OMB Staff Working Comments on EPA's Final Agency/Interagency Science Discussion draft Toxicological Review of Tetrahydrofuran (THF) and draft IRIS Summary (dated July 2011)

Oct 20, 2011

In these comments, OMB focused on EPA's response to the external peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

General Science Comments:

- While we note that the peer review report is already final, for future assessments it would be helpful if the peer review report provided short summaries of the background of the expert reviewers. It may also be helpful if the peer review reports were to include information discussing any monetary funding (perhaps through a grant, cooperative agreement, sole-source agreement, or competitive contract) that the expert reviewer may have received from EPA's ORD. This would be consistent with generally-accepted disclosure practices for peer reviewers, particularly for reviews with significant public policy implications.
    - In 2009 ORD/NCEA signed a Memorandum of Understanding with CalEPA/OEHHA to cooperate on the development of risk assessment methods and toxicological assessments. It would be appropriate and consistent with generally accepted practice for this to be disclosed in the report. We wonder if this reviewer can truly provide an independent assessment of EPAs work as the two offices are collaborating on the development of toxicological assessments.

- Concerns with the RfD:
    - EPA on page A-3 of the tox review, notes that the three reviewers who thought the critical endpoint was at most marginally adverse, minimal or non-adverse, collectively agreed that pup weight was the most appropriate critical effect. However it is not clear that this captures their concern. Dr. Corcoran notes his concern regarding the "absence of more extensive high quality data sets" and continues on to state that "the evidence of THF developmental toxicity remains tenuous." Similarly, Dr. Kerkvliet states "I am not convinced it is an appropriate critical effect" although she acknowledges that there "doesn't appear to be a better endpoint."
    - EPA in the response to the comments, states that they "agree with reviewers recommendations." Thus making it sound that there was strong support for using this critical effect stating that it may be related to alterations in neonatal development. However we think that EPA underestimates the reviewers concerns with the endpoint. Just because the endpoint is the best considering the data available, it is still not clear, based on reviewer comments, if this endpoint should be used at all. In addition EPA has not responded to the comments regarding the tenuous nature of the EPA determination as well as concerns regarding the fact that the effect did not carry forward into changes in growth or ability to reproduce (as noted by Dr. Kerkvliet). Of the 5 reviewers who commented, three of the five, the majority, had major concerns regarding whether or not this was an appropriate critical effect. Thus is it not clear why EPA is continuing to move

forward with quantifying this endpoint. We also note that the National Toxicology Program (NTP) in their interagency comments, August 2011 stated "We suggest that EPA should consider not deriving [an] RfD based on the fact that none of the oral toxicology studies in the literature are defendable for risk assessment purposes."

- Regarding the BMD modeling, EPA acknowledges that 4 of the reviewers recommended or highly recommended the use of the $BMDL_{1SD}$ rather than the $BML_{0.05}$. In the response, EPA notes that the reviewer suggestion is indeed consistent with the draft BMD Technical Guidance. However, EPA then rejects this approach based on the fact that the endpoint is in pups and the approach does not necessarily consider biological significance. This response is confusing, because if EPA considers reviewer comments on B2, it is not clear that any of the effects seen are biologically significant. Additionally, EPA notes that since the endpoint is in pups, there is a difference in suggested endpoints. The reviewers were likely keenly aware that the endpoint was in pups (as per response to B2) thus it is not clear why the suggestions from the majority of reviewers, including the statistical/modeling expert on the panel (Dr. Gaylor) were rejected. EPA states that the reviewers' suggestion was added to Appendix B and led to a nearly identical result. It was not clear to us exactly where in the Appendix this is presented. Additionally, Dr. Gaylor presents an analysis in his reviewer comments and derives a value of 601 mg/kg. This is almost double the EPA derived value. At a minimum, EPA should clearly explain why the value they derived is so different from the value derived by Dr. Gaylor. We suggest that EPA reconsider the comments they received from the majority of reviewers, including Dr. Gaylor.

