# EPA's Response to Major Interagency Scientific Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Trichloroethylene September 2011

# **Purpose:**

The Integrated Risk Information System (IRIS) assessment development process of May 2009, includes two steps (Step 3 and 6) 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 6) for the draft IRIS Toxicological Review of Trichloroethylene (dated June 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting the final Toxicological Review. 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 <a href="www.epa.gov/iris">www.epa.gov/iris</a>.

# Comment #1 – Fetal cardiac malformation data

DoD commented that EPA should better justify the use of the fetal cardiac malformation data as a candidate critical effect. Specifically, DoD questioned the dose-response reported in the Johnson et al. (2003) study and whether the individual data from that study obtained by EPA via personal communication was peer reviewed. DoD further requested that EPA apply Hill criteria to the study.

# EPA Response

EPA has included justification and further discussion of the use of the fetal cardiac malformations as a candidate critical effect in response to SAB suggestions. Regarding the dose-response, the SAB noted that the non-monotonic dose-response reported in Johnson et al. was consistent with other, subsequent studies. The information on the incidence of cardiac malformations provided to EPA by Dr. Johnson via personal communication was for the same study and findings that were previously published in the peer reviewed literature, and thus are considered by EPA to be peer-reviewed. These data will be provided in the HERO database, to further facilitate transparency. While EPA did not explicitly mention the Hill causality criteria for this endpoint, EPA did conduct a weight-of-evidence analysis of the epidemiologic data and in vivo and in vitro laboratory studies, the conclusions of which were supported by the SAB. Finally, EPA has incorporated suggestions from the SAB as to strengthening the discussion of this endpoint, which is now sound and sufficiently detailed.

# Comment #2 – Immunotoxicity data

NIEHS/NTP recommended adjustments in the interpretation and use of immune data. The first major recommendation questioned the use of thymus weights from the Keil et al. (2009) study, suggesting it was an insensitive and non-specific measure of immunotoxicity. The second major recommendation was to consider the observation of ds- and ss-DNA autoantibodies as a LOAEL with concurrent use of a LOAEL to NOAEL UF of 10. A third point was a suggestion to delete

a statement indicating that certain indicators of immunosuppression (e.g., PFC response) were not considered adverse in and of themselves.

# EPA Response

Regarding the first recommendation, although thymus weight may have the potential to be an insensitive measure of immunotoxicity, the effects observed in Keil et al. (2009) were quite large and robust, and consistent with the broader database indicating TCE immunotoxicity. Thus in this specific case, EPA does not believe it is an insensitive endpoint. Upon revisiting the characterization of the autoantibody endpoints, EPA increased the LOAEL:NOAEL UF for that effect from 1 to 3, taking into account the magnitude and nature of the response at the LOAEL to reflect their being considered an early marker for an adverse effect as per EPA's *A Review of the Reference Dose and Reference Concentration* (U.S. EPA, 2002). The kidney damage seen in this study did not appear to be related to an inflammatory or autoimmune pathology. EPA agrees with the third suggestion regarding the interpretation of the PFC response, and this statement was deleted. Specifically, EPA agrees with the commenter that as per WHO guidance EHC 180 *Principles and Methods for Assessing Direct Immunotoxicity Associated with Exposure to Chemicals* certain indicators of immunosuppression may be considered adverse, and the statement in the text noted by the commenter was modified to reflect this.

# Comment #3 – Non-cancer reference concentration and reference dose

CDC/ATSDR and CEQ commented that they support both the RfC and RfD. However, CEQ questioned why the RfD was not based on the most sensitive candidate value alone from the Peden-Adams et al. study (2006) but on three co-critical studies (Peden-Adams et al., 2006; Keil et al., 2009; Johnson et al., 2003).

# EPA Response

EPA considered using the lowest candidate RfD. However, given how close the lowest candidate RfDs were (within a range of approximately 1.4-fold), it was preferable to base the final value on multiple effects for the reasons articulated in the assessment (Section 5.1 in the Toxicological Review). In so doing, EPA felt that choosing a more central estimate to reflect the multiple effects would be more scientifically defensible. This decision was supported by the SAB, and the overall approach was endorsed in the NRC's 2011 *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*.

Comment #4 – Use of PBPK modeling in deriving reference concentration and reference dose DoD questioned why EPA does not use the PBPK-modeled internal dose-metrics prior to dose-response modeling to identify the studies and endpoints that lead to the more sensitive candidate RfCs and RfDs for TCE, and recommended EPA follow EPA's A Review of the Reference Dose and Reference Concentration (U.S. EPA, 2002). NASA also cited the same document.

# EPA Response

EPA has clarified the text to address these points and that the approach used is consistent with the recommendations of EPA's *A Review of the Reference Dose and Reference Concentration* (U.S. EPA, 2002; Section 5.1 in the Toxicological Review). In particular,

due to the large number of studies, EPA initially identified candidate studies on the basis of applied dose to increase efficiency. However, several studies were selected in each health endpoint domain. Because the same dose metrics would be applied for studies of the same endpoint domain, the dosimetric adjustment would be the same (including any non-linearities) across those studies and thus would not change the relative sensitivities of studies within an endpoint domain. Therefore, the use of PBPK-modeled internal dose metrics prior to identifying the more sensitive studies and endpoints would lead to the same result.

# Comment #5 – Use of uncertainty factors in deriving reference concentration and reference dose

CDC/ATSDR and CEQ commented that they agreed with the uncertainty factors used by EPA. OMB recommended more discussion of the public comment regarding appropriately accounting for human variability when using the PBPK model in combination with uncertainty factors.

# EPA Response

EPA notes that the SAB agreed that the application of uncertainty factors followed accepted Agency practice as described in EPA's *A Review of the Reference Dose and Reference Concentration* (U.S. EPA, 2002), while acknowledging that future research can improve the current methodologies. In response to OMB, EPA has revised Appendix I of the Toxicological Review to note that the SAB future research recommendation to develop an approach using distributions to characterize uncertainty in a Bayesian approach would help to address these issues for future assessments.

# Comment #6 – Carcinogenicity of TCE

CDC/ATSDR commented that they supported EPA's conclusion that TCE is carcinogenic to humans. DoD commented that they disagreed with EPA's conclusion, citing analyses by other groups (Kelsh et al., 2010; Dourson et al., unpublished review) that support a cancer descriptor of "likely to be carcinogenic to humans" or "suggestive evidence of carcinogenic potential" for TCE.

