Department of Defense Comments on the Draft TCE Toxicological Review; Peer Review Charge, June 2009					
Comments submitted by: Chemical Material Risk Management Directorate			Organization: Department of Defense	Date Submitted: August 27, 2009	
*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major (M) 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	Charge Questions	Questions 1 and 5	These charge questions are generally well-written, but it would be useful to specifically ask the peer reviewers about the interpretation of each individual animal tumor endpoint, in light of the strengths and weaknesses of the database. We believe the best question to address this would be as part of Question #5.	Suggest adding a sub-question to #5 to address the interpretation of each individual animal tumor endpoint in light of the strengths and weaknesses of the database.	S, M

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2	Charge Questions	Question 1.d	Charge question 1. Expanding the MOA aspect of this question would be useful.	We suggest framing the MOA part of this question (part d) in the context of the USEPA (2005) cancer guidelines and the ILSI/IPCS mode of action/human relevance framework. Some key references for the ILSI/IPCS framework: Meek, M; Bucher, J; Cohen, S; et al. (2003). A framework for human relevance analysis of information on carcinogenic modes of action. Critical Reviews in Toxicology 33:581-653. IPCS (International Programme on Chemical Safety) (2006) IPCS framework for analysing the relevance of a cancer mode of action for humans and case studies. (http://www.who.int/ipcs/methods/harmonization/areas/cancer_mode.pdf)	S, M

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3	Charge Questions	Question 4a	This charge question does not address the quality of the studies that the screening process for non-cancer effects identifies as defining "candidate critical effects" nor does it address the reproducibility of the effects (and the comparative quality of the studies that did not observe the same effects), the mode of action, or the possible relevance to humans of the candidate critical effects.	Suggest that the charge question be expanded to ask if the systematic review, the screening process and the development of toxicity values includes appropriate steps that evaluate the quality of the studies that the screening process identifies as defining "candidate critical effects". The charge question should ask if the screening process and development of toxicity values address the reproducibility of the candidate critical effects (and the comparative quality of the studies that did not observe the same effects), the mode of action, and the possible relevance to humans of the candidate critical effects.	S, M

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4	Charge Questions	Question 5	There is no charge question which addresses the cancer weight of evidence characterization. The toxicological review characterizes TCE as "carcinogenic to humans." Alternative interpretations of the available epidemiology and experimental animal data are possible, however, leading to other weight of evidence findings of : • "Likely to be carcinogenic to humans," due to suggestive evidence of carcinogenicity in humans and evidence of cancer in two experimental animal species; • "Suggestive evidence of carcinogenicity," due to the suggestive evidence in humans with conflicting experimental animal information; • "Inadequate information to assess carcinogenic potential," due to the conflicting epidemiology and experimental animal data. We would also like to see the charge question address whether the animal and human studies support one another in development of the weight of evidence. Page 4 of 5	Suggested text for the charge question is below. Ideally this would be added as a new stand-alone charge question. "Under the EPA's 2005 Guidelines for Carcinogen Risk Assessment, the Agency categorized trichloroethylene as carcinogenic to humans by all routes of exposure. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified? A) How does the panel interpret the available human and experimental animal information in light of the evident or potential internal conflicts described in the assessment? B) How do the epidemiology and experimental animal data support each other (or not) in the evaluation of weight of evidence? C) How does this resulting TCE weight of evidence compare to chemicals with better characterized evaluations, e.g., vinyl chloride (human carcinogen) and acetonitrile (inadequate information to assess carcinogenic potential due to conflicting evidence)?"	S, M

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5	Charge Questions	Question 5	It seems reasonable to direct the peer reviewers to the EPA 2005 Cancer Guideline text relative to alternative dose response assessment approaches. For example, in light of the multiple possible MOAs for various tumor types, and within each tumor type, which have some supporting data, it seems reasonable for EPA to consider alternative dose response assessments. Such as different techniques at different parts of the dose response curve (see EPA, 2005, page 3-22: "If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur."	Suggest adding text to Question 5 that directs the reviewers to the cancer guidelines text relative to dual modes of action and also add the following details to the question: "Does the behavior of TCE in kidney carcinogenesis suggest a possible dual mode of action? If so, how should EPA approach the dose response assessment for this endpoint?"	S,M