will be reflected in any revised Executive summary.

Chapter 1:

I assume this Chapter will be rewritten when the document is revised; I nevertheless provide comments on this Chapter as well as on the material in subsequent chapters.

p. 1-13, l. 24: From what we know from existing studies, there may be some indication of the co-pollutants of particular concern in teasing out the influence of NOx as opposed to co-pollutants. I would like the document to acknowledge the co-pollutants of greatest concern and to indicate where they have or have not been considered. There are parts of the document that appear to accept that consideration of co-pollutants is adequate if the issue is partially addressed.

p. 1-16, ll. 13-20: Given the potential role for co-pollutants, it might be useful to provide a brief understanding of the biological plausibility for the co-pollutants of greatest concern.

ll. 23-26: to what extent were co-pollutants addressed in this study?

p. 1-17, ll. 19-33: to what extent were co-pollutants addressed in theses studies?

p. 1-19, ll. 32-35: Can we say anything about the biological plausibility of the relevant co-pollutants of concern?

p. 1-20, ll. 14-18: I am concerned about the roles of EC and OC as well.

p. 1-21, ll. 9-10: See above comment.

p. 1-23, l. 13: See above comment.

p. 1-24, ll. 14-16: or that traffic was not appropriately characterized. I don't find this to be a strong argument.

p. 1-25, ll. 1-3: Were these results independent of relevant co-pollutants?

p. 1-27, section 1.4.7: There could be some discussion of nitro-PAHs and known carcinogens that form when NOx is present on the atmosphere. Also, the issue of latency or of the historical levels of NOx should be discussed.

p. 1-29, Table 1: OC should also be mentioned as co-pollutant of interest. The biological plausibility argument ignores the mixed results seen in experimental studies. Recent studies provide some additional evidence but do not resolve the issue of whether NOx effects are independent of co-pollutants. There is remaining uncertainty that need be mentioned.

p. 1-30: I am also concerned about the limited studies that also examined co-pollutants, particularly EC and OC, which have been shown to be associated with cardiovascular effects in other studies.

p. 1-31: See above comment.

p. 1-32: See above comment.

p. 1-33: See above comment.

p. 1-27, l. 2: add OC as well.

ll. 11-12: This does not mean that NOx is a poorer surrogate than other pollutants; it does suggest that the correlations between NOx and other pollutant s are not constant over the gradient from roadways. The value of a pollutant characterizing traffic is dependent on how one defines that gradient. Unfortunately, we generally only have data from the monitoring station.

ll. 15-26: Given the higher correlations between NOx and CO and EC (I would also add OC.), more attention should be given to these pollutants in the document.

ll. 32-33: the key co-pollutants are in line 33 except possibly for PM in line 32. There are also some findings to the contrary. This summary ignores the many cases where co-pollutants did change the results for NOx.

p. 1-41, ll. 23-28: there are also studies where the contrary is true: a traffic effect persists and the NOx association goes away with adjustment for traffic; hence there are two sides to this argument and the document only discusses one side.

p. 1-43, ll. 3-17: This discussion should also discuss differences in measurement error.

p. 1-49, ll. 5-11: Indoor exposures could also play a role here.

p. 1-54, l. 24: I would delete the word “compelling”.

p. 1-55, l.4: There are also people who travel on roads.

p. 2-70, l. 8, l. 19: define “moderately”.

This section also needs to consider EC and OC in more detail and to differentiate between spatial and temporal correlations.

Table 2-4: Add a column EC (and possibly OC).

p. 2-77, Figure 2-19: Add rows for EC, OC.

p. 2-84: ll. 4-6: This may explain why there are seasonal differences in results as presented in Chapter 5.

ll. 10-20: This result troubles me and its implications for the study results in Chapters 5 and 6 need be discussed.

p. 2-85, Table 2-9: What is the difference between “ambient” and “outdoor”?

p. 2-90, Table 2-10: It would be interesting to see what the correlations are between personal NO2 and ambient levels of relevant co-pollutants.

p. 2-93, ll. 8-20: Good discussion.

p. 4-3, l. 19: for ozone, PM, and CO. But can we say anything about EC, OC, UFP, or organics?

l. 25: are these concentrations relevant?

p. 4-4, ll. 6-8: and the low correlations between personal exposures and ambient levels of NO2.

p. 4-13, l. 15: Is there a clear and accepted definition of “adverse”?

p. 4-31, Figure 4-1: Can this be redrawn with results when co-pollutants were considered?

p. 4-33: Why is there a discrepancy in the Holguin results presented in Table 4-7 and in Figure 4-1?

p. 4-34: The Spira-Cohen et al. results suggest that another pollutant (EC) is more important. This indicates the difficulty of making inferences when the focus is on only one pollutant.

p. 4-35: Why is there a discrepancy in the Dales et al. results presented in Table 4-7 and in Figure 4-1?

