			Department of Defense Comments	on	
			TCE IASD final draft Tox Review redli	ne.pdf	
	submitted by: Ch nt Directorate	nemical Material Risk	Organization: Department of Defense	Date Submitted: 7/15/2011	
	-	nce or methods (S); Edit on of the assessment.	orial, grammar/spelling, clarifications needed (E); or	Other (O). Also please indicate if Major i.e. affects	the outcome,
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

	1			1	1
			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 5		information and not investigated the impact.		
			These changes are made more important by the		
			data inconsistencies between the two cited		
			methods of analysis.		
	1	1	EPA has failed to adequately address review	As noted during previous review, EPA needs to	
		Table 4.00	comments regarding their evaluation of the	consistently evaluate the carcinogenic MOA for	
5	1.4	Table 4-68	MOA. The structure and format of the tables for	each tumor site. Please use the MOA Human	S
			kidney MOA and liver MOA are very inconsistent	Relevance Framework to consistently and	

			(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

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			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

12	1.8.3.1.11	1-684, lines 18-24	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</i> <i>Assessment,</i> , especially when the data exist to re- analyze the data per-litter.	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.	S
13	1.8.3.1.6.2	1-666 Table 1- 100	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	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 developement of the RfD. Please apply Hill's causality guidance to the Johnson et al. study.	S/M

			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 communicaiton. 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.		
			Photolysis of TCE in the atmosphere is		
	2.2.2		portrayed as proceeding slowly, yet the half-life		
1 1	2.2.2		is indicated as being 1-11 days, which in the	Characterization should be consistent with other	6
14	Environmental		draft EPA Design for the Environment Criteria	EPA guidance documents.	S
	Fate		would be characterized as "low" environmental		
			persistence.		
			The figure of annual emissions of TCE was		
15	Figure 2-3		removed and replaced with a map of emissions	Add the figure for TCE back into the document.	E
			of ethyl acrylate.		
			DoD appreciates the level of effort EPA authors	EPA authors should follow the published	
16	5.1	5-1	have spent analyzing the noncancer toxicity of	technical documents it references, and develop	S
			TCE. An assessment of this significance	several candidate RfDs and RfCs on	
				<u> </u>	<u> </u>

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		
				<u> </u>	

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

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
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
21	5.1.5.2	5-119 line 15	"0.00006" ppm should read "0.0006" ppm.	Please fix typographical error.	E
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
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
			a ppm basis. In <i>Methods for Derivation of</i> <i>Inhalation Reference Concentrations and Application</i> <i>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.	

				a	1
			individual strengths and weaknesses of the	should be dropped from the analysis.	
			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.		
			EPA cites use of a Maltoni study in this section	1	
			(and elsewhere, see comment above).	EPA needs to recalculate the cancer slope	
24	6.2.2.1.2	6-34, line 17	However, EPA precluded the use of all	factor without the use of the Maltoni study, as	S
			Ramazzini Foundation studies during 2010. Has	per EPA (2010) directive.	
			this EPA directive been overridden?		
					1
			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		
25	6.1.4	6-11	additional meta-analysis by Kelsh et al. (2010) of	Reconsider the cancer descriptor.	S/M
-			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.			

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

			Department of Defense Comments	on	
			TCE IASD Draft IRIS Summary.po	df	
Comments submitted by: Chemical Material Risk Management Directorate			Organization: Department of Defense	Date Submitted: 7/19/2011	
	categories: Science or implementation		orial, grammar/spelling, clarifications needed (E); or	Other (O). Also please indicate if Major i.e. affects	the outcome,
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.	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 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