Supplemental Step 6 SBA Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Tetrachloroethylene (PCE) (dated June 2011)

September 2, 2011

1. In various places through the NRC report, the committee notes that EPA needs to produce a document with a "more balanced, transparent and inclusive approach" in considering the evidence. (See page 65 regarding genotoxicity evidence, as an example). "The draft critiques of studies are often uneven; studies that found no association are criticized more often that studies that found a positive association even if they had similar methodologic limitations." Page 82. We are concerned that EPA continues to struggle with these transparency and balance issues even with the revised draft. Given our resources, and the large number of pages to review, we have only skimmed the surface on identifying these problems. We urge EPA to redouble its efforts to identify and resolve these continuing concerns. We provide two examples below:

2. The Mundt et al (2003) study was taken out of context, as described in the June 2008 HISA comment below, but EPA failed to revise the original text. EPA should now conform the text to provide full transparency and explain the negative cancer findings more objectively. We have not had the opportunity to review EPA's disposition of the other public comments or the NRC comments on specific studies (other than a very few), but we are apprehensive that this problem may be widespread in this new draft.

   Page 4-281 Redline

   "*Mundt et al. (2003) reviewed a body of epidemiologic studies similar to U.S. EPA's and presented conclusions as to whether an association was "likely" or "not likely." The authors 4 reported that little support existed on which to base a conclusion that tetrachloroethylene was a strong occupational risk factor, but that "because of a number of positive findings suggested from some of these epidemiological studies, one cannot definitely rule out the possibility that associations between PCE [tetrachloroethylene] and some cancers exist in humans." This conclusion is consistent with conclusions in this assessment, although it is expressed differently*."

   June 2008 HSIA Comment:

   The Agency refers to a statement by Mundt et al. (2003) that "one cannot definitely rule out the possibility that associations between tetrachloroethylene and some cancers exist . . . [as] ...consistent with this [EPA] assessment, although stated differently." This is a flagrant example of taking an isolated statement out of context in order to suggest consensus where none exists. Mundt et al. are

*clearly not convinced, stating that the evidence "argues against any tetrachloroethylene-specific association . . . [and that] a relationship between tetrachloroethylene and cancer is "unlikely" for cervical and lung cancer." Evidence is considered "inadequate for laryngeal, kidney, esophageal, and bladder cancer" (Mundt et al., 2003). Lynge et al. (1997), Weiss (1995), and the IOM (2002) draw similar conclusions (**Table 3**)*

3. The current revised draft does not accurately portray the views of the dissenting member or the NRC committee members regarding the key PPARα activation MOA issue with regard to the mouse hepatic cancers (section 4.3.5). As the NRC committee indicated in several sections regarding the initial draft, EPA "does not clearly describe the weight of evidence approach for [analyzing] the possible MOAs presented" (p. 63) and that "the draft IRIS assessment seems to be more concerned with critiquing the current dominant view in the field that the peroxisome-proliferator MOA may not be relevant to human epatocarcinogenesis than with providing evidence of links between tetrachloroethylene and this MOA." (p. 65). It is not clear that EPA has succeeded in this second try in addressing these NRC concerns and other recommendations. EPA appears to continue to have difficulty in providing a "more balanced, transparent and inclusive approach." In addition, the Appendix discussion, needs improvement. Here are suggestions for new and more accurate text.

A. Section 4.3.5 page 4-153: "Plausible Predominant Mechanism" instead of "Strongly Favors Key Role of PPARa Activation"

The dissenter states that the "weight of evidence" strongly favors a "key role for PPARa activation in the mice", whereas the EPA only reports his view as reporting that PPARa is "the plausible predominant mechanism." See excerpted text below from Appendix B of the report.

"In the members' opinion, the weight of evidence strongly favors a key role of PPARα activation in tetrachloroethylene-induced hepatocarcinogenesis in mice; furthermore, this MOA lacks relevance for human hepatocarcinogenesis. Because of the deficits in the respective presentation in the IRIS draft, the following paragraphs will briefly compile the essential data supporting the PPARα MOA for tetrachloroethylene, the role of trichloroacetic acid (TCA) as the major responsible metabolite of tetrachloroethylene, the potential roles of other MOAs, new mechanistic data supporting the lack of relevance of the PPARα MOA for humans." Page 144.

"In conclusion, there is no evidence available to suggest that MOAs other than PPARα activation have a significant impact on mouse hepatocarcinoma formation bytetrachloroethylene. Therefore, the weight of evidence supports the PPARαMOA" Page 160.

"In conclusion, the weight of evidence clearly favors a key role of PPARα activation by TCA in tetrachloroethylene-induced mouse hepatocarcinogenesis. The available evidence does not support a substantial contribution of other MOAs to hepatocarcinogenesis by tetrachloroethylene." Page 163.

Instead, EPA reports his views as simply being that PPAR α activation is the "plausible predominant mechanism", which is substantially different from "clearly favors" a "key role". Page 4-153. Although this is the description written by the NRC committee, it is more accurate to quote the dissenter about his own views. EPA should modify the description to be more accurate.