p. 4-53, ll. 26-28: Can we have a Table or Figure which clearly shows the influence of co-pollutants on the Estimated NO2 effects. I also have problems with lumping all co-pollutants together; some are clearly more correlated with NO2 than others. It is the more highly correlated pollutants that need be addressed.

p. 4-55, l. 13: Do not lump all co-pollutants together.

p. 4-85, ll. 8011: Why is this result not presented in Chapter 3?

p. 4-86, Figure 4-2: Can results with co-pollutants be added to this Figure? Why is the all subject personal exposure result of Delfino not represented in this figure?

p. 4-88: Why is there a discrepancy in the Greenwald et al. results presented in Table 4-14 and in Figure 4-2?

p. 4-100, ll. 4-6: It should be noted that co-pollutants were not considered in these results. I also think the differences between indoor and outdoor exposures in Greenwald et al. are relatively ambiguous.

p. 4-101, 1l. 3-30: I would urge the authors to consider each co-pollutant separately.

p. 4-102, ll. 23-30: Ozone and SO2 are less relevant co-pollutants as others, such as CO, EC, OC.

p. 4-108, l. 18: But there are counter examples as well: Greeenwald et al., Lin et al., and Timonen et al.

p. 4-108, ll. 30-32: But there are also the cases where there is little correlation between personal and ambient exposures. See p. 2-84. To be fair these results should also be discussed here.

p. 4-113, l. 13: are these exposures relevant?

p. 4-124: Can we include results with co-pollutants in Figure 4-3? Why are the results of Schildcrout et al., Gillespie-Bennett et al., and Zora et al. not included as well as the wheeze results of Spira-Cohen et al.?

p. 4-136, l. 5: What does "imprecisely associated" mean?

l. 34: can the authors provide a range of multidays.

p. 4-137, ll. 9-12: Although the estimates are positive they are not statistically significant. Positive results are noteworthy, but statistical significance also plays a role, and given the numerous tests in a given study, the multiple comparisons issue should also be raised.

l. 14: I don't think one can fairly support the "independent association" assertion. The only co-pollutants considered are not the most relevant ones: CO, EC, OC. Several studies found effects of the other pollutants as well. Anderson et al. reported significantly diminished results when NO2 was considered jointly with PM10.

l. 36: and in some cases lost statistical significance.

p. 4-144, l6: Robust in what way? Across cities, robust to consideration of co-pollutants?

p. 4-145: l. 19 but lost statistical significance.

p. 4-146, l. 1: "Robust" in what sense?

P. 4-153, ll.. 1-4: Do you mean to imply that Cakmak et al. did not consider single pollutant models?

p. 4-154: Many of the associations presented on this page were not statistically significant; although statistical significance is not the "end-all", it is noteworthy and it should be clearly indicated whether a result is or is not statistically significant. I also note that there are often many statistical tests performed within the context of a specific study or paper; hence there is also a multiple comparisons problem which is rarely addressed. This could impact results that are barely statistically significant, such as the result of Son presented on p. 4-153.

ll. 7-8: were these associations statistically significant; it would useful to present the estimates and confidence intervals for the shorter lag results.

p. 4-155, ll. 31-33: what is meant by "remained robust"; remained positive but not statistically significant?

p. 4-158, ll. 1-7: This portrays one of the conundrums we face with NO2 results. Associations tend to be stronger in the warmer months when NO2 levels are lower. Some discussion of this issue should be included; it could be that individuals spend more time outdoors in warmer months; hence personal exposures may be higher. Do we have any data to address this possibility?

p. 4-160, ll. 17-18: it should be noted that although this result is positive, it is not statistically significant.

p. 4-167, Figure 4-5: I find the results of Darrow et al. curio8us. Why is the association between day and night exposures so different? I would expect daytime exposures to be more highly associated with personal exposures. Some discussion of this issue could be of value.

p. 4-167, l. 20: “positive”, but not statistically significant.

p. 4-171, ll. 11-12: Can we generalize to all central monitors? I suspect the results are dependent upon monitor location with respect to sources and terrain.

p. 4-173, ll. 9-12: Results were positive but not statistically significant.

p. 4-176, ll8-13: It would be better to consider the possible co-pollutants individually rather than lumping them all together.

p. 4-177, Figure 4-9: can results with co-pollutants be included here as well.

p. 4-179, ll. 20-22: were results statistically significant?

p. 4-184, ll. 17-19: It should be noted that BC, EC, UFP, PNC appear to influence the results of NO2 associations more than other pollutants.

p. 4-185, ll. 12-14: I find this result troubling. If NO2 per se were responsible for effects, we would expect stronger results for personal exposures.

ll. 27- : There nevertheless remain uncertainties; to be comprehensive, this paragraph should mention these as well.

p. 4-186, l. 7: I would delete the word “compelling”.

p. 4-197, l. 32: which other pollutants?

p. 4-198, ll. 1-15: did these studies consider co-pollutants?

ll. 18-24: the results using personal or indoor exposures should also be presented here as well as the results for co-pollutants.

