Department of Defense Comments on
Tetrachloroethylene Tox Review - IASD - REDLINE.pdf

Comments submitted by: Chemical Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: 8/8/2011

*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	1, 3 and References	various	It has been several years since the last version of the tetrachloroethylene document was reviewed by the agencies and new DoD reviewers have since joined the review team. Several editorial/science issues were noticed relative to references and definitions of key IRIS terms. These comments are not all related to EPA's response to the external and public review but we wanted EPA to be aware of these issues and consider making changes in the document to address them. 1) The definitions of RfD and RfC are not compatible with each other and are not consistent with the IRIS glossary. Specifically, the RfC is said to be for continuous exposure, implying by comparison, that the RfD is not. (Page 1-1)	1) EPA should use its definitions in the IRIS glossary for IRIS documents, or justify the deviation. Inconsistent definitions lead to confusion. 2) The reference should be added, or explain why it is not relevant to this document. 3) EPA should use its definitions in the IRIS glossary for IRIS documents, or justify the deviation. Inconsistent definitions lead to confusion. 4) At this stage of the review, only references that are used should be in the introduction and in the list of references. 5) If these and other references were available online prior to October 2010, EPA should indicate when they were to avoid confusion. If	S

			2) We noted that the latest NRC risk assessment document, i.e., Science and Decisions is not cited. 3) The definition of "slope factor" is not consistent with the IRIS definition. Specifically, the glossary definition is “An upper bound, approximating a 95% confidence limit” and the text is a plausible upper bound. (Page 1-1) 4) The references listedin the Introduction seem to be boilerplate and not all utilized in the document. (Page1-1) 5) The text states that the literature search concluded in October 2010, yet the reference section has many citations that are from 2011, e.g., Colt et al. 2011, Corbin et al. 2011, Lynge et al. 2011, and Seldén and Ahlborg 2011. (Page 1-2) 6) The references cited in this paragraph are not specific to PCE. The conclusions stated are those of EPA, not necessarily the authors. (Page 3-14, lines 12-20) 7) In reviewing the references, DoD noted that several had lacunae in the authors, e.g., Colt, J. S.; Karagas, M. R.; Schwenn, M.; Baris, D.; Johnson, A.; Stewart, P., . . . Silverman, D. T. (2011) and Corbin, M.; McLean, D.; Mannetje, A.; Dryson, E.; Walls, C.; McKenzie, F., . . .	the references were not available online prior to October 2010, EPA should change this statement. 6) DoD would prefer that this speculative paragraph be deleted. For clarity and transparency, if EPA chooses to retain the paragraph, it should clearly indentify which conclusions belong to which authors. 7) Suggest EPA complete the references, at the draft final stage of a document one should expect all the authors to be listed.	

			Pearce, N. (2011). (global)		
2	3.3.3.2. Glutathione (GSH) Conjugation Pathway	3-12, 1-3	This conclusion requires a reference, as it is not supported by the data presented. Indeed the next sentences seem to refute this unqualified conclusion.	EPA should provide a reference or delete this sentence. New, unreferenced and otherwise unsubstantiated conclusions should not be added at this stage of the document, i.e., after public comment and external peer review.	S/M
3	3.5.1.2.3	3-48, lines 19-25.	The text asserts that the Chiu and Ginsberg (in press) article resolves problems with previous PBPK models by stating "...GSH conjugation may be high or low in humans with high uncertainty or variability."	The conclusion may be correct, but more information is needed, particularly for data that are not available for review.	S/M
4	4.3.5.2. Genotoxicity	global	DoD notes that EPA has not distinguished between genotoxicity and mutagenicity. As neither is defined in the IRIS online glossary, it is not possible to determine what effects are meant when these terms are used.	EPA should define and distinguish between genotoxicity and mutagenicity in this and other IRIS documents. The two terms are generally NOT considered interchangeable, especially as genotoxicity can include epigenetic events. This distinction is particularly important as a mutagenic mode of action has consequences that a genotoxic mode of action does not.	S/M
5	4.10.3. Mode-of-Action Summary	4-290	DEHP and Wy-14,643 are cited as the comparison chemicals for PPARα induction, and the National Academies judgment with regard to TCE and this mode of action's relevance to human liver cancer are not discussed.	EPA should either rely more on the data from TCE than other, less similar chemicals, or EPA should explain why data on TCE are not relevant for this discussion.	S/M
6	5	5-14	This is not a sentence, it is lacking a verb. As this information is critical to understanding the study selected for estimating the RfC, the absence of a verb is not trivial.	EPA should state whether these analyses were or were not performed by the authors.	S