# EPA Response

EPA notes that the SAB supported EPA's conclusion that TCE is carcinogenic to humans. The reviews cited by DoD each examine parts of the TCE database (i.e, human only, animal only), whereas EPA's characterization of the hazard of TCE examines the database as a whole, and in an integrated manner. In addition, with respect to epidemiology, EPA analyzed all plausible alternative hypotheses as to bias and confounding, and did not find support for an adequate alternative explanation for the epidemiologic findings. EPA also added several analyses: a meta-analysis of lung cancer in cohort studies, a comparison to observed kidney cancer risks in smoking cohorts, and an evaluation of the evidence on kidney cancer and metalworking fluid exposures to quantify its possible contribution to uncontrolled confounding (Appendix B of the Toxicological Review). EPA did not find heterogeneity in the kidney cancer findings after applying objective study selection criteria, as suggested by NRC (2006) and described in Section 4.1 of the Toxicological Review.

# Comment #7 – Mode of Action for TCE-induced kidney tumors

CEQ commented that they agreed with EPA's conclusion regarding a mutagenic MOA for kidney tumors and with the application of the default ADAFs. OMB commented that based on the SAB comments regarding support for a possible cytotoxicity mode of action for kidney tumors, there is uncertainty in the mutagenic MOA and, therefore, results of a non-linear model/extrapolation should be presented. For the same reasons, OMB also commented that there is uncertainty in the application of the ADAFs which should be discussed.

# EPA Response

EPA has made clarifications in the text to address these points more clearly. In particular, EPA made an affirmative finding of a mutagenic MOA that supports the use of linear extrapolation and the recommended application of the ADAFs, conclusions supported by the SAB. EPA notes that the SAB did not describe cytotoxicity as an alternative (i.e. mutually exclusive) MOA, but rather an addition to the mutagenic MOA. Therefore, EPA believes the SAB conclusions regarding the potential role of cytotoxicity in the mode of action for TCE carcinogenesis (which EPA revised to be in agreement with the SAB conclusions; Section 4.4.7 in the Toxicological Review) do not imply any discounting of the mutagenic MOA; the fact that multiple mechanistic processes may be involved in TCE carcinogenesis does not change the finding of a mutagenic MOA. In sum, the conclusions regarding the mutagenic MOA, use of linear extrapolation, and application of the ADAFs are consistent with the findings of the SAB.

# **Abbreviations and Acronyms**

ADAF Age-dependent adjustment factor

CDC/ATSDR Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry

CEQ White House Council on Environmental Quality

DoD Department of Defense

EPA U.S. Environmental Protection Agency HERO Health and Environmental Research Online

IRIS Integrated Risk Information System LOAEL Lowest observed adverse effect level

MOA Mode of action

NASA National Aeronautics and Space Administration

NOAEL No observed adverse effect level NRC National Research Council

NIEHS/NTP National Institute of Environmental Health Sciences/National Toxicology

Program

OMB Office of Management and Budget
PBPK Physiologically based pharmacokinetic

RfC Reference concentration

RfD Reference dose

SAB U.S. EPA Science Advisory Board

TCE Trichloroethylene

# References

- Johnson, P; Goldberg, S; Mays, M; Dawson, B. (2003). Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111: 289-292.
- Keil, D; Peden-Adams, M; Wallace, S; Ruiz, P; Gilkeson, G. (2009). Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. J Environ Sci Health A Tox Hazard Subst Environ Eng 44: 443-453. http://dx.doi.org/10.1080/10934520902719738.
- <u>Kelsh, M; Alexander, D; Mink, P; Mandel, J.</u> (2010). Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. Epidemiology 21: 95-102. http://dx.doi.org/10.1097/EDE.0b013e3181c30e92.
- NRC. (National Research Council). (2006). Assessing the human health risks of trichloroethylene: Key scientific issues. Washington, DC: The National Academies Press.
- NRC. (National Research Council). (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press.
- Peden-Adams, M; Eudaly, J; Heesemann, L; Smythe, J; Miller, J; Gilkeson, G; Keil, D. (2006).

  Developmental immunotoxicity of trichloroethylene (TCE): Studies in B6C3F1 mice. J Environ Sci Health A Tox Hazard Subst Environ Eng 41: 249-271.

  http://dx.doi.org/10.1080/10934520500455289.
- <u>U.S. EPA.</u> (U.S. Environmental Protection Agency). (2002b). A review of the reference dose and reference concentration processes. (EPA/630/P-02/0002F). pp. 192. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=51717.
- <u>WHO.</u> (World Health Organization). (1996). Environmental health criteria 180: Principles and Methods for Assessing Direct Immunotoxicity Associated with Exposure to Chemicals. Geneva, Switzerland.

**Appendix: Interagency comments** 



# Memorandum

**Date:** July 13, 2011

**From:** Agency for Toxic Substances and Disease Registry

**Subject:** Comments on EPA's Toxicological Review of trichloroethane (TCE)

**To:** Environmental Protection Agency

We appreciate the opportunity to review EPA's Toxicological Review of TCE and the accompanying Science Advisory Board (SAB) peer review. Overall, we found the draft IRIS Toxicological Review and fact sheet well-written, comprehensive, and convincing.

We consider the RfD of 0.0005 mg/kg/d to be sufficiently supported by studies indicating heart malformations in rats, adult immunological effects in mice, developmental immunotoxicity in mice, and toxic nephropathy in rats. We agree with EPA's use of uncertainty factors applied to the PODs for these calculations. We also believe the RfC to be sound, as it is based mostly on the same studies as the RfD. Finally, we agree with the SAB peer review and the final EPA document stating that TCE is a human carcinogen based on convincing evidence that TCE exposure can cause kidney cancer, as well as very strong (though maybe not yet convincing) evidence that TCE can cause both NHL and liver cancer.

# Department of Defense Comments on TCE IASD Draft IRIS Summary.pdf

Comments submitted by: Chemical Material Risk Management Directorate

Organization: Department of Defense

Date Submitted: 7/19/2011

\*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	General		The TCE Toxicological Review is very long and complex and will therefore be used to a lesser degree than typical reviews; the IRIS Summary will, therefore, be heavily relied upon for information by State, Federal, private sector risk assessors, risk communicators and the public. This makes it very important for the IRIS summary to clearly convey salient information regarding TCE toxicology. The summary is 45 pages long and when placed into the IRIS database will likely be ~ 75 pages long (about double the length of benzene's IRIS Summary); yet it does not clearly convey relevant information that will be useful in assessing and communicating risk of TCE. The departures from EPA guidance used to assess TCE toxicity are not explained nor justified, and the use of toxicity values using non-standard practices will not be clear to risk assessors whom are required	If the Summary has not been reviewed by EPA personnel that use IRIS documents such as Region risk assessors and Region risk communication specialists it would be useful for NCEA to request such reviews to ensure the Summary's clarify and usefulness. More detailed comments are provided below.  Perform a quality control review in addition to a review by the user community.	S/M

