EPA's Response to Selected Major Interagency Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Trichloroacetic Acid

September 30, 2011

Purpose:

The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and 6b) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Discussion step (Step 6b) for the draft IRIS Toxicological Review of Trichloroacetic Acid (dated July 2011). All interagency comments provided were taken into consideration in revising the final draft assessment prior to posting on the IRIS database. The complete set of all interagency comments is attached as an appendix to this document.

For a complete description of the IRIS process, including Interagency Science Discussion, visit the IRIS website at www.epa.gov/iris.

July 2011 Interagency Science Discussion Draft IRIS Assessment—Selected Major Comments and Responses:

Topic #1: Selection of the Cancer Descriptor in the Weight-of-Evidence Narrative – *OMB commented that the descriptor of "likely to be carcinogenic to humans" did not seem appropriate in light of peer review comments in that it did not appear that any of the reviewers explicitly supported EPA's determination and presentation of the cancer descriptor. OMB recommended that the choice of the descriptor be reconsidered, and at a minimum the IRIS assessment should be revised to indicate that that the evidence for carcinogenicity is at the low end of the spectrum of "likely to be carcinogenic to humans."*

> **EPA Response:** Taking into consideration the comments received during the Final Agency review/Interagency Science Discussion step of the IRIS process (Step 6), EPA reconsidered the external peer review comments related to the cancer descriptor of "likely to be carcinogenic to humans" presented in the external peer review draft. The broad range of views on the weight of evidence for TCA carcinogenicity expressed by the peer reviewers reflects the challenges in weighing the evidence for TCA carcinogenic potential.

There are no studies of TCA in humans. In animals, the scope of carcinogenicity testing is limited. Overall, TCA: 1) has consistently tested positive in males in one strain of mouse in one lifetime and several less-than-lifetime studies; 2) has not been tested in lifetime studies in female mice, has been shown to induce tumors in one of two less-than-lifetime studies in female mice; and 3) has tested negative in one lifetime study that was conducted in male rats only. While the consistent observation of tumor formation in male mice is compelling, the overall weight of evidence is tempered due to a lack of studies on female animals in general and the negative results in male rats.

EPA's *Guidelines for Carcinogen Risk Assessment* (or Cancer Guidelines) (U.S. EPA, 2005) emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. Each cancer descriptor may be applicable to a variety of potential data sets and represent points along a continuum of evidence. The available tumorigenic evidence for TCA could be considered a borderline case between two descriptors—"likely to be carcinogenic to humans" and "suggestive evidence of carcinogenic potential." For example, TCA has tested positive in more than one sex of $B6C3F_1$ mice, which minimally corresponds to one of the examples provided in EPA's Cancer Guidelines for the descriptor "likely to be carcinogenic to humans." The example states that supporting data for this descriptor may include "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans."

In evaluating this borderline case, EPA considered Section 2.5 of the Cancer Guidelines that states that the descriptor "likely to be carcinogenic to humans" is appropriate when "the weight of evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor carcinogenic to humans." The Cancer Guidelines further state that the descriptor "suggestive evidence of carcinogenic potential" is appropriate when "the weight of evidence is suggestive of carcinogenicity, a concern for potential carcinogenic effects is raised, but the data are not judged sufficient for a stronger conclusion."

Thus, although either descriptor of "likely to be carcinogenic to humans" or "suggestive evidence of carcinogenicity" is plausible, EPA attached greater weight in the re-evaluation of the weight of evidence for TCA carcinogenicity to the lack of effects outside the $B6C3F_1$ mouse than to the replication of positive results in this one strain.

Accordingly, EPA revised the assessment to conclude that there is "suggestive evidence of carcinogenic potential" for TCA.

In addition, the cancer weight of evidence narrative in Section 4.7.1 of the Toxicological Review was revised to improve the characterization of the overall weight of evidence for TCA, and the summary of external peer reviewer comments in Appendix A was expanded to more fully reflect the range of views offered by the external peer reviewers.

Topic #2: Cancer Mode of Action – *OMB commented that EPA appears to have made some minor revisions and edits to the text in response to comments critical of the cancer mode of action (MOA) discussion and the application of the EPA MOA framework from the 2005 Cancer Guidelines; however, they noted that it is not clear that the changes were sufficient to make the section consistent with EPA guidance. In addition, OMB commented that EPA did not appear to add tables as recommended by multiple reviewers.*

EPA Response: Considerable revisions were made to the text of Section 4.7.3 (Cancer MOA Information) in response to peer reviewer comments, and were presented in the Final Agency review/Interagency Science Discussion draft of the Toxicological Review. The evaluation of the hypothesized peroxisome proliferator-activated receptor (PPARα) MOA followed the framework outlined in EPA's *Guidelines for Carcinogen Risk Assessment* (or Cancer Guidelines) (U.S. EPA, 2005), including identification of key events; consideration of biological plausibility, consistency, specificity of association; evaluation of dose-response concordance; and consideration of human relevance of the MOA. In response to peer reviewer comments, EPA also presented an expanded discussion in the Toxicological Review of several other effects that have been hypothesized to be associated with liver cancer induction, including Kupffer cell activation, DNA hypomethylation, decreased intercellular communication, and genotoxicity. The MOA framework was not applied to these effects because the available information was not adequate to support this more in-depth analysis.

