

Department of Defense Comments on the PBPK model for PCE

Comments submitted by: Chemical Material Risk Management Directorate	Organization: Department of Defense	Date Submitted: 28 September, 2011
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*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*
		Global	DoD is very pleased that EPA decided to perform an external peer review of its modified PBPK model. DoD notes that, even though this analysis was published, peer review for journal articles differs from that required for a regulatory analysis, else the critical review of the published literature that EPA performs as part of its IRIS program would not be necessary. It appears, however, that this letter review may not have included a teleconference in which the reviewers could discuss their differences of opinion. Such a teleconference would also allow stakeholders a chance to provide information to the reviewers.	DoD would encourage EPA to always include a discussion among the external peer reviewers. Even for a letter review, this conversation can be a teleconference to keep costs to a minimum.	O
		Global	The reviewers appear to conclude that, although the presentation is not clear (to these experts in the field), it is the best that can be done with the available data. The reviewers were asked whether the model was “used appropriately”. In our opinion, the critical question is whether the model is <i>sufficiently accurate</i> to base toxicity values that will affect regulatory decisions.	DoD suggests that, in the future, external peer reviewers not only be asked if the model was used appropriately, but also if, in their opinion, the model is sufficiently accurate as compared with contemporary PBPK models and modeling efforts.	S,M
	3.5.1.2.1	3-37, line 1	Although in this case, the external peer reviewers appear to have reviewed the draft journal article as well as the EPA draft document, most reviewers of the EPA document will not have the resources, including time, to obtain and review the primary article, especially when it is “in press” during the time of the review. Thus, as mentioned by the reviewers, the EPA document should have	DoD strongly suggests that EPA perform a high level of quality control, especially with regard to the critical studies and especially for the documents that are in their final version. While all studies should be accurately reported, even small errors in the presentation or analysis of the most critical studies may jeopardize the perception of the integrity of the	S,M

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			sufficient detail to stand alone, e.g., by incorporating the manuscript as an appendix. Moreover, to the extent that EPA considers a study to be critical to its analysis, e.g., the Chiu and Ginsberg paper, it is especially important that all statements about that paper be precisely accurate. For example, the statement that the validation of the model was “within three-fold” is incorrect. The paper states that <i>most</i> of the validations were within three-fold and the rest were within an order of magnitude.	document. The statement should be corrected.	