			to use IRIS values.  Numerous cross-references to the Toxicoligical Review are incorrect.		
2	I.A.1 and I.B.1	2 and 10	Candidate RfDs and RfCs will be unfamiliar to most IRIS users and requires definition.	Recommend defining as a footnote to the table or in the associated text.	S
3	I.A.2 and I.B.2, second paragraph	3 and 11	Tha advantages of the candidate RfD and RfC approach is described, but it is not stated that this is a novel approach and is a deviation from EPA guidance.	Justify the use of the candidtate RfD and RfC approach in terms of EPA guidance and discuss why EPA believed the deviation was necessary for characterizing TCE hazard.	S
4	I.A.3	6	General information regarding uncertainty factors is easily obtained in referenced material; it is not necessary to include it here.	Recommend deleting the five paragraphs describing uncertainty factors.	Е
5	I.A.3 and I.B.3	7 and 12-13	Justification for UFs assigned a value of 1 is missing. It is not clear at all how the Johnson et al. study could possibly have a composite UF of 10 applied to it.	List and justify selection of all the UFs.	S
6	I.A.3, I.B.3	7 -8 and 13	Abbreviations used for the various uncertainty factors is much different than EPA's standard practice and will be confusing to many users.	The standard abbreviations should be used or the departure from them explained.	S
7	I.B.5	14	There is no discussion of the RfC being developed from route-to-route extrapolated values, it seems that would have some influence on the certainty and confidence in the value.	Please include a discussion relative to the RfC being based upon drinking water studies as well as whether extrapolation is reasonable and the influence it has upon the confidence of the RfC.	S
8	Section II.A.2 para a, b and e		The length of these sections could be reduced if only the most relevant studies were discussed.	Consider reducing the length of these sections.	E

			It doesn't seem necessary to discuss a multitude of studies here.		
9	Section II.A.4.	26	A lot of text is devoted to modes of action that EPA does not believe are operative.	Suggest deleting text relative to PPARalpha.	S
10	II.B.1.1, last paragraph	28	It is not clear why a factor of 5 was used to develop the OSF. Additionally, the reference to Section 5.2.2.3 is incorrect.	Include a brief explanation for the five fold adjustment to account for NHL and liver cancer risks in adition to citing the correct section of the Toxicological Review.	S
11	II.B.1.3	28	This section should clearly justify the reasonableness of extrapolating from inhalation to oral exposures for development of the OSF	Add text (or cross-reference) to justify the extrapolation from inhalation exposures and whether it is reasonable.	S
12	II.B.3	29	The text states that the ADAF adjustment for kidney cancer will minimal impact on full lifetime risk and "might reasonably be omitted given the greater complexity of the ADAF calculations for TCE." The text then states that "Nonetheless, for exposure scenarios with increasing proportions of exposure during early life, the impact of the ADAF adjustment becomes more pronounced and the importance of applying the ADAFs increases." With the exception of figurative speech, it is not all clear how an individual's childhood (or early life) might be extended.  For purposes of assessing human health exposures to releases of TCE into the environment, risk assessors will be required to apply the ADAF to TCE unless it is explicity	Clearly define when application of the ADAFs would/would not be required, it seems that it would be applicable for assessing exposures to school or daycare-type scenarios,  Correct 5.2.3.3.3 to 5.2.3.1.5, we believe this is the correct section.	S/M

			stated that it is not required.  Additionally, the reference to section 5.2.3.3 is incorrect.		
13	II.C.1	31	Similar to above, justify the four fold adjustment to account for NHL and liver cancer. The reference to Section 5.2.2.2 is incorrect.	Include a brief explanation for the four fold adjustment to account for NHL and liver cancer risks in adition to citing the correct section of the Toxicological Review.	S
14	II.C.2	32-33	Existing guidance that describes the consideration of multiple tumor types and the resulting adjustments made to the OSF and IUR is not cited.	Please better describe the adjustments made to account for mutiple tumor types and put into context with existing EPA guidance. If this is a novel procedure it should be so stated and the rationale from deviating from guidance provided.	S
15	II.C.2	33	Section II.B.1 states that a five fold adjustment was made to account for the mulitiple tunor types, but in this section shows 4 as being justified.	Correct or explain the discrepency.	S

# Department of Defense Comments on TCE IASD final draft Tox Review redline.pdf

Comments submitted by: Chemical Material Risk Management Directorate

Organization: Department of Defense

Date Submitted: 7/15/2011

\*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	Global	Global	The DoD appreciates EPA's effort to include some of the most current peer-reviewed data into their analysis.		s
2	Global	Global	DoD is very concerned about the apparent lack of consistency in the evaluation of TCE and PCE, the latter also under interagency review. As the PCE document states, "Tetrachloroethylene is closely related structurally to trichloroethylene, and the two chemicals cause similar toxic effects, many of which are attributed to metabolic activation of the parent compounds." Given EPA's stated objective of considering toxicities of closely related chemicals together, DoD finds the lack of consistency troubling.	EPA should provide consistency in its evaluation of chemicals that are very similar in structure and toxicity, or explain why there are significant differences. Both the TCE and PCE documents cite result for other chemicals, not just metabolites, so these inconsistencies need to be resolved.	S/M
3	Global	Global	DoD believes that the EPA TCE Toxicological Review fails to appropriately organize the information in a clear and transparent manner;	We hope that future IRIS documents are not be organized and presented in a manner similar to this TCE document.	S/M

			While generally well written, this document is		
			extraordinarily long and complex, and is not		
			organized in a way that effectively analyzes and		
			resolves the critical issues, which limits its		
			transparency and impact. Review of the		
			document is significantly hindered by the length		
			and organization of the information within.		
			Several prior review comments have indicated		
			similar concerns.		
			Review of the fianal draft documents were		
			hindered by Sections 2,3 and 4 in the red-line		
			version being misnumbered all as Section 1. It		
			was very difficult to follow changes made to the		
			text;		
			The SAB indicated that more discussion of the		
			inconsistencies in the level of activity of the		
			glutathione conjugation pathway metabolites		
	Appendix I and		was needed and that EPA should present the		
	general response		impact of divergent pathways more	Undertake a more critical analysis of the impact	
4	to charge		transparently. EPA's apparent response is to	of the secondary pathway and possible	S
	question 3		place a caveat on the utility of the glutathione	analytical differences.	
	question o		information and not investigated the impact.		
			These changes are made more important by the		
			data inconsistencies between the two cited		
			methods of analysis.		
			EPA has failed to adequately address review	As noted during previous review, EPA needs to	
5	1.4	Table 4-68	comments regarding their evaluation of the	consistently evaluate the carcinogenic MOA for	S
		. 33.3 . 30	MOA. The structure and format of the tables for	each tumor site. Please use the MOA Human	
			kidney MOA and liver MOA are very inconsistent	Relevance Framework to consistently and	
		<u> </u>	<u> </u>		