Two peer reviewers offered suggestions for tables: one reviewer recommended a table presenting a review of the consistencies and inconsistencies in data for major peroxisome proliferators, and a second reviewer recommended tables organized around proposed key events and the elements of the MOA framework from EPA's Cancer Guidelines. In general, EPA agrees that tables can be an effective tool for evaluating MOA information. However, as discussed in Section 4.7.3 of the Toxicological Review, the MOA for TCA

carcinogenicity is complex; multiple MOAs that are not mutually exclusive may be involved, and while PPARα-related events represent some of the major components of the overall MOA, it is premature to conclude that this is the only MOA for TCA. Therefore, a broader analysis of other major peroxisomes proliferators would not impact the conclusions of the cancer mode of action for TCA presented in Section 4.7.3 of the Toxicological Review.

EPA considered the recommendation to develop tables organized around proposed key events and elements of the MOA framework. Much of the data supporting cancer MOA for TCA, however, comes from in vitro studies with doses that are not comparable to those used in two-year bioassays. Thus, presentation of a table (or tables) of TCA MOA information organized around proposed key events to examine dose or temporal concordance would not be informative.

Topic #3: Comparison of the Hepatocarcinogenic Potencies of Three Haloacetic Acids (HAAs) – *NIEHS commented that the document could be strengthened by providing a brief discussion of the relative hepatocarcinogenic potency of TCA, dichloroacetic acid (DCA), and monochloroacetic acid (MCA), particularly related to hypothesized peroxisome proliferator-activated receptor (PPARα)-dependent and independent MOAs.*

EPA Response: EPA agrees that a comparison of the hepatocarcinogenic potencies of the three haloacetic acids (HAAs)—TCA, DCA and MCA—and information on cancer MOAs could be an interesting scientific analysis. It is not clear, however, that such an analysis would strengthen the cancer assessment for TCA. Overall, the carcinogenicity profiles for the three HAAs are considerably different.

- The available cancer bioassays for MCA (including a 1992 National Toxicology Program bioassay in F344 rats and B6C3F_1 mice and two drinking water bioassays in F344 rats) provide no evidence of carcinogenic activity of MCA. Exposure to DCA, on the other hand, induced liver tumors in both B6C3F_1 mice and F344 rats (see Toxicological Review of Dichloroacetic acid, http://www.epa.gov/iris). These cancer profiles differ from TCA, which has been shown to induce liver tumors in B6C3F_1 mice only.

- Available information suggests differences in the cancer MOA for DCA and TCA. The two chemicals are similar to the extent that MOAs for both are

complex and likely involve multiple MOAs that may not be mutually exclusive. In DCA carcinogenicity, the inhibition of various enzymes appear to play a major role, and a PPARα-dependent MOA is not likely to be important (see Toxicological Review of Dichloroacetic acid, http://www.epa.gov/iris). In TCA carcinogenicity, however, PPARα-related events represent some of the major components of the overall cancer MOA, although other MOAs may be operative.

In light of the differences in cancer profiles for TCA, DCA, and MCA, EPA did not consider that a comparison of the hepatocarcinogenic potencies of the HAAs would help inform the cancer assessment for TCA.

Appendix
Comments on the Interagency Science Discussion Draft
IRIS Toxicological Review of Trichloroacetic Acid

National Institute of Environmental Health Sciences (NIEHS) Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Trichloroacetic Acid (dated July 2011)

Comments on the Draft EPA Toxicological Review of Trichloroacetic Acid

Michelle Hooth, Ph.D. (NIEHS/NTP)

Overall, the document was well-written and provided a comprehensive review of the available literature. The rationale for selection of the DeAngelo et al., 2008 study for derivation of the RfD was clear and well justified. The document adequately and appropriately identified and described the limitations in the carcinogenic database for TCA. The discussion regarding the potential MOA, particularly related to PPARα-mediated events, was particularly thorough and balanced supporting the conclusion that the TCA MOA is complex and PPARα agonism may not be the sole MOA.

If appropriate, consider including a couple of sentences in the chemical and physical property section about the levels of TCA found in finished drinking water and the factors contributing to the formation of TCA in drinking water.

The document could be strengthened by providing a brief discussion of the relative hepatocarcinogenic potency of TCA, DCA and MCA, particularly related to hypothesized PPARα-dependent and independent MOAs.

Office of Management and Budget (OMB) Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Trichloroacetic Acid (dated July 2011)

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

August 12, 2011

Due to the limited time provided for interagency science consultation, OMB focused only 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 thus seems a bit awkward that one of the expert reviewers is from the OEHHA office. 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.

