

**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

			<p>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.</p> <p>Review of the final 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;</p>		
4	Appendix I and general response to charge question 3		<p>The SAB indicated that more discussion of the inconsistencies in the level of activity of the glutathione conjugation pathway metabolites was needed and that EPA should present the impact of divergent pathways more transparently. EPA's apparent response is to place a caveat on the utility of the glutathione information and not investigated the impact. These changes are made more important by the data inconsistencies between the two cited methods of analysis.</p>	Undertake a more critical analysis of the impact of the secondary pathway and possible analytical differences.	S
5	1.4	Table 4-68	EPA has failed to adequately address review comments regarding their evaluation of the MOA. The structure and format of the tables for kidney MOA and liver MOA are very inconsistent	As noted during previous review, EPA needs to consistently evaluate the carcinogenic MOA for each tumor site. Please use the MOA Human Relevance Framework to consistently and	S

			(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 consistent 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	<p>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.</p> <p>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.</p>	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

			<p>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.</p>		
10	1.5	1-302 through 1-543	<p>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.</p>	<p>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.</p>	S
11	1.5.7.1.5	1-443	<p>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 carcinogenesis, 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.</p>	<p>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.</p>	S

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

			<p>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.</p> <p>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.</p>		
14	2.2.2 Environmental Fate		<p>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.</p>	<p>Characterization should be consistent with other EPA guidance documents.</p>	S
15	Figure 2-3		<p>The figure of annual emissions of TCE was removed and replaced with a map of emissions of ethyl acrylate.</p>	<p>Add the figure for TCE back into the document.</p>	E
16	5.1	5-1	<p>DoD appreciates the level of effort EPA authors have spent analyzing the noncancer toxicity of TCE. An assessment of this significance</p>	<p>EPA authors should follow the published technical documents it references, and develop several candidate RfDs and RfCs on</p>	S

		<p>certainly warrants this level of care.</p> <p>Unfortunately, EPA fails to follow a Risk Assessment Form technical panel report referenced and characterized as having been used in this Toxicological Review; titled <i>A Review of the Reference Dose and Reference Concentration Processes</i> (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,</p> <p>“For example, the dose-response curves would be modeled for <i>several</i> [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 chemical-</p>	<p>appropriately 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.</p>	
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			<p>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).”</p>		
17	5.1	5-1 and Figure 5-1	<p>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 RfCs/RfDs (cRfCs or cRfCs) based on applied dose. This was done to reduce the large number of noncancer health endpoints and studies prior to selecting the critical effects for deriving RfC or RfD. Once candidate critical effects are selected for those endpoints with the lowest cRfCs or cRfD, internal PODs (iPODs) are calculated, to 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</p>	<p>The authors should follow the Risk Assessment Forum document it references (U.S.EPA 2002) for developing RfDs/RfCs, or provide evidence that calculating HEC or HED prior to dose modeling will not identify more sensitive endpoints than those identified using the current standard of practice that everyone else uses, including EPA.</p>	S/M

			<p>that of deriving an RfC or RfD based on a single effect, provides more robust estimates of RfC and RfD because it highlights the multiple effects that are yielding very similar candidate values.</p> <p>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 dose-response 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.</p>		
18	5.1.1	5-5, line 29	Equivalence is not assumed among species on	EPA should follow this 1994 EPA methods	S

			a ppm basis. In <i>Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry</i> (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.	O
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 acknowledge 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	<p>The Henschler et al. studies were complicated by contamination with epichlorohydrin. This was noted in public comments and was not adequately addressed by EPA.</p>	<p>EPA needs to recalculate the cancer slope factor without the use of the Henschler et al. study, as per public comments.</p>	S
27	6.1.1	6-1	<p>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.</p>	<p>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.</p>	S

**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		<p>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</p>	<p>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 clarity and usefulness. More detailed comments are provided below.</p> <p>Perform a quality control review in addition to a review by the user community.</p>	S/M

			<p>to use IRIS values.</p> <p>Numerous cross-references to the Toxicological Review are incorrect.</p>		
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	The 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 candidate 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.	E
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 addition 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	<p>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.</p> <p>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 explicitly</p>	<p>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,</p> <p>Correct 5.2.3.3.3 to 5.2.3.1.5, we believe this is the correct section.</p>	S/M

			<p>stated that it is not required.</p> <p>Additionally, the reference to section 5.2.3.3.3 is incorrect.</p>		
13	II.C.1	31	<p>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.</p>	<p>Include a brief explanation for the four fold adjustment to account for NHL and liver cancer risks in addition to citing the correct section of the Toxicological Review.</p>	S
14	II.C.2	32-33	<p>Existing guidance that describes the consideration of multiple tumor types and the resulting adjustments made to the OSF and IUR is not cited.</p>	<p>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.</p>	S
15	II.C.2	33	<p>Section II.B.1 states that a five fold adjustment was made to account for the mulitple tunor types, but in this section shows 4 as being justified.</p>	<p>Correct or explain the discrepancy.</p>	S