			(Tables 4-54 and 4-68) and lend to a lack of transparency. Please use the same method of evaluating data for each tumor site. Further, a MOA table for pulmonary carcinogenicity is lacking.	transparently assess MOA data for kidney, liver and pulmonary tumors.  Construct the MOA tables using a consisitent format and add an MOA table for pulmonary carcinogenicity.	
6	1.4.7	1-283 through 1- 302	The DoD agrees with EPA's choice to concur with the SAB recommendation and remove the kidney studies from the pool of principal studies and critical effects for the RfD and RfC. However, the uncertainties underlying this decision are not adequately represented within the kidney MOA section.	Please transparently discuss the uncertainties in the kidney effects within the MOA section.	S
7	1.4.7	1-285, Table 4-54	The phrase "Mutations cause cancer" in this table is extremely simplistic to the point of almost being incorrect. Cells that have lost the ability to repair mutations and mutations within tumor suppressor or oncogenic genes can lead to cancer, and genotoxicity coupled with unscheduled DNA synthesis can lead to cancer. However, cells with intact DNA repair mechanisms and properly controlled cell cycle effectively repair mutations. EPA is not presenting the entire pathway or sequence of events that are necessary for tumor development. Further, EPA has not distinguished mutations that may be directly related to TCE-mediated neoplasm formation versus those that may arise during the general unregulated cellular proliferation following cell	Please clarify the phrasing of "Mutations cause cancer".	S

			initiation.		
8	1.4.7	1-285, Table 4-54	EPA has failed to adequately address review comments regarding their evaluation of the MOA. Table 4-54 is poorly constructed and inadequate. The major headings for the hypothesized MOA is confusing; as written it appears that there are three hypothesized MOAs, two of which are entitled "Mutagenicity". The main section headings in the table should follow the hypothesized MOA pathway in sequential order, with the subheadings in the first column as the sequential key steps. The second column should have salient citations and also present the negative findings in a balanced manner. It is not a "weight of evidence" evaluation without equal presentation of the negative information.  As mentioned in previously submitted comments, tables evaluating the potential MOAs should clearly include the pathways and sequences of key events for dose-response and temporality with regard to the tumor endpoint.	Please appropriately evaluate the multiple MOAs for each tumor endpoint using the MOA/Human Relevance Framework. Please revise Table 4-54.	S
9	1.4-1.7		EPA has failed to adequately respond to review comments pertaining to their evaluation of TCE MOA. EPA needs to conduct an analysis of the dose-response of key events in all of the hypothesized MOAs; the footnote that was	As per previous suggested revisions, please conduct a thorough MOA Human Relevance Framework evaluation of all of the hypothesized MOAs, which should include analysis of the dose-response concordance.	S/M

			added regarding the Cancer Guidelines review (Guyton et al., 2008) is insufficient to justify not considering the toxicokinetic differences across species, especially when EPA asserts that metabolism of TCE is a key event within the MOA. It is completely inappropriate for EPA to claim that metabolism of TCE is necessary for toxicity, and then to say that evaluation of the toxicokinetic processes that lead to formation and distribution of the active metabolites are not part of the MOA.		
10	1.5	1-302 through 1- 543	EPA has failed to sufficiently respond to peer- review comment and strengthen their conclusion that DCA may play a role in TCE-induced liver effects and that TCA cannot adequately account for liver effects of TCE.	EPA needs to add specific quantitative and qualitative discussion within the liver MOA discussion on the role of DCA and TCA in liver toxicity of TCE.	S
11	1.5.7.1.5	1-443	The newly added discussion regarding Guyton et al. 2009 and DEHP and PPAR alpha is not necessary and only adds more length to an already cumbersome document. The added language does nothing to strengthen EPA's argument regarding PPAR alpha; given that the SAB agreed with EPA that there is inadequate support for PPAR alpha-mediated liver carcinogensis, it is unclear why EPA felt it necessary to add the additional text. Tables 1-66 and 1-67 are not related to TCE and text does not clearly describe how the information within those tables is relevant.	Consider deleted or drastically reducing the added text regarding PPAR alpha. This text does not seem to be in direct response to an external review comment and is unnecessary.	S

			EPA reports that the Dawson et al. observed		
			cardiac anomalies with no NOAEL (LOAEL = 1.5		
			ppm), while Johnson et al. observes a NOAEL of		
			2.5 ppb. First, Dawson et al. reported statistical		
			significance based only on a per-fetus analysis		
			instead of basing it on per-litter analysis. It	Please follow EPA developmental guidance and	
			appears that EPA is going against its own	appropriately analyze developmental effects	
40	400444	4 004 11 - 40 04	guidance. Watson et al. reports that there is no	related to exposure during pregnancy on a per-	
12	1.8.3.1.11	1-684, lines 18-24	statistically significant increase in CHD when	litter basis. Please correct this error in various	S
			Dawson et al. data are analyzed based on per-	locations as it has been repeated throughout the	
			litter basis. Analysis of developmental effects	document, i.e. 4-643, line 21.	
			related to exposure during pregnancy on a per-		
			fetus basis is not consistent with EPA's		
			1991 Guidelines for Developmental Toxicity Risk		
			Assessment,, especially when the data exist to re-		
			analyze the data per-litter.		
			<u> </u>		
			As noted in prior reviews, the technical basis for		
			relying on studies with known serious limitations	We acknowledge that the SAB reviewers	
			remains unclear. EPA has not adequately	accepted use of Johnson et al. (2003) to derive	
			addressed these prior comments. Percent litters	reference points for development of the RfD,	
			with fetuses with abnormal hearts/number litters	though they provided recommendations for a	
			did not show a dose-response relationship. In	stronger argument for its use. The observed	
		1-666 Table 1-	addition, the magnitude of change between 250	results do not reflect typical solvent toxicity.	
13	1.8.3.1.6.2	100	ppb and 1100 ppm, a 4400-fold difference, only	EPA should better justify how a study of	S/M
		100	yielded a 1.5-fold difference in response, with	questionable quality and no observed dose-	
			the intermediate concentration (1.5 ppm)	response can be selected as a basis for a critical	
			exhibiting a lower response than the 250 ppb.	effect. EPA should justify the use of data that	
			There is, therefore, no exposure-response	has not been peer reviewed for developement of	
			pattern in Johnson et al. (2003). Moreover,	the RfD. Please apply Hill's causality guidance	
			Watson et al. (2006) reported that Johnson et al.	to the Johnson et al. study.	
			later presents the 250 ppb as not significantly		

			linked to congenital heart defects (CHD). In view of this information, it is unclear how EPA can use this effect as a candidate critical effect. It appears that EPA is going against its own guidance regarding application of Hill's causality criteria in conducting human health risk assessment.  The Johnson et al. data was peer reviewed and		
			published on a per-pup basis. For purposes of dose-response modelling EPA utilized data on a per-litter basis obtained from the author via personal communication. While use of the per-litter basis is in conformance with EPA guidelines for developmental toxicology, we are very concerned that the data used for dose-response and development of the RfD was not peer reviewed.		
14	2.2.2 Environmental Fate		Photolysis of TCE in the atmosphere is portrayed as proceeding slowly, yet the half-life is indicated as being 1-11 days, which in the draft EPA Design for the Environment Criteria would be characterized as "low" environmental persistence.	Characterization should be consistent with other EPA guidance documents.	S
15	Figure 2-3		The figure of annual emissions of TCE was removed and replaced with a map of emissions of ethyl acrylate.	Add the figure for TCE back into the document.	Е
16	5.1	5-1	DoD appreciates the level of effort EPA authors have spent analyzing the noncancer toxicity of TCE. An assessment of this significance	EPA authors should follow the published technical documents it references, and develop several candidate RfDs and RfCs on	S

certainly warrants this level of care.

