

STEP 3 IRIS INTERAGENCY COMMENTS (OMB)

OMB Comments on EPA's Draft Trichloroacetic Acid Tox Review

(page numbers refer to the redline dated May 2009)

General Comments:

- OMB was pleased to see that the DeAngelo study was peer reviewed and released during the period that EPA was responding to interagency comments. We applaud EPA's decision to rely on the recent peer reviewed literature. This is clearly the most important and biggest change that EPA made to the assessment during this period.
- We appreciate that EPA addressed our minor editorial comments; however, our larger comments regarding the science were not addressed. In particular, EPA continues to state that the relevance of mouse peroxisomal proliferation to human health is uncertain (see page 105, 124, and elsewhere). While we acknowledge that NAS was reviewing TCE and not TCA in 2006, as part of its review. NAS looked at TCA as it is a major TCE metabolite. NAS stated page 179: "There is sufficient weight of evidence to conclude that the MOA of TCA as a rodent liver carcinogen is principally as a liver peroxisome proliferator in a specific strain of mouse"; page 180: "Induction of peroxisome proliferation in human liver is not a prominent feature; therefore this key event related to TCA liver carcinogenesis is not likely to occur in humans"; page 424, general statement regarding peroxisomal proliferation: "Whereas the MOA is plausible in humans, the weight of evidence suggests that this mode of action is not likely to occur in humans based on differences in several key steps when taking into consideration kinetic and dynamic factors." EPA bases its determination essentially on two studies (Yang 2007 and Ito 2007). We suggest that EPA add a clear question to peer reviewers about this new determination. We note that charge question C3 asks if the determination is transparent and objective. However, the charge should also ask the peer reviewers if they agree with the EPA conclusion that the data are insufficient. As this is critically important for TCA, and will also be important for TCE, a specific charge question on sufficiency would be very helpful.

Specific Comments:

- Page 63, EPA typically presents what the authors determined to be the NOAEL/LOAEL and if no information is provided, then typically EPA states a determination they make using the data. For the DeAngelo study, the authors determined a NOEL of 6 mg/kg/d. To be transparent, since this study is used for the quantitation of the RfD, EPA should also present this determination, in addition to EPA's own determination.
- Page 109, EPA deleted the clause "though at the low end of the spectrum" when characterizing the TCA cancer risk as "likely to be carcinogenic to humans." This type of text can be very informative to risk assessors and risk managers. Wouldn't it be more transparent to provide a thorough discussion of why EPA believes it is on the low end of the spectrum? EPA's cancer guidelines encourage these types of clear descriptions rather than only relying on the classification category.

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- Page 110, considering the NAS findings regarding TCA and a PPAR α mode of action (MOA), it is not clear why EPA is stating that significant gaps in knowledge exist for this MOA. Is there a citation that is more recent than the 2006 NAS review that can be referred to here?
- Page 119, 2nd full paragraph. To be transparent and to follow up the NAS quote with their overall determination on human relevance, EPA should also add the language from page 180 of the 2006 NAS report which states: “Induction of peroxisome proliferation in human liver is not a prominent feature; therefore this key event related to TCA liver carcinogenesis is not likely to occur in humans.” This language would also be a helpful addition to improve transparency regarding the NAS findings if added to page 158 as well.
- Page 142, EPA states that they chose the log-logistic model as it had the lowest AIC. We note that the AIC value for this model was 30.42. Is this considered significantly different from 31.85? 31.85 was the AIC value for the Gamma, multistage and Weibull models. Should these models have also been considered as equally plausible as they had essentially similar model fit? This is important because these other models yield a POD that is more than 2x the value using the log-logistic model. We also note that these three other models are quite consistent in their POD determination, each coming out with a POD of 37.6 mg/kg-day.
- Page 143, EPA states that “hepatocellular necrosis also had the highest severity score. Since the POD is 18 mg/kg/d and since the severity was O (no lesion) at the NOAEL (8 mg/kg/d) and only 0.5 (between no lesion and minimal severity) at 68 mg/kg/d (the next highest dose; we suggest that EPA expand on this statement and present exactly what the severity score for hepatocellular necrosis would be at the determined POD.
- Page 156, section 5.1.5, it is unclear why EPA has now removed language that provides a comparison to the previous RfD that was derived in EPA’s disinfectants and disinfection byproducts rule in 2006. Wouldn’t this type of information be helpful?
- Page 158 EPA discussed different interpretations of the MOA data regarding PPAR α . It may be helpful for EPA to include an interpretation reflecting the NAS 2006 finding that it is not relevant to humans. Shouldn’t this option, with reference to the NAS evaluation, be included (with a discussion of the two new studies which EPA believes change the overall NAS finding)?

Comments on the draft Charge:

(these comments are in addition to charge edits stated in above sections)

- B2, we note that EPA determined that the NOAEL from the DeAngelo 2008 study was 8 mg/kg, while the authors themselves determined a NOEL to be 6 mg/kg. (The authors describe the lowest dose group as being 6-8 mg/kg; thus, both EPA and the authors are likely referring to the same dose group.) It is possible that the difference in the adversity determination (NOAEL vs NOEL) is due to the minimal severity of the necrosis that was identified (see table 4-4). It would be helpful to add a question to this charge question that

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asks the peer reviewers to specifically consider the severity of the effects in making their determination.

- Under C1, it is not clear why EPA is stating that TCA is likely to be carcinogenic by “all routes of exposure.” EPA has not previously used this “all routes of exposure” characterization, and this language is not present in the current tox review. If EPA wishes to use it, please provide discussion of carcinogenicity via the dermal and inhalation routes. We did not see these pathways thoroughly evaluated in the tox review.
- Under C1, while we hope it will be obvious to reviewers to consider the possible mechanism of action underlying the liver tumors, it may be helpful for EPA to explicitly ask the peer reviewers to consider the mode of action of the liver tumors in evaluating the weight of evidence descriptor.
- The only cancer evaluation conducted is for the oral pathway. Under C5, in the 1st sentence please clarify that an estimate of cancer risk was quantified for the oral pathway only.
- Question C6 seems very general. It would be helpful if EPA could add some more specific language asking reviewers to comment on the specific modeling approach, assumptions, calculations (e.g., linear extrapolation from the UED) and choices made to determine the oral slope factor (e.g., using the study of longest duration despite its having the greatest statistical variability). Reviewers should also be asked to comment on EPA's final choice (from the 5 studies presented) for the oral slope factor. This type of question would be more consistent with previous charge questions EPA has used.
- EPA may want to consider adding a charge question about the decision to not quantify an inhalation cancer risk