- Page 2-1: The first sentence is very hard to read, for example it starts with "Betachloroprene monomer" and the relationship to neoprene is very confusing. We suggest this be revised to reflect the IUPAC name. We also suggest to begin the sentence with "The monomer..." and to remove the reference to neoprene as it is mentioned later in the paragraph.
- Page 2-1: There is much discussion on chloroprene in the environment yet there is no mention of exposure pathways. Exposure pathways should be discussed as well. Moreover, a statement should be added here, and more importantly on Page 4-1, that human exposure to chloroprene is primarily occupational.
- 3) There is no mention in the document that the International Agency for Research on Cancer has classified chloroprene as a Group 2B, possibly carcinogenic to humans. There are a number of places where this should be mentioned, i.e., page 6-2 where assessments of the carcinogenic potential of chloroprene in humans are discussed.
- 4) Page A1: Response to Charge Question 1: There is no mention of the comment from Melnick regarding his question as to why consideration was not given to the conclusion that chloroprene is "carcinogenic to humans" based on the animal data, mechanistic findings, and "the reasonably consistent" evidence of increased risk of liver cancer mortality "among workers exposed to chloroprene in different cohorts in different continents." Please explain.
- 5) Response to charge question B2 -Five of the reviewers supported the selection of a portal of entry effect (nasal lesions) as the critical effect for this chemical. However, several of these reviewers questioned combining the lesions (atrophy and necrosis). It is unclear from this response to this question, that EPA performed modeling of additional endpoints and selected splenic hematopoietic proliferation as the "new" critical effect. CEQ suggests further explanation and justification for this change (i.e., due to changes in the BMR and application of the DAF, increased incidence of splenic hematopoietic proliferation in female mice was chosen as the critical effect based on the observation that this endpoint had the lowest POD) in the response to this charge question for completeness.
- 6) A BMR of 5% was used in the modeling of splenic hematopoietic proliferation, the selected critical effect for the derivation of the RfC in this draft. However, for increased splenic hematopoietic proliferation there are no severity data presented and the footnote in Table 4-26 and 5-1 indicate that average severity and statistical significance was not reported by NTP. Section 5.3 indicates that "for increased incidence of splenic hematopoietic cell proliferation in female mice, definitive data do not exist to further inform the selection of what the appropriate BMR should be. However, the observation was made that the incidence and severity of this lesion increases in low dose animals compared to control animals; therefore a BMR of 5% extra risk was chosen based on the assumption that a 5% increase in incidence of this effect is minimally biologically significant." Was severity of splenic hematopoietic proliferation reported by NTP or did NTP state that the severity of this lesion increased in the low dose animals compared to controls? If there an additional biological basis for selecting the BMR of 5% for this endpoint in particular? The rationale for

selection of a BMR of 5% for splenic hematopoietic proliferation could be clarified and made consistent in Sections 5.2.2 and 5.3 (also in Appendix A).

- 7) Page A-7, line 9-10 states that Figure 5-1 has been removed from the document. This figure still appears in Section 5.2.6.
- 8) Page A-17, lines 27-31 and page A-32 lines 29-31- One reviewer suggested consideration of an alternative model incorporating the assumption of saturating metabolism in the model structure and provided an extensive example using the mouse data. It is not clear what is meant by the statement "The suggested alternative modeling approach incorporating saturating metabolism was a constructive approach that EPA will consider with regards to future methods developed for human health risk assessment." Is there a scientific basis to not pursue this model (i.e., lack of data to support these assumptions)?
- 9) Page A-28, lines 32-33-The following statement is made regarding possible confounding of alcohol co-exposure: "Alcohol cannot be a confounder if it is not both related to the exposure of interest (chloroprene) and the outcome of interest (liver cancer)." It is unclear why even though alcohol may not be related to the exposure of interest, it could not have been a significant confounder (given its relationship to liver effects and cancer). Please clarify.
- 10) A-29, lines 1-11-This text was removed from Section 4.7.1.1.1, CEQ suggests that the response should reflect the fact that this text was removed.
- 11) A-15, lines 31-34 and other places in Appendix A- The following statement is made regarding toxicokinetics: "A more complete and detailed discussion of metabolism and toxicokinetic differences between species was added to Section 3.3, to indicate that differences in epoxide production in the lungs of mice and humans are not 50-fold, but may be as little as 2- to 10-fold." Please consider addition of references supporting these statements to these responses in the Appendix.
- 12) Did EPA consider that the lack of a reproductive toxicity study that extends beyond two generations and the absence of a developmental toxicity study are of particular concern due to the genotoxicity of chloroprene, i.e., the possibility that resulting genetic damage to the germ cells of the F1 generation may not be detected until the F2 generation? (See response to comments on the database uncertainty factor)