Unfortunately, EPA fails to follow a Risk Assessment Form technical panel report referenced and characterized as having been used in this Toxicological Review; titled *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002). The text we are referring to is located on page 4-22. EPA authors developed 80 draft RfDs and RfCs for a plethora of potential critical effects and not the "several" as dictated in this 2002 Risk Assessment Forum document. Specifically,

"For example, the dose-response curves would be modeled for **several** [emphasis added] adverse endpoints and the corresponding BMDs and BMCs and their lower 95% confidence limits (BMDLs/BMCLs) calculated (U.S. EPA, 2000c) or NOAELs determined if dose-response modeling is not possible. Next, duration adjustment to the continuous exposure scenario would be performed for each endpoint, with further adjustment to the corresponding HECs using the RfC methodology (U.S. EPA, 1994) or adjusted BMDLs or NOAELs for oral or dermal exposures (see Section 4.4.3 for further discussion). These adjusted values would represent the POD for each relevant endpoint. Then, uncertainty/variability factors that take into account a variety of issues, including chemicalappropriately judged critical effects, and not the shotgun approach exemplified in the TCE document. Derivation of 80 RfDs and RfCs for a plethora of effects, without evaluation of adversity of endpoint, duration of exposure, or study/endpoint confidence and/or uncertainty, is not consistent with EPA's guidance and does not provide a scientifically sound assessment for a chemical with such importance and impact as TCE.

			specific data, such as known toxicokinetic		
			differences between the laboratory animal		
			species tested and humans, and mode of action		
			information would be applied to the adjusted		
			values for each relevant endpoint. The sample		
			reference values would then be compared		
			across endpoints and organ systems to		
			determine which are the most relevant for use in		
			deriving the final reference value for each		
			exposure duration that will be protective of the		
			human population (including susceptible		
			subgroups)."		
			EPA has not adequately addressed prior review		
			comments regarding their modeling approach for		
			the RfD/RfC. EPA goes through a screening		
			process based on applied dose, identification of		
			a POD based on applied dose and application of		
			uncertainty factors to derive candidate	The authors should follow the Risk Assessment	
			RfCs/RfDs (cRfCs or cRfCs) based on applied	Forum document it references (U.S.EPA 2002)	
			dose. This was done to reduce the large number	for developing RfDs/RfCs, or provide evidence	
		5-1 and Figure 5-	of noncancer health endpoints and studies prior	that calculating HEC or HED prior to dose	
17	5.1	1	to selecting the critical effects for deriving RfC or	modeling will not identify more sensitive	S/M
			RfD. Once candidate critical effects are selected	endpoints than those identified using the current	
			for those endpoints with the lowest cRfCs or	standard of practice that everyone else uses,	
			cRfD, internal PODs (iPODs) are calculated, to	including EPA.	
			the extent possible, by application of a PBPK		
			model. HEC or HED are then calculated and		
			application of PBPK model-derived UFs results		
			in PBPK model-based candidate RfC or RfD (p-		
			cRfC or p-RfD) for each candidate critical effect.		
			EPA believes that this approach, compared to		

that of deriving an RfC or RfD based on a single effect, provides more robust estimates of RfC and RfC because it highlights the multiple effects that are yielding very similar candidate values. Using a pharmacokinetic model, EPA has calculated internal dose-metrics for various endpoints (see Section 5.1.3.1.1). We are not sure why EPA does not simply use these PBPK modeled internal dose-metrics prior to doseresponse modeling to identify the appropriate POD for deriving the RfC or RfD for TCE. In our experience, dosimetric conversion of concentrations or doses to HEC or HED prior to dose-response modeling can result in sufficiently different dose-response shape with its attendant changes in the risk value derived. EPA itself has also reported instances where use of internal dose-metrics has resulted in several-fold changes in the reference value (see, for example, 5-86, lines 3-18, Section 5.1.3.1.8). This should have raised flags for the EPA to identify the most sensitive endpoint(s) using internal dose metric-based dose response modeling. EPA has not demonstrated that a more sensitive endpoint has not been missed by the current approach. S 18 5.1.1 5-5, line 29 Equivalence is not assumed among species on EPA should follow this 1994 EPA methods

			a ppm basis. In Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA 1994) EPA dictates that a dosimetric adjustment be made on the basis of experimental conditions and species.	document, cited as a reference utilized in development of the TCE assessment.	
19	5.1.2	5-10 Table 5-2.	EPA has developed standard symbols for these uncertainty factors. EPA has not clearly explained why an alternative approach is warranted in this assessment.	Authors should use standard EPA symbols.? ?EPA should explain why it believes and alternative approach is warranted for this assessment.	0
20	5.1.3.2	5-74, Table 5-9	EPA announced during the summer of 2010 that it would not rely on studies from the Ramazzini Foundation, such as the Maltoni studies, for evaluations of toxicity. Has that position since changed?	EPA should drop its use of the Maltoni study, or clearly explain the basis for its use.	S
21	5.1.5.2	5-119 line 15	"0.00006" ppm should read "0.0006" ppm.	Please fix typographical error.	E
22	5.1.5	5-110	EPA has not adequately addressed prior review comments made by DoD and by the external peer review regarding the MOA analysis. EPA needs to conduct a seasoned analysis of the critical effect(s), emphasizing understanding of mode of action and the underlying fundamental biology. We do not believe that the text and tables added to the TCE document fully address the recommendations made by the panel.	EPA needs to argue from biological grounds why one effect over another might constitute the critical effect in humans, for example, in text descriptions of Tables 5-26 and 5-27. The expected MOA in humans should be an integral part of this argument; this comment has been raised during previous review by DoD and others.	S/M
23	6.2.2.1.2	6-33	Throughout this section, EPA carries on an analysis of multiple tumor endpoints and comparisons with apparent little regard for the	The authors should follow EPA cancer guidelines in their comparison of tumor endpoints. Endpoints with little confidence	S