7	5	5-17	Assuming the analyses mentioned in the previous comment were done by the authors of the study under discussion, this conclusion does not seem accurate. If the analyses on page 5-14 included "logistic regression analyses adjusted for **effects of age** [emphasis added], alcohol consumption, and smoking" it is not clear why "the normal ranges are influenced strongly by age, which was not available for the data set at a similar level of resolution as the normative data." The former statement suggests that the authors already adjusted for age.	EPA should resolve this inconsistency and adjust its calculation of the RfC appropriately	S/M
8	5	5-18	The need for the LOAEL to NOAEL UF is based solely on EPA's lack of a BMD. As results of the attempts of BMD modelling are not provided, DoD cannot independently judge why none of the data were amenable to the models. It is also not clear if EPA used only its preferred dose metric or whether it tried other dose metrics that might have provided a good fit for BMD modeling. Furthermore, the document states that "The variability in the available data was not amenable to modeling with available models." For other chemicals on which the toxicity values are based on epidemiological data, EPA has use models outside those available from the BMD software.	For clarity and transparency, more information on why BMD modeling was rejected should be provided, possibly in an appendix. EPA should also clarify if it has used more than one dose metric, and under what conditions it will examine the effects of alternative dose metrics, i.e., as a quantitative measure of uncertainty. The document should provide information on when and why IRIS will go beyond the models available in EPA's BMD software for evaluating epidemiological data.	S/M
9	5	5-18	DoD believes that the explanation given for the	The UF should be reduced to 1.	S/M

			database UF actually establishes the needlessness for this UF. If, as EPA states, "The relative lack of data taken together with the concern that other structurally related solvents have been associated with immunotoxicity, particularly relating to autoimmune disease (Cooper et al., 2009) contributes to uncertainty in the database for tetrachloroethylene.", then EPA should use those data to complement the PCE data and eliminate the need for this UF. Furthermore, EPA is inconsistent in its evaluation of the epidemiology studies. If the current, residential studies "were judged to be limited for developing an RfC", then it cannot conclude that the residential studies yielded the most sensitive neurotoxic endpoint associated with tetrachloroethylene exposure, decrement in VCS." If the data were sufficiently robust to establish VCS as a valid effect of PCE, EPA would have used those data to calculate an RfC. As EPA did not do this, the data must not be sufficiently robust to establish that VCS is an effect of PCE exposure, and the lack of such a determination is not sufficient reason on which to base a UF of 10. Anecdotal observations are not data.		
10	5.2.1	5-26	The text argues that inhalation exposure can be converted to a RfD; this is an unacceptable way to calculate an RfD because of route of exposure concerns. One might conceivably	Alternate studies should be selected for the derivation of the RfD.	S/M

			argue that inhalation exposure in conjunction with oral exposure is possible because of the high volatility and low aqueous solubility of PERC; however, inhalation exposure under these circumstances is IN ADDITION TO oral exposure, not IN LIEU OF same. Also, as stated above, there are serious issues with the credibility of the PBPK model, making it an inadequate means of dealing with first pass metabolism.		
11	5	5-29	As the RfD used the same studies as the RfC, the comments on the UFs are equally relevant, as are the resulting adjustments	Changes made in the RfC should be reflected in the RfD.	S/M
12	5	Table 5-1	This table is inconsistent, with some calculations rounded to one significant figure and others with four significant figures.	DoD recommends that, unless the data can support more significant figures, the results of all calculations be rounded to one significant figure.	S
13	5	Table 5-2	PCE is sometimes referred to as “solvent”, e.g., “Studies in animal models reporting effects concordant to observed solvent associated effects in humans were considered preferable.”	The document should always use PCE rather than “solvent”. In the case cited, the reader might consider the “solvent” to be referring to a solvent-control in the animal studies.	E
14	5.2.3	5-30	It is not clear that the endpoints cited reflect irreversible neurological changes in the test subjects. If the effects are not permanent changes, then they likely reflect temporal adaptations that are restored once exposure ends.	EPA should indicate whether or not these effects persist and are true endpoints, or merely transient effects. If they are transient effects, their use as endpoints is questionable.	S/M
15	5.2.3	5-30	Text cites the RfD as being equivalent to a drinking water concentration of 0.21 mg/L,	Text should be made more clear and state that this value is derived as if drinking water were the	S

			however this ignores relative source contribution from water and other orally-ingested (i.e. food, etc.) sources.	only source of exposure, or else define a relative source contribution and alter the number accordingly.	
16	Table 5-14		The purpose of this table is unclear. Without identifying the nature of the challenging chemicals, incidence of tumors is not relevant, and is an improper use of the data. Of more value would be the historical incidence on spontaneous tumors found in these studies. About the only conclusion one can draw from these data is that male mice are more likely to develop liver and spleen tumors than female mice.	EPA should remove or modify this table to provide useful and valid information.	S/M
18	5	5-63	EPA's use of only one of the models available in the BMD suite is neither consistent with the purpose of the modeling (as discussed in its draft BMD technical guidance) nor is it consistent with past EPA practice.	EPA should follow its normal procedure of evaluating many BMD models and choosing the model according to its selection criteria. The cancer potency should be adjusted appropriately.	S/M
19	5	5-63	The statement that "The multistage model has been used by EPA in the vast majority of quantitative cancer assessments, initially because of its parallelism to the multistage carcinogenic process." is inaccurate. Until EPA's 2005 cancer guidelines, EPA used the linearized multistage model, as required by its 1986 guidelines. The two models have significant differences, as one is unconstrained and the other has a significant constraint. Thus, most of EPA's cancer potencies have been	The statement requires correction.	S