- In certain cases, in preparing Appendix A, EPA seems to overlook some important comments from the peer reviewers. To improve transparency, it would we helpful if EPA acknowledged these comments and responded to them directly. A few examples are provided below:
    - Page 10 of the external peer review report: Dr. Fenner-Crisp notes that the MOA

discussion is “non-compliant with the Agency’s own framework described in the 2005 cancer guidelines.”

- Page 27 of the external peer review report: Dr. Stern notes that “the rationale presented for the selection of a BMR or 10% for continuous data is not valid.”
- Page 29 of the external peer review report: Dr. Pereira notes that “Also, the use of 10x the UF for human variation needs to be better justified…”
- As per comments below, it is not clear that EPA has appropriately portrayed peer reviewer comments regarding the cancer classification (see external peer review report pages 34-38).

- In light of the external peer review comments, it does not seem appropriate for EPA to continue to use the “likely to be carcinogenic” descriptor as EPA has presented it. In looking at the peer reviewer comments 6 of the 9 reviewers are very clear that as presented it is not an appropriate descriptor. In reviewing the comments (see external peer review report pages 34-38), it does not appear that any of the reviewers explicitly support EPAs determination and presentation. As per expert reviewer comments, we suggest that EPA reconsider their choice of descriptor. If EPA retains the descriptor (which is not our preferred choice as the majority of expert reviewers clearly rejected this classification), at a minimum, chapter 5 and 6 of the tox review and the IRIS summary should be explicit that the evidence is at the low end of the spectrum.
  - Of the 6 explicitly negative reviewers, it seems that Dr. Gaylor would be satisfied if EPA clarified that the characterization is appropriate to high doses only. Additionally, another reviewer (Melnick) would likely be satisfied if EPA clarified that the evidence for this descriptor was very weak and that it was at the low end of the scale compared to other chemicals with this descriptor. We do not see any of this suggested clarifying language in the revised tox review or IRIS summary.
  - Of the remaining three reviewers, Dr. Moore states that the conclusion is based on a lack of evidence, but does not comment on whether or not it is correct.
  - Dr. Rusyn states that the agency did a good job presenting their justification but does not comment on whether or not he agrees with it.
  - Dr. Salmon (from CalEPA) is the only reviewer to state that he thinks the data meet the criteria. Notably, Dr. Salmon also notes that “It is worth pointing out that current guidelines do not limit the characterization to this simple categorization, but also require provision of a narrative statement of the overall context of the finding, including comparison of the strength of the evidence and the degree of “likeliness” or “possibility” of an identified carcinogenic risk to humans.” On page A-12, EPA notes

that the data is at the low end of the spectrum, however we do not see this language incorporated appropriately into the tox review or the IRIS summary.

- EPA received some very critical comments on the mode of action discussion and the application of the EPA mode of action framework (see external peer review report pages 39-45). To address these comments, EPA appears to have made some minor revisions and edits to the text, including some clarifying text. However, it is not clear that the changes are sufficient to make the section consistent with EPAs guidance provided in the mode of action framework. In addition, multiple reviewers suggested the addition of tables, including tables that provide dose information, and EPA did not appear to add these tables. It is apparent that some of the expert reviewers were likely put on the panel because of their expertise and knowledge associated with the mode of action framework, thus it is not clear why EPA is not revising the document as suggested by these expert reviewers. We recommend that EPA revise the section as suggested and incorporate the recommended tables.

- Last month, EPA announced improvements to the IRIS assessments that would lead to: "reducing volume and redundancy of assessments; fuller discussion of methods and concise statements of criteria used in studies for hazard evaluation; clearer articulation of the rationale and criteria for screening studies; implementing uniform approaches for choosing studies and evaluating their findings; and describing the determinants of weight that were used in synthesizing the evidence." Although we understand that such improvements will take time to implement and may not be possible for all the assessments currently underway, considering the importance of this assessment it would be helpful for EPA to transparently describe the changes that have been made to achieve the goals mentioned in the EPA announcement.

Specific Comments on Appendix A:

- Page A-1, in response to reviewer comments that the document was not concise, EPA states "the toxicological review was revised as much as possible to streamline the document and reduce redundancy." In reviewing the redline, it was not clear exactly what revisions were made to streamline and reduce redundancy. More clarity on the changes would be helpful.

- Page A-7, notes that the justification for the selection of the 10% BMR was reconsidered. However, it seems that EPA is using the same approach as in the proposal and retaining

the 10% BMR. Thus it is unclear what is meant by “reconsidered”. Appendix A should provide a clear justification from EPA regarding rejection or acceptance of peer reviewer comments.

- Page A-8, in responding to the peer reviewer comment, EPA should explain why EPA has retained the determination that the data do not support a determination that TCA induces hepatocellular effects solely by peroxisomal proliferation. The reviewer also notes that the effects are not relevant to humans, however, EPA on page A-8 does not explain why the agency thinks they are relevant.

- Page A-11 through A-13, as per comments in the section above, EPA should revise the characterization of the reviewer comments regarding the cancer description, as well as the response.

- Page A-15, as per comments in the section above, EPA should make changes in the tox review to improve compliance with the EPA mode of action framework and should describe the changes in the appendix A response.

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.