			individual strengths and weaknesses of the resulting slope factors. Another approach, and one favored by EPA (2005) and other expert bodies, is to approach the choice of a study and model as one that will yield the most confident results. This latter approach yields one or at most several (~5 or less) slope factors for comparison with correspondingly greater confidence.	should be dropped from the analysis.	
24	6.2.2.1.2	6-34, line 17	EPA cites use of a Maltoni study in this section (and elsewhere, see comment above).  However, EPA precluded the use of all Ramazzini Foundation studies during 2010. Has this EPA directive been overridden?	EPA needs to recalculate the cancer slope factor without the use of the Maltoni study, as per EPA (2010) directive.	S
25	6.1.4	6-11	We still disagree with, EPA's categorization TCE as "carcinogenic to humans".  We acknowldge that the SAB agreed with EPA's classification but other reviews have drawn similar conclusion as we did in our review, that "likely to be carcinogenic to humans" is better applied as the descriptor. For example, an additional meta-analysis by Kelsh et al. (2010) of the epidemiology data suggested no better than "likely to be carcinogenic to humans," whereas a review of the experimental animal data by Dourson and colleagues at TERA would suggest the phrase "suggestive evidence of carcinogenic potential." In neither of these analyses would the phrase "carcinogenic to humans" be scientifically appropriate.	Reconsider the cancer descriptor.	S/M

26	6.2.2.1.2	6-34 line 23	The Henschler et al. studies were complicated by contamination with epichlorohydrin. This was noted in public comments and was not adequately addressed by EPA.	EPA needs to recalculate the cancer slope factor without the use of the Henschler et al. study, as per public comments.	S
27	6.1.1	6-1	New text was added into the summary section on exposure and does not adequately discuss levels of TCE in indoor air from consumer products as the main source of TCE in residential homes. Although this information was discussed in Section 2, it is not adequately captured in the summary section. Further, the added sentence regarding vapor intrusion implies that the indoor air sampling results are from vapor intrusion from contaminated soils or groundwater only. Vapor intrusion may contribute to indoor air contamination at sites where subsurface TCE contamination has been documented; however, alternate indoor sources (cleaning agents, solvents, and levels in tap water) must also be accounted for as part of any vapor intrusion study.	Please modify the first paragraph of section 6.1.1 to include the contribution of TCE in consumer products as a source for indoor air TCE. Vapor intrusion may contribute to indoor air contamination at sites where subsurface TCE contamination has been documented; however, alternate indoor sources (cleaning agents, solvents, or domestic use of contaminated water) must also be accounted for as part of any vapor intrusion study.	S

Council on Environmental Quality (CEQ) Comments NCEA Interagency Communication #128b (Transmission of science discussion draft assessment appendices for trichloroethylene) July 15, 2011

Thank you for the opportunity to review and comment on the draft Toxicological Review of trichloroethylene (TCE) dated June 2011. The draft Toxicological Review does an excellent job summarizing the available literature on TCE. We applaud the extensive external review and response to comment to which the TCE IRIS Review has been subject (http://cfpub.epa.gov/ncea/iris\_drafts/recordisplay.cfm?deid=215006).

CEQ finds that the derived risk values are appropriately presented according to EPA guidance. We support the proposed RfD but question why the most sensitive candidate RfD (4x10-4 mg/kg-day; Peden-Adams et al. 2006) was not selected on its own. Instead, three co-studies (Peden-Adams et al. 2006; Keil et al. 2009; Johnson et al. 2003) were selected, and the end result is that the RfD increased to 5x10-4 mg/kg-day. Has EPA considered alternatively using these three co-critical studies to justify setting the overall RfD at 4x10-4 mg/kg-day under the premise that the most sensitive effect should be used as the basis for the risk value?

We agree that the applied uncertainty factors are appropriate and are consistent with EPA guidance. CEQ also supports the proposed RfC and the derived cancer slope factors. Finally, CEQ agrees with the finding of a mutagenic mode of action and with the recommendation to apply the default age-dependent adjustment factors where appropriate.

#### NASA COMMENTS ON THE FINAL DRAFT TCE IRIS RISK ASSESSMENT

#### **JULY 2011**

NASA thanks EPA for the opportunity to review and comment on the final draft TCE IRIS risk assessment, reviewing EPA's response to interagency, public and external peer review comments. We appreciate that EPA provided general supporting documentation of three specific areas identified by the external peer review and EPA's subsequent response. NASA's global and more specific comments are provided below.

### **Global Issues:**

- NASA does appreciate that EPA did add specific language additional or more current studies to clarify and support its assessment in three areas identified by the external peer review. However, NASA is not aware of nor has been provided with a formal response to comments documentation from EPA on its response to significant interagency issues with scientific and technical aspects of the draft assessment. Lack of a response to comments document and the extremely verbose nature of the draft inhibit interagency participants' review of EPA's response to previous version of this draft. In addition, the provided redline document exhibited errors in the organization and numbering, making a review of the changes difficult and confusing.
- NASA's notes that the TCE draft reflects the systemic issues with the lack of clarity, transparency, support of scientific decision making and adherence to established EPA guidance and methods that the NAS detailed in its review of EPA's formaldehyde draft IRIS risk assessment. The TCE draft continues to exhibit all these fundamental weaknesses that the NAS identified as consistent issues with numerous IRIS assessments. EPA did add specific statements in direct response to the external peer review for specific clarification on several issues but the resulting document is in excess of 3000 pages and offers the reader a most daunting task to review and understand EPA's assessment and establishment of the proposed TCE RfD and RfC. EPA indicates it plans to address these significant, systemic weaknesses in future draft IRIS assessments. However, the current TCE draft lacks clarity, transparency and consistency with EPA policies and guidance. NASA questions whether the current draft is of sufficient quality and clarity to be ready to finalize, especially on such a significant concern as TCE.
- EPA cites studies for chemicals that are not the target chemical or its documented metabolites.
   This concern has been identified during interagency review on other draft IRIS reviews.
   Inclusion of non-targeted chemicals in such a complex IRIS review confuses the reader, offers little insight into EPA's evaluation process and raises technical questions about EPA's internal review process. EPA is encouraged to address this issue prior to finalizing the draft TCE IRIS draft.

- Significant issues identified by the peer review were not adequately addressed in this draft.
   Examples of outstanding issues and recommendations by the peer review that require additional EPA action include:
  - o MOA and the assessment of kidney and liver data
  - o Discussion and definition of mutation
  - o Explanation of liver data
  - Consistency with established EPA guidance, such as the 1991 Guidelines and the 2002
     RFD and RFC guidance and EPA's modeling criteria for RfDs and RfCs
  - Appearance of preference for studies with detrimental results, especially at low level doses while not appearing to consider studies which show no impacts
  - Previous interagency comments mirrored many of the same technical and scientific issues, as well as weaknesses in clarity and transparency, as stated by the peer reviewers.

