

**Department of Defense Comments on the
Draft External Peer Review Charge for Methanol**

Comments submitted by: Office of the Secretary of Defense Chemical and Material Risk Management Directorate			Organization: Department of Defense	Date Submitted: 20 November 2009	
*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	A.1.		We would prefer that the text “objectively and” be retained.	Please retain “objectively” explicitly in this question.	S
2	B.1.& 2		Several recent NAS reports have recommended that risk assessments move from the historical practice of selecting one critical study to represent the quantitative analysis. It might be useful to ask the reviewers if they believe the results of the three analyses should be combined, and if so, how would they recommend that they be combined.	Suggest adding to the question: “Do you recommend that the results from more than one study should be used quantitatively for dose-response assessment, and if so, what techniques would you recommend to accomplish combine or compare the data?”	S
3	B.3. first bullet		Some of the “subtraction from background” included a time-dependant change. We recommend that this adjustment be specifically called-out for review.	We recommend that an additional sentence be added to convey the following concept: “Some of the ‘subtraction from background’ procedures included a time-dependant change, i.e., because the level of methanol in the blood of control animals changed with time. Was this adjustment appropriate and was it performed properly?”	S/M
4	D.3. last sentence.		It is not clear whether “addressed” in the phrase “clearly described and addressed” asks the reviewers to consider if, given these issues, these data are appropriate for dose-response modeling for estimating human risks.	We recommend changing “clearly described and addressed” to “...clearly described and appropriately selected for dose-response modeling for estimation of human cancer risks.”	E

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5	D.4. first sentence		Our interpretation of EPA’s toxicological review (TR) is that the clearance of metabolize methanol was being used as a surrogate for the production of formaldehyde or formate and that it is possible (given the values in the text) to measure formate in the blood. If this interpretation is accurate, we recommend editing the charge question to reflect these facts.	We recommend that the question be phrased in the following manner: “If the metabolites of methanol cannot be measured in blood, i.e., formaldehyde, or were not measured in blood, i.e., formate, is it appropriate to use clearance of metabolized methanol as a surrogate? Is there a procedure that might provide a better estimate from this surrogate than assuming equivalence of the surrogate and the concentration of the metabolite?”	S/M
6	D.4. second sentence		Our understanding from the TR is not that metabolism “may differ” among species but that metabolism in primates and rodents is known to differ. As one major difference, the TR states that metabolism is a one-step process in rodents and a two-step process in primates.	Assuming our reading of the TR is accurate, we recommend that this sentence be revised to read, “The metric of formaldehyde production is uncertain because: (1) metabolic processes are known to differ between rodents and primates and metabolism is a one-step process in rodents and a two-step process in primates. [Note: we recommend both changes as the first, i.e., a different enzyme, might only affect rate while the second might affect the form, i.e., requiring a function rather than a constant, of any recommended conversion.]	S/M

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7	D.5. and D.7		We noted that after the PBPK model was used for interspecies extrapolation, the risk assessors also applied the default interspecies extrapolation of BW3/4 that had already been used to derive some of the parameters for the PBPK model. We recommend that the external peer reviewers be asked to opine on this issue.	Add the following to the end of this charge question. "Specifically, should the human-equivalent dose that has been derived from a PBPK model based on clearance of metabolites be further adjusted by the ratios of BW3/4 as was done for methanol?"	S/M