Department of Defense Comments on the Draft Toxicological Review and Draft Charge to External Peer Reviewers for Dichloromethane		
Comments submitted by: Chemical Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: 28 January 2010

*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	Page & Paragraph (enter "Global" if report section-wide)	Comment	Suggested Action, Revision and References (if necessary)	Category*
1	Page 1	General charge questions: #1	The first sentence addresses clarity. In order to not be redundant, the second sentence should address accuracy and appropriateness.	Either replace "clearly" with "accurately and appropriately" or add the phrase after "clearly". Also suggest adding the following sentence: "Were the major decisions and conclusions easily identifiable?"	S
2	Page 1	Chemical-specific questions: (A) PBTK Modeling #1. & 2.	It is our understanding that both the rat and mouse PBTK models were modified by EPA. As many aspects of the models that were used (as well as the models that were not used) were discussed, it was difficult to be ascertain exactly which changes were made and why. It would facilitate a quality review by identifying the changes to the models and their effect on the analyses.	If either or both the rat and mouse models were modified, then the charge question relative to PBTK modeling should specifically address those modifications made should be asked. Similarly, it appears that some of the parameters for the rodent models were significantly changed. These also should be specifically mentioned in the charge.	S/M
3	Page 2	Chemical-specific questions: (A) PBTK Modeling #3.	While many of the issues raised with regard to the PBTK models are worth indentifying specifically in charge questions, two are of particular importance, i.e., the use of mouse data rather than rat or hamster to estimate missing human parameters, and EPA's observation that the human model appears to result in unexposed people receiving an internal dose of dichloromethane metabolites.	Suggest adding the following questions to section A.3. "When information for human parameters for the PBTK model are missing, under what circumstances (e.g., those that affect the GST pathway) does the choice of animal surrogate for allometric scaling (i.e., from rat or mouse or hamster) matter? Should it be based on the animal model from that will be used for	S/M

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				estimating the interspecies equivalence?" "The human PBTK model estimates a non-negligible internal dose for humans that are not exposed. Is this finding unusual and sufficient to raise concerns about the model?"	
4	Page 2	Chemical-specific questions: (B) Noncancer Toxicity of Dichloromethane	The internal dose to the same organ system assuming the same mode of action produced different toxic effects. The experts' opinion of the seeming inconsistency would be useful for this and future analyses.	Suggest adding a final question to this section. "The same PBTK model was used for determining an internal dose to the liver, yet the toxic endpoint differed. What explanation would best describe this difference in toxicity given the same assumptions of internal dose?	S
5	Page 3	Chemical-specific questions: (C) Carcinogenicity of Dichloromethane #1	The basis for this conclusion (as given in the document) should be restated here so each aspect can be discussed.	Add "*based predominantly on evidence of carcinogenicity at two sites in 2-year bioassays in B6C3F1 mice (liver and lung tumors with inhalation exposure in both sexes, liver tumors with drinking water exposure in males only).*" to the end of the first sentence.	S
6	Page 3	Chemical-specific questions:	A question should specifically address the different statistical analyses and conclusions of the original authors and EPA's analysis and conclusions of the	We suggest additional questions: "What consideration should be given to the differing statistical analyses, and therefore	S/M

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		(C) Carcinogenicity of Dichloromethane #1	Serota male mouse data. The peer reviewers should be asked to comment on the scientific justification that DCM is carcinogenic by **all routes** of exposure (emphasis). EPA should also clarify what they mean by "all routes of exposure" absent a discussion of dermal exposure.	conclusions and the classification, of the authors of the study and that of EPA's authors? If the authors' conclusions were accepted, how would this affect EPA's classification [emphais added] of as "**likely** to be carcinogenic to humans by **all routes** of exposure"	
7	Page 3	Chemical-specific questions: (C) Carcinogenicity of Dichloromethane #2	These questions do not address the issue of human relevance for this mode of action. Two issues should be addressed. First, dichloromethane may (or may not) have a mutagenic mode of action for mice. Second, given the number of species/strains that were negative, it may (or may not) be relevant for humans.	At the end of the second sentence, add the following, "for mice?" and then, "Does the scientific evidence support EPA's conclusion that this mode of action is relevant to humans?"	S/M
8	Page 3	Chemical-specific questions: (C) Carcinogenicity of Dichloromethane #3	Concern about the lack of a dose-response trend should be addressed, for this as well as future analyses.	After the first sentence, add "When the hepatocellular carcinomas and adenomas were combined, the dose-response trend analysis was not statistically significant."	S/M
9	Page 3	Chemical-specific questions:	EPA's mode of action depends on the saturation of the CYP pathway before the mutagenic GST pathway becomes a significant factor in	After the first sentence, add "EPA's mode of action includes the mutagenic effects of the GST-mediated metabolites becoming	S/M

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		(C) Carcinogenicity of Dichloromethane #4	metabolism. Given that EPA believes that the mode of action is known, a nonlinear extrapolation should be considered. In particular, although a GST-mediated metabolite is assumed to be the proximate mutagen, EPA's mode of action requires that a significant obstacle, i.e., saturation of the CYP pathway, occur before these metabolites are expected to occur above small amounts, i.e., those found in rats and hamsters that do not cause tumors. It is difficult to see how saturation of the CYP pathway could occur at low levels of exposure. The charge questions should specifically ask about EPA's choice to rely on animal data instead of human data estimating inhalation and oral risks. The charge should explicitly ask for comments on the appropriateness of these choices, based on a consideration of the available scientific evidence for tumorgenicity and whether these experts consider the liver and lung tumor modes of action (MOAs) to be the same and therefore not independent tumors. Particular consideration should be given to the spontaneous liver tumors in the particular strain of mouse used to derive the oral cancer slope factor (OSF), and whether the	significant after saturations of the CYP pathway. Should a nonlinear extrapolation from the POD also be considered? The POD is at a dose level where tumors were observed, i.e., where the CYP pathway is saturated. Should an attenuation factor be included in the extrapolation?" We also suggest adding the following questions: "Is the sensitivity of the male mouse liver for cancer for short, chlorinated hydrocarbons of this strain of mice relevant, given the negative results for two strains of rat and Syrian hamsters?" "To what extent should the uncertainties in the data identified by EPA affect the quantitative assessment? In particular, are the re-analyses of the data for interspecies extrapolations appropriately incorporated into the quantitative analysis?"	

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			slight increase in male liver tumors observed in this strain of mouse was within the normal fluctuations. A charge question should be added regarding the extent the EPA conclusions (Chapter 6) and convey the great amount of uncertainty in the evidence (as discussed in chapters 3, 4, and 5), and the effects of these uncertainties' implications for the resulting unit risk estimates. The External Peer Review charge questions should specifically address the "Interspecies extrapolation of dosimetry and risk" in Section 5.3.		