Page numbers refer to document
[cis- and trans-1,2-DCEs_Toxicological Review_IASD-Final AR draft_7-30-10a_TRACK CHANGES.pdf]

1) - Physical and Chemical Properties Section: One of the peer reviewers asked for more information in this section (page 44 in the 'post meeting comments' document) on how these compounds are produced, production volume, releases registered under TRI, and current information from groundwater surveys. In addition information was requested on the degradation reactions and the identification of the isomer (or ratio of isomers) produced by anaerobic degradation of trichloro- and tetrachloroethylene. None of this information has been added or pointed to (i.e., noted briefly with references). Please explain.
2) - Page 54: Paragraphs 2 and 3 should be combined since ¶ 3 refers to data from the Freundt and Macholz study which is introduced in ¶ 2.
3) Page A-1-A-2, Response to Charge Question 1: One reviewer noted EPA should consider additional toxic endpoints for deriving candidate PODs for setting oral RfDs for cis- and trans-1,2-DCE, and should consider the unpublished study of Kelly et al. (1999) for a possible RfC for trans-1,2-DCE yet there is no response to this point. Please clarify and note in part (D) Inhalation Reference Concentration (RfC) for trans-1,2-DCE (page A-12) that the Kelly reference is discussed.
   a) In the discussion of potential critical effects for the RfC for trans-1,2,-DCE, effects observed by DuPont (1998) including dose-related hematological changes at both 45 and 90 days in male and female rats such as decreased WBC (up to 18 to 20% in male and female rats) and lymphocyte counts (up to 22 to 25%) were considered. The document cites the study authors conclusions that the decreases in WBC and lymphocyte counts were attributable to the release of endogenous glucocorticoids that can cause redistribution of lymphocytes from the circulation into the lymphoid tissue and may, therefore, be considered a secondary effect associated with stress (Jensen, 1969; Brondeau et al., 1990). The Toxicological Review also states that while this hypothesis is plausible, there are no data to support this conclusion. In addition, similar effects were observed in the NTP (2002) oral study. However, due to the lack of histopathological changes in the spleen and thymus in the DuPont (1998) study these effects were not selected as the critical effect for the derivation of the RfC for trans-1,2-DCE. The critical effect selected for the RfD for trans-1,2-DCE was an immune endpoint (suppression of the humoral immune status supported by alterations in thymus weight). Isn't it possible that the decrease in lymphocytes and WBC observed by DuPont (1998) represents a chemically-induced immune response? One of the reviewers (Luster) also raised this point in the comments on charge question D1. CEQ suggests that EPA include a discussion of the potential of trans-1,2-DCE-induced immunotoxicity following inhalation exposure to trans-1,2-DCE for completeness given the oral database and selected critical effect for the derivation of the RfD for trans-1,2,-DCE.

4) Page A2-One of the reviewers commented that corn oil may exacerbate hepatotoxicity of chloroalkenes. The response provided by EPA indicates that this comment is irrelevant because an alternative endpoint (kidney weight) was selected as the critical effect in this draft. Liver effects were still considered in the selection of the critical effect for the RfD for cis-1,2-DC E. CEQ suggests that EPA's response and the study include a discussion of this point.
5) Page A4 and Sections 4.6.1.1. and 5.1.1.1- The reviewers commented on the discrepancies noted between the published and unpublished versions of the McCauley et al. study. EPA indicated that "These discrepancies were not considered to compromise the integrity of the data since the inconsistencies were more likely an issue of the quality of the report writing than an issue with the findings themselves." Can EPA further clarify what is meant by "issue of quality of report writing"? Does EPA mean that there were differences in the reported results between the unpublished and published? Did one report contain more detailed information regarding protocol and results than the other? CEQ suggests providing detail regarding the actual discrepancies for clarity.
6) Page A6-Are there any studies that demonstrate differences in CYP2E1 activity in humans? Perhaps, addition of these studies to the Susceptible Populations or Metabolim section would further address peer reviewer comments related to the intraspecies UF.