Department of Defense Comments on the *Interagency Science Discussion and Final Agency Review draft Toxicological Review of cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* August 2010					
Comments submitted by: Chemical Material Risk Management Directorate		Organization: Department of Defense		Date Submitted: 30 August 2010	
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1	N/A	Global	Although we found EPA to be generally responsive to the external peer review panel's recommendations for cis- and trans-1,2-dichloro-ethylene (1,2-DCE), we noted fairly extensive changes/additions to the August 2009 draft version that underwent interagency (August 2009) and external peer review (December 2009), compared to this "Final Agency Review draft," dated August 2010. Some of the resulting issues associated with these changes include the following: • Change in critical effect for cis-1,2-DCE • New modeling and statistical procedures • Charge Questions related to liver effect • Battelle study evaluated for trans isomer For example, a number of the "Charge Questions" that the external peer review panel members deliberated and responded to, as seen in Appendix A and the *"FINAL REVIEWER COMMENTS External Peer Review Meeting on the Toxicological Review of cis- and trans-1,2-Dichloroethylene"* dated 19 January 2010, were related to selecting the relative weight change in the liver (McCauley et al. (1990, 1995)) as the critical effect for deriving the newly proposed reference dose (RfD) for cis-1,2-DCE.	Given the rather long list of changes prompted by the external peer review we would like to discuss with EPA what degree of change to a Toxicological Review might prompt them to send a Review back for additional peer review, and the degree of the review the changes we are seeing in the final draft, did receive.	S, Major

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2	Section 4 and 5; Appendix B	Tables 4-1, Page 21; Table 5-1, Page 83; Table B-3, Page B-8; Table B-4, Page B-11; Appendix B.1.2, Page B-8.	EPA has reevaluated the liver and evaluated the kidney data based on 2 panel members' comments concerning the potential impact of corn oil as a vehicle in the gavage rat study, resulting in possible confounding of the results of the liver weight change data. This contributed to EPA's decision to change the critical effect for the cis-isomer to the relative change in kidney weights from the same study (McCauley et al. (1990, 1995)), to derive their proposed RfD for this isomer based on new benchmark dose (BMD) modeling methodology and new "goodness –of-fit" statistical analyses. Actually, one of the five reviewers, had recommended that BMD modeling be applied to kidney weight data. Several other peer reviewers also suggested EPA reevaluate these kidney data if they still decided to set an RfD for the cis-isomer despite the problems with this study. One reviewer recommended not setting an RfD due to these discrepancies. The 2010 Final draft document presents both relative liver and kidney weight increases as	EPA should consider including the calculation for the RfD for the cis-1,2-DCE and assign the change in relative kidney weight as a LOAEL as one of the reviewer's recommended, especially considering that the relative weight change and clinical chemistry findings were not considered adverse effects according to the study authors, and the majority of the external peer reviewers. See the comment above relative to inclusion of new information and modeling procedures and level of review these changes have received.	S

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			potential candidates for the critical effect for cis-1,2-DCE (August 2010) and shows that the point of departure (POD) for cis-1,2-DCE resulted in a more "sensitive" RfD when the kidney data were used for benchmark dose (BMD) modeling and "goodness of fit" calculations. However, it seems that the external peer review panel has not yet had the opportunity to evaluate these modeling procedures and statistical analyses for the kidney data, or give their recommendations for uncertainty factors based on the new critical effect for the cis-1,2-DCE RfD.		
3	Global; 3.2; 3.3.3; 4.1;4.6.1.1; 5.3; Appendix A	Table 3-1; Pages 7, 8, 13, 18, 65, 95; A-5	EPA did not accept the recommendations of 3 of the 5 external peer reviewers to lower the uncertainty factors (UFs) for both the cis-and trans-1,2-DCE compounds. The cis-1,2-DCE RfD is based on a "critical effect" that has no known biological significance at this time and is believed by a number of the panel members and others to be a precursor to an adverse effect (if that, as the McCauley authors felt it was related to body weight change and not a significant effect). A number of external peer reviewers and EPA authors pointed out that the	We suggest that EPA reconsider their application of several of the UFs or provide stronger justification for them. More justification should be provided for a 10x UF for subchronic to chronic extrapolation based on external peer reviewer comments and previous interagency comments. We support the majority of the peer reviewers' recommendations to reduce the interspecies UFs from 10 to 3 based on: (a) the data presented by the reviewers that the rat is more	S, Major

