Comments on Integrated Risk Information System (IRIS) Trichloroethylene (TCE) Review

General Comments

Trichloroethylene is a chlorinated hydrocarbon mainly used for degreasing metal. It is not tested for in the FSIS National Residue Program.

In this review it appears that diet (food) is addressed as an exposure route (ingestion). On page 21 the text mentions that FDA has limits on TCA for use as a food additive in decaffeinated coffee and extract spice oleoresins (21 CFR 173.290). The authors present two studies referencing levels in food, which are presented in Table 2-9, an IARC 1995 study which reports the average concentration of TCE in limited food samples collected in the United States, and a Flemings-Jones and Smith (2003) study which measured volatile organic compounds (VOCs) collected from 1996 – 2000 as part of FDA's Total Diet Program. Section 2.4.1.2 Ingestion, Table 2-12, page 26 presents preliminary estimates of TCE intake from food ingestion.

Comments to the Charge Questions for external Peer Reviewers

- In relation to charge questions, page 1186 of the Toxicological Review notes that there is conflicting data as to which GST isoforms are responsible for the TCE conjugation, alpha-class GST's and mu and pi –class GST's. Have reviewers specifically address/offer opinion on this concern.

- While the review supports oxidative metabolism as necessary to produce TCE-induced effects, page 1190 indicates that the particular metabolite/metabolites responsible is less clear. Have the reviewers address this finding.

- In reviewing the cardiac section of the report, under developmental effects on page 1194, the authors note conflicting results from different studies and offer an opinion as to why this occurred. They should specifically ask the reviewers if they concur or offer another plausible hypothesis.

- The authors are not convinced if nephrotoxicity is one of several key events in a MOA, if it is a marker for an "upstream" event (such as oxidative stress) that may contribute independently to both nephrotoxicity and renal carcinogenesis, or if it incidental to kidney induction. The reviewer's should be asked to comment on this interpretation.

Comments on the Major Conclusions/Toxicological Review of Trichloroethylene

- Is it worthwhile to look at other oxidative factors more deeply? The authors state the cytochrome P450 isozyme, CYP2E1 is generally accepted to be the CPY

form most responsible for TCE oxidation at lower concentrations, though other forms may also contribute. (Page 39)

- The summary states "TCE is characterized as carcinogenic in humans by all routes of exposure. This conclusion is based on a causal association between TCE exposure in humans and kidney cancer." Is "causal" the proper descriptor here? Page 1195

- The authors acknowledge the challenges and constraints with evaluating the genotoxicity of TCE and its metabolites on pages 265 and 287-288, specifically, and offer caution in any interpretations drawn. Can author/reviewers offer potential alternative studies to mitigate the ambiguities?

- On page 420, the authors refer to renal cell carcinoma subtypes. In the rest of the section, I was anticipating hearing about clear cell, papillary, chromphobe, oncocytomas etc. Does this need clarification?

- In Section 4.3.4, page 425, the authors refer to lesions in the text, but certain tables, for example Tables 4.3.5 and 4.3.6 mention toxicity and tumor formation (adenoma and adenocarcinomas). Is the term lesion properly used in this context?