Department of Defense Comments on HCE Tox Review		
Comments submitted by: Chemical Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: 5/18/2011

*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	5.4.3	109	The last two statements of section 5.4.2 are unclear, and potentially incorrect. "It is recognized that an alpha 2u-globulin-associated mode of action may, in fact, be responsible for the tumors observed in male rats and that more than one mode of action may be operating to induce the nephropathy observed across species and sexes. In that case, the renal tumors would be utilized for quantitation of cancer risk as they would be characterized as not relevant to humans."	Recommend that the last two sentences be edited for accuracy and clarity.	S
2	5.1.5 Previous RFD Assessment	93	The added statement *"in accordance with current risk assessment practices"* requires a reference. In particular, we believe this is in accordance with IRIS practices, not necessarily EPA practice.	Please provide the relevant reference, with page number if it is a document. Risk assessors may disagree as to what is "current practice", and regulatory risk assessments may differ from state-of-the-art risk assessments due to legislative or other constraints.	S
3	5.3	104	This page states that *"There are no available human occupational or epidemiological studies of inhalation exposure to HCE."* However, the studies presented in section "4.1. STUDIES IN HUMANS—	We recommend that EPA's IRIS program provide some of the criteria used to determine when	S

			EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS", reviews such studies. Although these exposures include chemicals other than HCE, EPA has used such studies as the critical one for quantitative analysis for other chemicals.	epidemiological studies, which always have exposure to more than one chemical, are deemed relevant for quantitative analysis. In this case, they appear to have been sufficiently relevant to be included in the review, but summarily dismissed in the quantitative analysis.	
6	5.1.3	93, third bullet	We agree with the reduction of the uncertainty factor for subchronic to chronic, but are unclear why this UF was not reduced to 1. The presence of chronic studies, plus EPA's statements that the severity of these effects does not appear to increase with increased exposure, suggest that this UF should be 1. In the peer review comments Dr. Kodell agrees (page 22 post-meeting comments), *"I recommend not applying a UFD, or equivalently, setting UFD=1."* Also, as Dr. Costa stated (post-meeting comments, page 19), *"a 300 UF applied to the BMDL10 derived from the Gorzinski et al. (1985) study would suffice, for a resulting RfD of 0.002 mg/kg/day."*	Recommend further consideration of adopting UF of 1 for subchronic to chronic.	S/M
7	4 and 5	N/A	While the revisions made to the Toxicological Review for Hexachloroethane further improve the clarity of the document and the rationale for the various decision/approaches taken in the risk assessment, there is room for additional improvements regarding redundancy of information and overall length of the document.	We understand the necessity of repeating some of the information throughout various sections of the document, the lengthy information can be synthesized in a more concise and brief manner. Recommend reducing the repetitive and lengthy information in the different sections of the document (e.g., Sections 4.6, 4.7 and specifically, Section 5). Further, recommend synthesizing the information in sections 4.5.1, 4.5.2,	S

				and 4.5.3 rather than present the information study-by-study.	
8	5.1.1 and Appendix A	86 and Pgs. A-2, A-3 and A-4	From our reading of the external peer reviewers' comments, it appears that EPA stressed the need for a NOAEL in order to perform a quantitative analysis. Preference for a NOAEL was justified prior to the use of BMD modeling. However, since EPA uses the (non-statistically significant) response at the NOAEL for its benchmark dose (BMD) modeling, the rationale for requiring a NOAEL is problematic. ?If the available data do not allow BMD modeling to estimate a point of departrue, then the presence of a NOAEL matters.	<u>As the BMD approach does not use the NOAEL explicitly, we recommend that EPA not include this criterion when evaluating the data for quantitative analysis.</u> If EPA wishes to continue this practice in future chemical risk assessments, they should either justify it or should use the NOAEL as a zero response. The current practice does not seem logical.	S
9		Global	We concur with Dr. Bishop's and Dr. Lash's comments (pages 5 and 7) that the document would benefit from inclusion of an upfront summary of these key points: 1) the relative paucity of literature on HCE and particularly the very limited data in humans; 2) the choices of principal studies and toxicity endpoints for calculation of the RfD/Cs, with the confidence in the final draft proposed values; 3) the principal studies and toxicity endpoints used to derive the cancer potency and why they differ from the previous values; and 4) a table listing all the "key" studies (with type/species/sex/strain) that EPA considered relevant to this review. We also recommend a brief mention upfront of the main areas of scientific differences of opinions voiced by the external peer reviewers to increase transparency and balance.	<u>We recommend that EPA strongly consider all of the reviewers' comments that relate to increased clarity or transparency</u>. If reviewers who have been selected for their expertise in this area are having difficulty understanding the document, others can be expected to have even more difficulty.	S
10	5.1.3. RfD	93	We agree with Dr. Lock who questioned the selection of the critical study	Consider further justifying the selection	S