			estimated using the **linearized** multistage model.		
20	5.4.4.2	5-94	In discussing relative roles of oxidation and GSH conjugation, text states that "...this pathway represents a greater fraction..." It is not clear to what "this" refers.	Clarify sentence.	E
21	5	5-99 and D-31	Despite EPA's advocating the multistage model, it appears that EPA did use other models and selected the Hill model.	Here and elsewhere in the text, EPA should make its text consistent, i.e., the discussion of the use of the multistage model does not seem relevant to this chemical. Moreover, "Michaelis-Menten model" should be changed to "Hill model" as that is how it is called in the BMD software, e.g., as clearly demonstrated by the difference in the caption of figure D-2 and the computer print-out below the caption	S
22	Appendix D	D-35	It appears that the exponent on dose in the Hill model was set at the value of one instead of allowing the software to determine the best fit. EPA has not provided any information to justify this constraint, and it is not mentioned in the main text. This is an important constraint, as the same data could be used with the same degrees of freedom with other assumptions, i.e., that the exponent equals 2.	For clarity and transparency, EPA should justify its artificial constraint of the model selected for use.	S/M
23	Appendix D	Global	In its tables on the results of different modeling efforts, EPA compares AICs of models with different degrees of freedom. This is not an accurate comparison.	EPA should re-examine the AICs with appropriate comparisons. This may affect which model(s) are selected and the resultant estimation of a cancer potency.	S/M

24	Global	Global	DoD is very concerned about the apparent lack of consistency in the evaluation of PCE and TCE. This 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 (as discussed in EPA's strategic plan), DoD finds the lack of consistencies listed below to be troubling. 1. EPA has acknowledged the NRC conclusion that TCE is not metabolized by humans by the PPAR-alpha pathway, yet EPA has retained this pathway for PCE (4.3.5.5.2.1. Activation of PPARα and associated markers and 4.3.5. Mode of Action for Murine Hepatocellular Tumors). Specifically, EPA states, "The peroxisome-related effects of tetrachloroethylene are most likely mediated primarily through TCA based on tetrachloroethylene metabolism producing more TCA than DCA, and the lower doses of TCA required to elicit a response relative to DCA." TCA and DCA are also	EPA should resolve these inconsistencies. 1. <u>The document should explain why the lack of human induction of PPARα for TCE is not relevant to PCE.</u> 2. <u>EPA should explain why it uses data on DEHP and Wy-14,643 rather than that of TCE for comparison with the potential mode of action for PCE.</u> In particular, even if EPA continues to cite the other data which DoD believes is less relevant, The document should explain why data on TCE are not more relevant and are not discussed when evaluating PCE's mode of action.	S/M

			metabolites of TCE, and this inconsistency in evaluating the same metabolites is not explained in either document. 2. Given the similarity of the two chemicals, DoD is unclear why such disparate chemicals as DEHP and Wy-14,643 are cited as the comparison chemicals for PPARα induction. We think that the justifications regarding this mode of action and TCE would be much more relevant.		
25	Gobal	Global	DoD is concerned that a major constraint on the model used by EPA to establish the cancer potency for PCE is not mentioned (except obliquely) in the text, and can only be inferred by a careful reading of the computer print-out in Appendix D. Thus, while EPA used the Hill model in the BMD software, without justification it constrained the exponent on dose to be equal to one. By artificially constraining the model, EPA has changed the more general Hill model to one of its subclasses, i.e., the Michaelis-Menten model. While EPA does use this term, as mentioned in the comments below, to most readers it would appear to be a misnomer of the model, not an unjustified constraint. As EPA decided not to call out this issue or to make its constraint on the model transparent, DoD is not surprised that no one commented on this fact.	For clarity, transparency, and openness, EPA should ensure that all of its chemical-specific modifications or other constraints imposed on its modeling evaluations are specifically discussed and justified in the main text of the document. Reviewers should not be required also to carefully examine the footnotes in the appendices and infer that which has been altered.	S/M

26	Appendix D	Table D-7	At first observation it seems that the authors did not follow EPA procedures for model selection, the model with the lowest AIC was not selected and there was no apparent justification given in the table. Both the Weibull and the Log-logistic models had the same, lower AIC. There is no footnote assigned to these models regarding unrestricted power and an unusable BMDL. EPA's comment about the unrestricted slope parameter might be inferred to be a justification for the choice of the Hill model, but if this is the case, the comparison is unscientific and unfair. EPA chose to restrict the slope parameter on the Hill model to be equal to one, while it did not choose to restrict the same parameter for the other models. The only fair comparison would be either with all of the models with an unrestricted slope parameter or with all of the models with a slope parameter set to one.	EPA should follow its own procedures and do so with clarity. If there is a scientifically justifiable reason why EPA chooses to deviate from standard procedures, the deviation should be clearly highlighted in the main text of the document along with the justification. Moreover, the assessment should only compare AICs of models that can be statistically compared. The results of a proper analysis may change the estimated cancer potency.	S/M