NASA thanks EPA for the opportunity to review and comment on the final draft of the TCE IRIS risk assessment.

# Comments on: The Draft IRIS Toxicological Review for Trichloroethylene (TCE) for Final Agency/Interagency Science Discussion

**Reviewer**: Andrew A. Rooney, NIH/NIEHS/National Toxicology Program **Comments**:

Although the document is lengthy, EPA has done a good job in presenting the body of evidence to support an RfD of  $5 \times 10^{-4}$  (and the RfC) based on the Keil et al. (1) data in female mice, the Peden-Adams et al. (2) decreased IgM antibody plaque-forming cell (PFC) response and increased delayed type hypersensitivity (DTH) response; Johnson et al. (2003) fetal heart malformations. Two important adjustments in the interpretation and use of immune data are strongly suggested.

- Autoimmune effects from the Keil (1) study in B6C3F1 mice should have been used in support of the
  combined RfD and to derive the RfC in place of the data on decreased thymus weight.

  Both autoimmune effects and decreased thymus weight were observed at the lowest dose in the Keil
  (2009) drinking water study of adult B6C3F1 mice (0, 1400, 14000 ppb TCE). The thymus data have the
  uncertainty of being an unreliable indicator of immunotoxicity while the autoimmune data have greater
  biological significance and are linked to human TCE-autoimmune effects.
  - a. Autoimmune effects:
    - i. Autoantibodies to (double stranded) ds DNA at 1400 and 14000ppb
    - ii. Autoantibodies to (single stranded) ss DNA at 1400 and 14000ppb
    - iii. Dose-response- high dose (14000ppb)effects on ds DNA 6 weeks before low dose
    - iv. Supported by renal pathology (may be associated with anti-dsDNA) observed at 1400ppb
    - v. 1400ppb (EPA converts to 0.35 mg/kg/d POD) is LOAEL
    - vi. EPA UF of 100 is too low (10-interspecies, 10-intrahuman, 1-LOAEL to NOAEL, 1-database)
    - vii. The LOAEL to NOAEL UF cannot be reduced from 10 to 1 for autoimmune or other immune effects at 1400ppb TCE in B6C3F1 mice because of the three clear autoimmune effects [1]autoantibodies to dsDNA, 2]autoantibodies to ssDNA, 3] renal pathology], the stimulation or hypersensitivity observed at this dose [4] increased DTH] which supports human data and may be related to the autoimmunity as well, and then finally the 5) suppression of PFC (1, 2). If the LOAEL to NOAEL were reduced from 10 to 3 (which we advise against) then an increase in the database UF from 1 to 3 or 1 to 10 is warranted because it is clear the database demonstrates multiple immune effects a the 1400ppb dose and there is a lack studies with data at lower doses.
    - viii. The total UF should be 1000 (10-interspecies, 10-human variation, 10-LOAEL to NOAEL)
    - ix. Therefore, the RfD should be 0.00035, which supports the Peden-Adams and Johnson RfDs.
    - x. Increased ds DNA is accepted biomarker for autoimmunity (3)
    - xi. Human data support association between TCE and autoimmunity, with the strongest data for systemic sclerosis (as concluded in the EPA draft assessment and (4, 5)); the autoimmunity is also related to hypersensitivity in humans and supported by DTH data cited in point vii above
  - b. Thymus weight was decreased at both doses (at 1400 and 14000ppb)
    - i. 1400ppb (EPA converts to 0.35 mg/kg/d POD) is LOAEL
    - ii. UF=1000 (10-interspecies, 10-human variation, 10-LOAEL to NOAEL)
    - iii. Thymus weight is a relatively insensitive or "unreliable indicators of immunotoxicity" (6); therefore, it may be an indicator of immunotoxicity but its use to derive an effect level should be done with caution or avoided if there are other options.
    - iv. Thymus weight change was not observed in the Peden-Adams study of B6C3F1 mice at the same dose (1400, and 14000ppb) in a developmental through 8 weeks of age

- v. Thymus weight is a non-specific marker of potential immunotoxicity and should not be used when there are better data, with functional significance and a clear link to the human data for effects of TCE.
- 2. Several statements were made in the draft TCE document that downplays the significance or predictability of IgM antibody plaque-forming cell (PFC) response data for the determination of immunotoxicity. These statements are incorrect, because PFC is highly predictive for immunotoxicity and a preferred functional immune assay for use in risk assessment (6, 8). The statement that "decreased PFC response may not be considered adverse in and of itself" contradicts the EPA's immunotoxicity testing guidelines(7) and is counter to the strong support of PFC data by immunotoxicologists (6, 8), and they should be corrected or removed. The statement that on lines 29-31 page 5-53 is incorrect and should be deleted, and the document should be searched and similar statements removed throughout:
  - 29 Although decreased PFC response may not be considered adverse in and of itself, a
  - 30 LOAEL-to-NOAEL UF of 10 was used because of the increased delayed-type hypersensitivity at
  - 31 the same dose.

In summary, the autoimmune effects (specifically increased autoantibodies to dsDNA and ssDNA with associated increase in renal pathology) in Keil et al. (1) study of B6C3F1 mice should have been used for the RfD and RfC in place of the thymus data because the thymus weight data is a less reliable indicator of immunotoxicity. Furthermore, the autoimmune data has clear support for functional significance and as strong link between the animal data on autoimmune endpoints and the evidence for TCE-related autoimmunity and hypersensitivity in humans. The statements discounting the reliability of the PFC should be deleted.

Best Regards,

Andrew A. Rooney, NIH/NIEHS/National Toxicology Program

### **References:**

- 1. Keil, D. E., Peden-Adams, M. M., Wallace, S., Ruiz, P., and Gilkeson, G. S. (2009) Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease, *J Environ Sci Health A Tox Hazard Subst Environ Eng* 44, 443-453.
- 2. Peden-Adams, M. M., Eudaly, J. G., Heesemann, L. M., Smythe, J., Miller, J., Gilkeson, G. S., and Keil, D. E. (2006) Developmental immunotoxicity of trichloroethylene (TCE): studies in B6C3F1 mice, *J Environ Sci Health A 41*, 249-271.
- 3. WHO. (2006) Principles and methods for assessing autoimmunity associated with exposure to chemicals. IPCS Environmental Health Criteria 236, In *IPCS Environmental Health Criteria 236*, p 312, International Programme on Chemical Safety, World Health Organization, Geneva.
- 4. National Research Council. (2006) Assessing the Human Health Risk of Trichloroethylene: Key Scientific Issues, pp 1-448, The National Academies Press, Washington, DC.
- 5. Cooper, G. S., Makris, S. L., Nietert, P. J., and Jinot, J. (2009) Evidence of autoimmune-related effects of trichloroethylene exposure from studies in mice and humans, *Environ Health Perspect 117*, 696-702.
- 6. Luster, M. I., Portier, C., Pait, D. G., White, K. L., Jr., Gennings, C., Munson, A. E., and Rosenthal, G. J. (1992) Risk assessment in immunotoxicology. I. Sensitivity and predictability of immune tests, *Fundam Appl Toxicol 18*, 200-210.
- 7. U.S. EPA. (1998) Health Effects Test Guidelines: OPPTS 870.7800 Immunotoxicity, In *Report*, pp 1-11, Office of Prevention, Pesticides and Toxic Substances, Washington, DC.
- 8. Ladics, G. S. (2007) Primary Immune Response to Sheep Red Blood Cells (SRBC) as the Conventional T-Cell Dependent Antibody Response (TDAR) Test, *J Immunotox 4*, 149-152.