- Regarding the choice of UF, it is not clear that EPA has adequately captured Dr. Kerkvliets concern which noted "I question the need to use such a large overall uncertainty factor when the oral toxicity of THF was so low that it was difficult to find an endpoint of concern." It would be helpful if EPA provided a response to this.
- Additionally, in EPA's response, it is clear that EPA has looked at each UF independently whereas the peer reviewers took a more holistic weight of evidence approach to evaluate the application of the UFs. It would be helpful if EPA could provide some discussion regarding why they feel the UF of 1000 in total is justified, considering the point of departure.
- Regarding the human variability UF, EPAs response focuses on possible differences in metabolism, but does not seem to respond to the peer reviewer comments regarding their statements that metabolism likely plays no role in metabolism. It would be helpful if EPA provided a more direct response to this concern.
- Regarding database uncertainty, the majority of reviewers that commented (3 of 5) clearly suggested decreasing this UF to 3x. Thus it unclear why EPA is sticking to the pre-peer review arguments and maintaining the 10x UF despite the comments. Again, it seems peer reviewers looked at the totality of the evidence rather than looking at what studies were present or missing. We suggest that EPA reconsider this UF, and consider reducing it to 3x, in light of the recommendations from the majority of reviewers. If EPA reduces the uncertainty, it would then be more consistent with the proposed confidence rating. Simiarly,without the application of so many high uncertainty factors, IRIS users would likely have more confidence in the value.

- Concerns with the RfC:
  - Page A-7 is confusing. It appears all reviewers agreed that the 105 week inhalation study was the best choice, however EPA notes on Page A-7 that the charge question was incorrect and that EPA instead relied on a 14 week subchronic study. Lines 12-16 describe a study but it is unclear whether the 105 or 14 week study is being described. Nor is it clear how reviewers feel about the 14 week subchronic study, since they were not asked to comment on it. Since three reviewers explicitly mention the 105 week chronic study as a preference, it is not clear if EPA has expert reviewer support for the 14 week subchronic study.

  - EPA proposed liver and CNS effects as co- critical effects and is now choosing to rely only on liver effects (increased liver weight in male mice) as per the fact sheet that was provided to interagency reviewers. However in the discussion on pages A-8 and A-9 of the toxicological review, it sounds as if EPA is still relying on the co-critical CNS and liver effects. This is not consistent with the fact sheet. Additionally, since two of the four reviewers thought the liver effects were only minimally adverse, and one preferred cytomegaly over liver weight, it is not clear why EPA is relying on liver weight. One reviewer commented that hepatomegaly is a "questionable critical toxicological effect." (see Dr. Corcorans comments at page 33 of the peer review report). Dr. Corcoran argued against the use of liver changes as a critical effect. No rational or response to the specific scientific comments of the reviewer s are provided. Appendix A should provide a scientific response to the reviewer comments. Additionally, more clarity regarding endpoint selection is needed as the documents are inconsistent with each other (the fact sheet and tox review differ in what endpoints are critical).

  - In response to Question C3, two reviewers commented on the lack of clarity regarding use of the Akaike Information Criterion as described in Appendix B. While EPA mentions these comments, we see no additional text in Appendix B to address the concerns raised. Similarly, it is unclear how EPA is responding to Dr. Christopher's comments where he states "therefore, the effect on liver weight cannot be used." The response to comments should provide a scientific rational for rejecting the reviewer's comments.

  - In C5 EPA acknowledges the comments from "some of the reviewers" that the UFs were overly conservative. However EPA has not provided a response to this. If EPA does not think they are conservative, EPA should explain why. Similarly, in response to C6 EPA should explain why the agency either supports or disagrees with the reviewer comments regarding rapid metabolism , low concern for immunotoxicity and the lack of relevance of inflammation at high exposures to low exposures.

- Regarding the cancer quantification, there is clear agreement that the weight of evidence is suggestive, as EPA has chosen. However, it is not clear why EPA is conducting linear low dose extrapolation and providing a quantitative value.
  - The 2005 Cancer Guidelines state (at page 3-2) "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data

generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence. These analyses generally would not be considered Agency consensus estimates."

