SBA Questions/Comments on Tetrachloroethylene (Perc) Tox Review 8/25/11 v.2

I. NRC on Use of Seeber (1989):

The NRC recommended the use of studies by Altmann et al. (1990), Cavalleri et al. (1994) as a baseline for Gobba et al. (1998), and Echeverria et al. (1995). EPA agrees with the NRC choices for RfD and RfC studies with the exception of using Seeber (1989) instead of the NRC – preferred Altman (1990) and Boyes (2009). EPA explains it prefers to use chronic studies over acute studies, and identifies Altman (1990) and Boyes (2009) as acute studies. Appendix A-4

EPA has chosen to use Seeber in the RfC and RfD derivations, despite this criticism below by NRC. Why is Seeber OK to use? EPA explains that it used Seeber (1989) because of its "strong exposure characterization, large number of subjects, and inclusion of an unexposed controlling confounding variables" but doesn't mention any weaknesses. Appendix A-4. Does EPA have more details from other peer reviewers or public comments about weaknesses of Seeber – what are the other strengths or weaknesses? NRC just listed one problem in its justification of excluding Seeber. EPA should disclose all strengths and weaknesses of all reports that are used or excluded – which is a strong theme of this NRC review and several others.

Pages 86-87 :

"The committee found that EPA reviewed all the relevant studies available at the time that the draft was written and agrees with many of the limitations that are noted, beginning on page 4-101. The committee also found, however, that the draft sometimes failed to consider weaknesses in study methods or inconsistencies in results, two factors that should carry great weight in selecting key studies for calculating an RfC.

For example, test outcomes (neurologic signs, emotional lability, choice reaction time, cancellation d2, and digit symbol) in a study by Seeber (1989) were worse in the low-exposure group compared with the high-exposure group. EPA's discussion of the study (Section 4.6.1.2.2) did not mention that discrepancy."

2. NRC on Altman (1990) and Boyes (2009)

Why does EPA reject the recommendation of Altmann (1990) and Boyes (2009)? This appears to be a strong recommendation, particularly for Boyes (2009) , which pales in comparison to EPA's rationale of preferring chronic to acute studies. Appendix A-4.

Page 41 :

"The committee recommends the use of studies by Altmann et al. (1990), Cavalleri et al. (1994) as a baseline for Gobba et al. (1998), and Echeverria et al. (1995). A new animal study by Boyes et al. (2009)

also provides a strong basis for a point of departure. Those five studies provide a stronger scientific basis for deriving the RfC and RfD."

3. NRC on Genotoxicity

What is the EPA response to this comment (still reviewing Appendix A)?

Page 50:

"The committee found that the publications cited and discussed by EPA are relevant but that the summary does not reflect the entire knowledge base available on the topic and does not provide transparent means for assessing the genotoxicity of tetrachloroethylene itself or its metabolites. The draft IRIS assessment predominantly reports positive studies, whereas good studies that had negative results are not mentioned or in some cases are incorrectly described as having had positive results. The committee therefore recommends that a more balanced, transparent, and inclusive approach be used to consider the evidence. The sections below offer some specific guidance."

Pages 57-8:

"In conclusion, there is no convincing evidence that tetrachloroethylene has important genotoxic or mutagenic activity in intact organisms. The committee agrees with EPA's conclusion that several metabolites of tetrachloroethylene are clearly genotoxic: TCVG, TCVC, N-Ac-TCVC, tetrachloroethylene oxide, DCA, and chloral hydrate. However, it is still questionable whether the metabolites of tetrachloroethylene play an important role in the mode of action of tetrachloroethylene carcinogenesis (see Chapters 6-8) in view of the absence of convincing evidence of mutagenic and tumor-initiating activity of tetrachloroethylene in vivo. Additional studies of genotoxicity in vivo with state-of-the-art methods would be valuable.

As noted above, the committee recommends that EPA provide an expanded and more integrated discussion of the genotoxicity data. The presentation could be improved by the use of tables detailing the primary evidence, by separate discussion of the genotoxic evidence on tetrachloroethylene and its metabolites, and by a more critical analysis of the studies."

4. NRC on JISA Study

What is the EPA response to this comment (still reviewing Appendix A)?