p. 4-199, ll. 5-9: Can estimates and confidence intervals be presented here? Were the results statistically significant?

p. 4-200: Table 4-25 should also present results for co-pollutants.

p. 4-209, l. 3: present numbers. What is “borderline”?

p. 4-232, ll. 12-14: can numbers be presented; to what extent were they attenuated or less precise. Which results were statistically significant?

ll.26-28: Given the limited consideration of the co-pollutants that are most relevant, this statement is an overstatement.

p. 4-236, l. 1: EC was not considered.

ll. 28-38: can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 4-237, ll. 8-9: But was EC considered in any co-pollutant analyses?

p. 4-246, ll. 4-5: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 4-247, ll. 9-11: but only a limited number of co-pollutants were considered; given this, the conclusion is too strong.

p. 4-248, l. 7: insert “limited” before “copollutant models”.

P. 4-254, Figure 4-16: It is important to identify which co-pollutants were considered in each case.

p. 4-255, Table 4-35: See above comment.

p. 4-256, ll. 7-8: Given the uncertainties and limited examination of results from co-pollutants, is this conclusion justified? I believe it is too strong.

Table 4-36: Some of the key co-pollutants (e.g., EC,OC) were not considered. In some cases the effects of EC were greater than NO2.

p. 4-267, ll. 19-21: what about other important co-pollutants?

ll. 24-27: which copollutants were considered?

p. 4-269, ll. 20-30: Was there any explicit consideration of NO2 per se?

p. 4-285, Table 4-41. It is important to articulate those copollutants considered. Grouping them is not helpful.

p. 5-5, l. 37: This result is not statistically significant.

p. 5-4-18: Section 5.2.2: This section should indicate whether any co-pollutants were considered? Also it is important to indicate which results were statistically significant and which were not.

p. 5-19-24: Section 5.2.2.2: The above comment applies here as well.

p. 5-24-34: Section 5.2.3.1: Same comment as above.

p. 5-36, ll. 3-26: Were any co-pollutants considered?

P. 5-37,l 4. : Can you provide numbers? What is meant by attenuated? Does significance change?

ll. 7-38: Were any co-pollutants considered?

p. 5-38, ll. 1-19: Were any co-pollutants considered?

p. 5-39, ll 16-27: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 5-41, Table 5-3: I don’t understand the first paragraph under Comments. Please clarify p. 5-42: Are there any co-pollutant model results for Gehring et al.

p. 5-45, L.4: Can numerical results and confidence intervals be presented? Were the results statistically significant?

l. 21-22: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 5-46, l. 8: what does” positive but imprecise” mean? Can numerical results and confidence intervals be presented? Were the results statistically significant?

ll. 17-28: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 5-47, l. 8: what were the other measures? Co-pollutants?

p. 5-48, ll. 1-7: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 5-49, ll.20-21: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 5-60, l. 29: does “fully adjusted” include adjustments for co-pollutants?

p. 5-71 ll. 1-2: what about EC and OC?

p. 5-72, ll. 4-5: I have problems with looking at the significance of correlation co-efficients; given enough observations, any non-zero correlation will be significant; I don’t know what this really means.

p. 5-84,ll. 17-20: This suggests the importance of considering co-pollutants in order to understand the role of NO2 in observed health effects.

l. 31: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 5-85, ll. 1-17: Are there any results from analyses with co-pollutants?

p. 5-93: Table 5-12: Please indicate which studies demonstrated statistically significant associations, with and without consideration of co-pollutants

p. 5-97, ll. 28-31: what about other co-pollutants EC, OC, PM?

p. 5-117, Table 5-13: Do any of these studies consider co-pollutants? Which ones?

p. 5-124, ll. 13-16: Do we really have sufficent evidence to make this assertion? To what extent were co-pollutants ruled out? How much of the limited evidence is statistically significant?

ll. 28-31: Do we really have sufficent evidence to make this assertion? To what extent were co-pollutants ruled out? How much of the limited evidence is statistically significant?

p. 5-25, ll. 6-9: Do we really have sufficent evidence to make this assertion? To what extent were co-pollutants ruled out? How much of the limited evidence is statistically significant?

p. 5-126, Table 5-15: Please indicate which results are statistically significant? And which have considered co-pollutants?

p. 5-132, ll. 9-13: Can numerical results and confidence intervals be presented? Were the results statistically significant?

ll. 23-32: Can numerical results and confidence intervals be presented? Were the results statistically significant?

l. 24: What is meant by “less precise”?

P. 5-133, 1-5: Can numerical results and confidence intervals be presented? Were the results statistically significant?

p. 5-143, Table 5-19: Please clarify the differences between Krewski et al. (2000) and Krewski et al. 2009. They appear to give conflicting results.

p. 5-156, Table 5-21: If there is an association between NO2 and cancer, there is clearly a latency period, and concentrations for the epidemiological studies in this table should reflect this latency.