- On page A-13 EPA states that "the utility of the quantitative risk estimate it that it characterizes the chemical's relative potency." However, it is not clear that the reviewers would agree that this characterization is scientifically defensible. Of the 5 reviewers that commented, the majority had major concerns.
  - Dr. Corcoran (page 13 of peer review report) in summarizing his greatest concerns notes that there is "an indefensible use of linear low-dose extrapolation to estimate the point of departure for a solvent that has a very strong weight of evidence showing that it is not genotoxic, but likely a promotional agent." He also notes that this will "almost certainly overestimate, by many magnitudes, the risk actually posted by this very weak possible human carcinogen."
  - Dr. Kerkvliet states (page 47 of the peer review report) "The application of a non-threshold model would be defaulting to a model that is clearly inappropriate and not based on sound scientific principles."
  - Dr. Rozman states (page 47 of the peer review report) "I am of the opinion that a linear extrapolation from the POD represents a vast exaggeration of risk which does not yield any benefit for public health." He also notes that the RfC would protect the public from any cancer risk. On page 56 referring to the approach he states "This is entirely unjustified."
  - Dr. Christopher (page 53 of the peer review report) emphasizes that "the weight of evidence presented by the authors strongly suggests that all the biological effects for THF are those which are commonly thought to exhibit thresholds." He also notes that "Although EPA's guidelines were followed to the letter, I believe these guidelines are misapplied in the case of THF."
- Considering the reviewer comments, and the cancer guidelines, which do not necessarily support quantification when the weight of evidence is suggestive, EPA should not feel compelled to conduct linear low-dose extrapolation to quantify a cancer risk. The science, as well as the peer reviewer record, do not support such an approach. We do not agree with Dr. Christopher that the cancer guidelines were followed to the letter as per the language in the cancer guidelines on page 3-2.

- The preface of the toxicological review notes that the intent of Section 6 "is to present the major conclusions reached in the derivation of the reference dose, reference concentration and cancer assessment, where applicable, and to characterize the overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing the quality of data and related uncertainties."
  - We could not find any discussion of uncertainties in this section.
  - A discussion of the overall confidence in the cancer assessment could not be found.
  - We are concerned that EPA has overstated the confidence in the RfC and RfD. The RfD is stated to have low-medium confidence. Considering that some reviewers (including

NTP) suggested not deriving an RfD and the total UF is 1000, it is hard to understand how the confidence value could be anything but low. While an UF of 1000 is not the largest that EPA can use, it still decreases the point of departure by three orders of magnitude. Similarly, EPA states that the confidence in the RfC is medium to high. As the total UF is 100, it is unclear how this could be considered nearing high confidence. Although EPA states that the confidence in the critical study is 'high' we question this confidence for use of deriving an RfC. If EPA had high confidence in this critical study for an RfC derivation, then EPA likely would not need to apply uncertainty factors in three different areas (interspecies, intraspecies and database uncertainty). If EPA maintains the RfD and RfC values, we would suggest considering, at most, a confidence value of low for the RfD and medium for the RfC.

- In certain cases, in preparing Appendix A, EPA seems to overlook some important comments from the peer reviewers. It would we helpful if EPA addressed these comments. A few examples are provided below:
  - Question A1 asks "Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazard." We did not see where EPA presented reviewer responses to this. For instance, the assessment does not mention Dr. Rozman's statement that: "This is a well-written, easy to read document with whose conclusions, however, I disagree."
  - Page 17 of the peer review report, Dr. Rozman notes that "clearly THF is less toxic orally due to first pass metabolism" but the document implies THF is more toxic orally (he presents comparison of RfD and RfC values). EPA has not provided a response to this overarching concern.
  - Page 54 of the peer review report, Dr. Gaylor presents BMC quantification values for incidence rates of adenoma and carcinoma in mice. We did not see where EPA has addressed his analysis.

Specific Comments on Appendix A:

- Page A-2, under Q B2 states that three reviewers commented that decreased pup weight represented a "minimally adverse or non-adverse effect." It is not clear that this accurately captures Dr. Christopher's and Dr. Corcoran's concerns. We suggest that EPA use direct quotes rather than paraphrasing whenever possible.
- Page A-22, EPA states "In accordance with peer reviewer comments, EPA continued to present a quantitative cancer assessment." This response seems inconsistent with at least some peer reviewer comments. See comments above for further details.

Specific Comments on the IRIS summary:

- The IRIS summary should provide a link to the interagency comments associated with this final document. If an outsider were to go to IRIS to find an IRIS summary, they would have no way of knowing there were interagency comments available. We understand that EPA is working on this and we hope this change can be made in time for posting of this assessment.