	Derivation		for the non-cancer effects. Although EPA states (page A-4) that *"All of the reviewers agreed with the selection of Gorzinski et al. (1985) as the principal study;"* Dr. Lock, in his post meeting comments states (page 9) *"…for the noncancer endpoint, the administration of hexachloroethane in the diet leads to loss due to sublimation and in the Gorzinski paper, although they attempt to take this into account, the actual dose the rats receive is still not very precise ... So I wondered why the more recent NTP (1989) 90-day study, where the dose was by gavage and hence the exposure somewhat more precise, was not used?"* Lack of accuracy on exposure has often been a reason that studies have been rejected by IRIS for quantitative (and sometime qualitative) analysis. Yet in this case, a study with an imprecise exposure is selected over one with a precise exposure, and no explanation is provided.	of the Gorzinski study in light of Dr. Lash's comment. We would further appreciate some standard information on the criteria used by IRIS for evaluating the quality of the exposure data, as we have observed apparent inconsistencies across IRIS evaluations. While we understand that there may be justifications for these discrepancies, absent any criteria, the choices may appear to be *ad hoc*, subjective, and potentially biased toward those studies that agree with the chemical manager's hypotheses.	
11	5.2.1	98 - 99	During the peer review Dr. Haber commented on the adequacy of the Weeks et al., data stating that (pg. 24*) "it appears to barely meet the guidelines for study adequacy, and more details need to be provided to document that it was sufficient as a principal study. The previous EPA evaluation was based on essentially the same database, and apparently did not consider the data adequate, in light of the absence of a current RfC."* We believe her comment should have been addressed in the text of the HCE Toxicological Review.	EPA should explain more clearly why a study that was deemed insufficient for quantitative analysis is now deemed sufficient. Furthermore, if there is such limited data available, we recommend that EPA consider not performing a quantitative analysis for this endpoint, as it has chosen to do for other chemicals. If a quantitative analysis is retained, EPA should explain why these limited data are sufficient when other, apparently similar data were not. Alternatively, EPA could provide an integrative analysis of all of the data from all routes of exposure, as we and	S

				the peer reviewers have suggested. In this case, however, the UF for database insufficiency should be reconsidered as well.	
12	5.4.3	108 and B-58	The male mouse hepatocellular carcinoma model results alone did not meet EPA's criteria for dose-response modelling, at least for the model presented. The chi square value is 0.9 and it our understanding that 1 is required for the model to be considered an adequate fit. The cancer potency that EPA might use for HCE if someone were to publish the one (of six) missing assays from the list of criteria in its document for alpha-2µ -globulin-related, aged male rat kidney tumors should be accurately presented.	Recommend reevaluating the male mouse liver tumor benchmark dose modelling and insure that it is accurate and that the model presentation and selection is appropriate.	S
13	General		Though EPA clearly discusses their rationale for using studies of male rat kidney cancer for deterimining the oral SF, we still believe that is alpha 2µ-globulin related. We agree with those external peer reviewers (top of page A-2 and A-14) that stated that the kidney cancer observed in male rats is alpha 2µ-globulin-related and therefore not relevant to human carcinogenicity. In 1991, EPA's alpha-2u-globulin analysis marked the first time that EPA deemed tumors in animals not relevant for carcinogenicity in humans. In 1997 after EPA's decision, ATSDR concluded (in its *Toxicological Profile for Hexachloroethane*"), "These tumors are considered to be unique to male rats and are not-indicative of tumorigenic potential in other species because they were associated with hyaline droplet nephropathy." This conclusion is found on a fact sheet on EPA's Superfund web site (http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/hexchlet.pdf) On page 10 of the post-meeting comments, Dr. Lock states (bold text is original) *"**I strongly recommend that somebody goes back to the rat***	Reconsider and revise.	S

			NTP 90 day study and confirms or refutes an increase in this protein using immuno-cytochemistry in the kidneys of male rats. *…I attach a recent review I wrote in collaboration with Dr Gordon Hard on this issue; current thinking supported by studies confirms that chemicals can exacerbate the progression of chronic progressive nephropathy in both male and female rat kidneys."* His review confirms the general acceptability of our position.		
14	Table 4-19. Oral toxicity studies for HCE	58	It is unfortunate that again the data for the key study needed to be corrected after the external peer review. Given the time taken for the preparation of these documents and the number of internal authors and reviewers listed, we recommend that each document have at least one person who has the responsibility of quality control on the data presented in the document. To quote Dr. Kodell, *"There are quite a few annoying errors in the text and tables in the discussion and summarization of the toxicology data that make it difficult at times to follow the presentation."* See also the DoD comment on the male mouse liver tumor benchmark dose modelling.	EPA should perform a quality review of the document before it is presented for interagency review. While we and other reviewers have found some of the mathematical errors or inconsistencies between text and tables, our short review time does not allow us to perform a complete quality review on the entire document.	E