Page 77 :

"In the 1993 JISA study, F344/DuCrj rats were exposed to tetrachloroethylene at 50, 200, and 600 ppm. The draft IRIS document focuses on the JISA report for cancer dose-response assessment because the study included a 50-ppm exposure concentration, which is one-fourth the lowest exposure concentration in the 1986 NTP study. As in the NTP study, there was a high incidence of MCL in the controls (22% in males and 20% in females). Against that high spontaneous incidence of MCL, the

incidence of MCL in male and female rats exposed to tetrachloroethylene at 50, 200, and 600 ppm was 28%, 44%, and 54% and 34%, 32%, and 38%, respectively. Moreover, the historical rate of MCL for the Japanese laboratory is very high. There was no incremental increase in MCL incidence in female rats with increasing dose. In contrast, EPA concluded that male rats displayed a dose-dependent increase in MCL although in the analysis background values were subtracted from the incidences in animals treated with tetrachloroethylene (Figure 5-6 in the draft IRIS assessment), and this may lead to a false impression. *Such manipulation of data is not widely accepted in statistical practice, because it artificially reduces the uncertainty caused by the variation in the background rate. [italics added]* As noted in reviews by Caldwell (1999) and Ishmael and Dugard (2006), the unusually high background rate of MCL in control (untreated) rats weakens the ability to separate the background response from possible chemically induced responses, particularly when the chemically induced response above background is low. The committee recommends that the statistical approaches applied by Thomas et al. (2007) to the NTP study be applied also to the JISA study.

*It is unclear whether MCL is a relevant predictor of human leukemias or other adverse health effects. [italics added.]*Thomas et al. (2007) argue that MCL is a large granular lymphocytic leukemia (LGLL) of natural-killer (NK) cell origin that shares "some characteristics" with a rare human NK-LGLL. However, they also note that in contrast with F344 rats, human NK-LGL leukemia is rare, occurs primarily in the young, and may be associated with Epstein Barr virus (EBV) although no such virus-leukemia association is known to contribute to the etiology of rat LGLL/MCL."

5. NRC on Rental Toxicity and Cancer

What is the EPA response to this comment (still reviewing Appendix A)?

Page 78:

"The EPA draft IRIS assessment concludes (p. 4-184) that the epidemiologic data "suggested an association between lymphoma and tetrachloroethylene." *The committee concurs with that conclusion but would add that the data are relatively weak and inconsistent. [italics added]* Associations between those cancers and exposure to tetrachloroethylene are based on very small numbers and thus are statistically unstable."

Page 80:

"The majority of the committee finds that EPA has not adequately justified the use of MCL data over the evidence for liver or kidney cancer in its cancer risk assessment. Evidence of tetrachloroethylene-induced leukemia from epidemiologic studies is limited and inconsistent. *The NTP (1986) and JISA (1993) study results of increased MCL incidences in F344 rats given tetrachloroethylene by inhalation are also questionable because of the high background rates of MCL in control animals. [italics added]* More thorough statistical evaluation of the data, such as the life-table analysis proposed by Thomas et al. (2007), could provide a stronger basis for drawing conclusions. However, MCL resulting

from tetrachloroethylene exposure has not been observed in other strains of rats or other animal species, and no definitive evidence is available to support a hypothesized MOA by which tetrachloroethylene increases MCL in F344 rats. Those are all sources of uncertainty surrounding the relevance of MCL to human cancer risk. The information is considered in the context of the other evidence on carcinogenicity in Chapter 11, where EPA's assessment of carcinogenic risks of tetrachloroethylene is evaluated."

6. NRC on General Review of EPI Studies

What is the EPA response to this comment (still reviewing Appendix A)?

Pages 81-2:

"The draft IRIS assessment does not provide the detail and methodology used for evaluating literature. Overall, it appears that the procedure was to accept the results of positive studies with little critical evaluation of validity and to dismiss null studies of similar or better methodologic rigor as flawed. If it is EPA's intention to err on the side of protecting public health when reviewing the literature, that should be stated clearly in the document. Otherwise, a clearer discussion of criteria used to identify studies of merit and a more balanced critique would strengthen the draft IRIS assessment.

The draft's critiques of studies are often uneven; studies that found no association are criticized more often than studies that found a positive association even if they had similar methodologic limitations."

7. NRC on Lynge Study [No Cancer Risk from Occupational Exposure to TCE – Laundry and Dry Cleaner Workers in Scandinavia]

What is the EPA response to this comment (still reviewing Appendix A)?

Pages 82-3:

"One of the most troubling misunderstandings is related to the dismissal of the results of the 2006 study by Lynge et al. In reference to that study's findings on non-Hodgkin lymphoma (and later on bladder cancer), EPA notes that exposure information was not available on about 20% of cases and of controls and that much of the exposure information came from next of kin. It then uses that to explain why Lynge et al. found no risk associated with tetrachloroethylene exposure and suggests an automatic bias toward the null due to misclassification. In the first instance, missing exposure data are analogous to nonresponse in that the subjects are not included in any classification group. Nonresponse will not introduce bias if it is nondifferential; if it is differential, it could bias an effect measure either toward or away from the null. In the second instance, exposure information from next of kin make it more likely that hazardous exposures will be overreported by the families of workers who developed cancer than by families of workers who did not; this would have resulted in overestimation, not attenuation, of the association. Similar arguments regarding the study are incorrectly made for other cancer sites, and the draft refers to the study as "uninformative." It is unclear why Lynge et al. (2006) received such critical review and papers that were methodologically less sound were accepted with little comment."