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

July 21, 2011

While we recognize that EPA has made important and likely very substantive changes throughout the document, considering its size (1393 pages of main text plus 1593 pages of technical appendices) and 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, solesource 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.
- It was difficult to review many portions of the response to peer review comments. For instance, appendix I at page 2 states that EPA made changes to address peer review comments and those changes can be seen in Section 3.5.7.4. However in both the clean and redline version provided to the interagency group, we cannot find a Section 3.5.7.4. Similarly there is no Section 3.5.5.2. Thus in these cases, and others as well, it is not clear what changes EPA has incorporated to address the peer review concerns. Appendix I unfortunately does not provide details as to the substance of the changes made. In addition to fixing the section numbers, it would be helpful to provide a more detailed description of the changes made in Appendix I.
  - Specifically, sections that are referred to in Appendix I as containing changed language which we could not find (and therefore could not review):

3.5.7.4	4.6.1.2.2	3.5.7.3.2
3.5.5.2	4.5.6.2.1	3.5.7.4
3.5.5.3	4.5.6.3.2.5	3.5.7.5
3.5.6.3	3.3.3.2	4.5.7.4
3.5.6.2	3.5.4.3	5.2.2.1.3
3.5.6.4	3.5.6.3.3	5.2.3.3.1
3.5.7.2	3.5.7.3.1	5.2.3.3.2

Last week, 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." We note that in 2006 NAS made recommendations that are similar to EPAs commitment (eg, using objective criteria, performing a sensitivity analysis, etc; see NAS 2006 for a full list of recommendations). 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.

- Appendix I, the response to peer review and public comments, does not provide any response to the NAS review of 2006. Since this is such an important and complex assessment (as reflected by both an NAS review in 2006 and SAB review in 2010), it would be helpful if Appendix I also addressed the major recommendations of the NAS review.
- In their comments on the Mode of Action (MOA), SAB stated (see page 2-3 and elsewhere in the SAB report: "The Panel agreed that the weight of evidence supports a mutagenic MOA for TCE-induced kidney tumors. However, the Panel concluded that the weight of evidence also supported an MOA involving cytotoxicity and compensatory cell proliferation and including these may more accurately reflect kidney tumor formation than does a mutagenic mechanism alone. The combination of cytotoxicity, proliferation and DNA damage together may be a much stronger MOA than any individual components." EPA notes this on page 14 of Appendix I, however it is not clear what analysis and changes have been made to address this comment.
  - O As a non-linear model, based on cytotoxicity and compensatory cell proliferation was found to have significant biological support, it is not clear why EPA continues to present only linear modeling. The EPA cancer guidelines (2005) at page 1-8 state: "When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision."
  - O We would like to see EPA implement the recommendation from page 1-9 of the Cancer Guidelines: "If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager."
- Considering the SAB comments above regarding a plausible mode of action for kidney tumors that does not involve a mutagenic mode of action, it seems that this would create uncertainty regarding the application of the age dependent adjustment factors (ADAFs). While SAB supported the use of the ADAFs for kidney tumors, some discussion is needed regarding their application since SAB also stated that "However, the Panel concluded that the weight of evidence also supported an MOA involving cytotoxicity and compensatory cell proliferation and including these may more accurately reflect kidney tumor formation than does a mutagenic mechanism alone. The combination of cytotoxicity, proliferation and DNA damage together may be a much stronger MOA than any individual components." In light of this SAB statement, a discussion of the uncertainty associated with using the ADAFs when there is a MOA that is not mutagenic is needed.

• While EPA states that they have added the recommended sensitivity analysis (in Sections 3.5.6.4 and 3.5.7.2, both of which we could not find), it is not clear how EPA has used the results of the sensitivity analysis to inform the final determinations and the confidence in them. Some discussion of this is needed in Sections 5 and 6.

# Specific Comments on Appendix I:

- It is not clear how EPA addressed SAB comments that were not in bullets. For instance, page 15 of the SAB report states, in regard to liver effects: "Less repetition and better integration of these sections would improve the readability of the document." It is not clear what changes EPA has made to address this statement, and other similar statements that are suggestions from the SAB, but are not included in a bulleted recommendation.
- In response to public comments, on page 5 of Appendix I EPA states that they have added data on TCA bioavailability to the TCA sub-model of the PBPK model. However, EPA then states that this was not incorporated into the PBPK model. Since TCA is such an important metabolite, further description of why this information was not incorporated into the model would be useful. Since EPA has the data, it would also be useful to discuss what the impacts on the final values would have been had EPA incorporated the information.
- While EPA acknowledges that SAB would like EPA to do a quantitative analysis of the
  relative contributions of TCA and/or DCA to TCE liver carcinogenisis, on page 13 EPA
  states that this analysis is precluded due to a high degree of heterogeneity. It would be
  helpful if EPA provided language discussing the impacts of this variability on the final
  determination.
- At page 21, EPA chose not to implement the SAB recommendation which stated that: "Chapter 5 should include the information on POD derivation from Table F-13 of Appendix F, including approach, selection criterion and decision points." The NAS has recently commented on the need for clear articulation of selection criteria and decisions points, and EPAs current approach to describing studies (as was done in Chapter 5 of the TCE draft) and in this case SAB specifically suggested a clearer presentation. We suggest that EPA reconsider the SAB recommendation.
- On page 37 of the SAB report, there are clear recommendations regarding the level of certainty for dose metrics and endpoints. It is not clear where this is addressed in Appendix I and how this suggestion is incorporated in the toxicological review.
- Page 24, notes that some public commenters were concerned that the PBPK model led to 'double counting' of variability. It would be helpful if EPA responded directly to this comment to address the concern.
- Page 27, we do not agree with the EPA statement that an analysis which looks at validation of the quantitative risk assessments should be beyond the scope of the assessment. It is important that EPA look to 'ground-truth' (or validate) modeled risk values whenever available data may exist.

# 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.