B. EPA's Description of the NRC Committee Review Omits Important Agreements with Dissenter on *PPARα Activation*

On page 4-153 of the draft IRIS Review, EPA states:

"However, in their rebuttal (also presented in Appendix B, NRC, 2010), the committee as a whole did not support these conclusions. Overall, the committee judged that many gaps in knowledge remain with regard to the MOA of tetrachloroethylene. They stated that the relevance of the peroxisome proliferator MOA to tetrachloroethylene-induced mouse hepatic cancer and to tetrachloroethylene-induced human hepatic cancer remains hypothetical and requires further rigorous testing. Hence, they concluded that it is premature to draw conclusions on the relevance of the PPARα MOA to tetrachloroethylene-induced human hepatic carcinogenesis (NRC, 2010). They encouraged an in-depth presentation of the relevant issues and data, particularly with respect to tetrachloroethylene studies. The discussion below, especially which in Section 4.3.5.4, follows these recommendations."

EPA does adequately describe the differences between the Committee and the dissenter. However, the key agreements were omitted, which are particularly important, since this relates to an issue of central importance to whether tetracholoroethylene causes cancer in humans. Indeed, it appears to the reader that the Committee's views are closer to the dissenter than with the views of NCEA, as expressed in either of the initial or revised Reviews. See additional excerpts below from Appendix B of the NRC Report in the section drafted by the committee:

"As noted by the dissenter and in Chapter 6 of the committee's report, the committee agrees that the EPA MOA characterization for hepatic cancer is inadequate and should be revised to provide a more focused and integrated analysis of the available evidence on tetrachloroethylene and its metabolites. The dissenter's statement is an attempt to provide an example of how such an analysis might be performed. The committee supports much of the dissenter's approach, but the dissenting member's conclusions go beyond those drawn by the full committee." Page 163.

The committee believes that the arguments presented are reasonable and advises EPA to review the considerations presented by the member and the recent literature cited carefully. However, the committee does not support the apparent conclusions regarding mouse hepatic cancer that TCA is the sole carcinogenic metabolite of tetrachloroethylene, that the only MOA of TCA is peroxisome proliferation, and that there is unmistakable concordance in the carcinogenic potency of tetrachloroethylene in the National Toxicology Program and Japan Industrial Safety Association bioassays and the corresponding studies of TCA. Overall, the committee judges that many gaps in knowledge remain with regard to the MOA of tetrachloroethylene and that the relevance of the peroxisomeproliferator MOA to tetrachloroethylene-induced mouse hepatic cancer and to tetrachloroethylene-induced human hepatic cancer remains hypothetical and requires further rigorous testing.

The committee generally supports the comprehensive literature review and analyses conducted by the dissenting member and recommends that EPA use them when reassessing its own evaluation. Pages 163-164.

Indeed, the committee is not yet convinced of the proof of the hypothesis that the PPARα MOA is the sole MOA of tetrachloroethylene in inducing mouse hepatic cancer. Hence, it is premature to draw conclusions on the relevance of the PPARα MOA to tetrachloroethylene-induced human hepatic carcinogenesis. Page 165.

In sum, far from disagreeing totally with the dissenter, the committee is simply "not yet convinced of the proof" of the dissenter's hypothesis the PPARa is the sole MOA, and directs EPA to carefully examine the literature and analyses conducted by the dissenter. We have been unable to verify that EPA has done so, but EPA does report that it has done so in the text. "*The discussion below, especially which in Section 4.3.5.4, follows these recommendations."* Page 4-153.

In view of the difficulty EPA had in explaining the NRC and dissenter views, we hope that EPA will increase its efforts in following the NRC recommendations. In at least one location, EPA still appears to disagree with the committee since it says "[g]*iven this knowledge, and the known complexity and heterogeneity in liver cancer development in general, the available evidence supports a hypothesis of multiple, contributing mechanistic effects that may, in turn, be affected by multiple modifying factors[.]" [page 4-181]*, whereas the committee seems to lean toward the single MOA and is simply "not yet convinced" of the single MOA. In contrast, EPA's statement on page 4-158, *"[g]iven the demonstrated mutagenicity of several tetrachloroethylene metabolites, the hypothesis that mutagenicity contributes to the MOA for tetrachloroethylene carcinogenesis cannot be ruled out, although the specific metabolic species or mechanistic effects are not known*," appears in line with the NRC committee view. Which view does EPA mean to convey? Perhaps, EPA should exercise some additional review of this text. The Appendix language on PPARa activation warrants a similar review.

4. Lastly, we are concerned that we are not reviewing the final draft assessment in Step 6, since the responses to the PBPK modeling have not yet been incorporated into this draft. While we welcome EPA's initiative in seeking important peer review comments on the PBPK modeling, our initial review of the peer review comments indicate that substantial revisions to the text are warranted (see specifically comments on page 5, for example, asking for additional explanation and clarity). We respectfully ask EPA to consider providing the final draft after incorporation of these peer review comments, for our review (perhaps in coordination of addressing the interagency responses).