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			relative potency of cis- and trans-1,2-DCE is not high as there is no strong evidence for hazardous behavior from exposure to environmental levels to-date, in the "limited" human studies available (Section 4.1, page 18). For the cis-isomer, the change in relative kidney weights is not considered adverse, and its biological significance is not clear. Considering that EPA's 2009 draft discussed why the kidney data should not be considered, we believe that a factor of 3 would be more appropriate. As EPA stated in a recent presentation to the Science Advisor Board's (SAB's) "Exposure and Human Health" Subcommittee, it is important for EPA also to consider the consequence of their actions for decision makers/risk managers. Cis- and trans-2,3-DCE isomers are good examples for not using default uncertainty factors based on consideration of the relative consequences to human health from environmental exposure as these chemicals are not deemed highly toxic to humans.	sensitive than the human; and (b) taking into consideration the critical effect for the cis-1,2-DCE RfD (which is of questionable biological significance and is not considered an adverse effect). The DCE isomers will likely continue to inhibit their own metabolic activation and thereby prevent adverse effects, no matter how long the exposures. A UF of 3 to account for database deficiencies is reasonable. It should also be recognized that administration of large quantities of corn oil promotes lipid accumulation and lipoperoxidative damage. Thus, the experimental design of the McCauley et al. study resulted in a more pronounced hepatic effect than would occur with applicable human exposures. This argues against adoption of such large UFs to protect against such a "modest effect." As the kidney effect for 1,2-DCE was less consistent response than the relative liver weight change and the BUN is a sign of kidney toxicity and decreased 40% instead of increasing, we believe that external peer reviewer comment on this issue would apply to the kidney data as well. The same	

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				reviewer also stated that the same reduction in the UF would also apply to the trans-1,2-DCE isomer. We also support the recommendation of the external peer reviewer to reduce the uncertainty factors for both the cis-1,2-DCE and trans-1,2-DCE. Their recommendation would also apply to the kidney data from the same study for cis-1,2-DCE subchronic to chronic UF from the full 10 to 3 based on their comments.	
4	Appendix A	Page A-2	EPA states on page A-2 that the critical effect was changed from increased liver weight to increased kidney weight (relative) based on peer reviewer comments on cis-1,2-DCE. "*Therefore, consideration of uncertainty in the RfD associated with potential influence of corn oil on the hepatotoxicity of 1,2-DCE was no longer relevant*." As noted by two peer reviewers, corn oil as the dosing vehicle in the gavage study of McCauley et	In light of the change to decreased kidney weight as the critical effect, we believe that it may be helpful if EPA discussed the extent to which corn oil as a dosing vehicle also may have the potential to influence the rat kidney.	S

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			al. (1995) is believed to constitute a confounding factor in the evaluation of the cis-1,2-DCE relative liver weight change data. It is been shown that corn oil may exacerbate the hepatotoxicity of chloralkenes, leading to a greater liver effect than if the 1,2-DCE was ingested in water or food and not introduced via corn oil gavage (Raymond & Plaa, 1997). One reviewer mentioned that the effect of corn oil on the kidney as a vehicle was less than the liver. Review of a publication entitled "*Influence of Corn Oil and Diet on Reproduction and the Kidney in Female Sprague-Dawley Rats*," (Sato et al., Toxicological Science, 156-164 (2000)) reported that administration of corn oil at the usual dose rate of 10 mg/kg as a vehicle of a test agent to pregnant and lactating rats resulted in toxic effects on the kidney (for example, fatty degeneration of the proximal tubule, etc.). Others have also reported histopathologic alteration of the kidney by corn oil (Bachmann & Weber, 1990). It appears that the pregnant and lactating rat are more susceptible to these kidney effects from corn oil/ but nevertheless, we felt that EPA may wish to address this since there has been other studies		

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			reported in the scientific literature and thus this may need to be briefly addressed for clarification as the external peer review Charge Questions did not address the kidney.		
5	Sections 5.1.1.1-5.1.1.3, 6.1, 6.2, and Appendix A; Appendix B	Pages 82, 85; Page B-8, Table B-3; Table B-4, Page B-11; Page A-3	Page A-3 states that all five reviewers agreed that the McCauley et al. (1995) study is the best available study and should be used to derive the RfD for cis-1,2-DCE. Dr. Longstreth stated that an RfD for cis-1,2-DCE not be derived in light of the discrepancies noted between the published and unpublished versions of the McCauley et al. study (1990, 1995). She also expressed concerns with use of the liver data due to the potential impact from the use of corn oil as the vehicle in this gavage study. The corn oil-related confounder seems to have been eliminated by EPA's selection of another critical effect. However the reviewer also suggested that EPA contact the lead author to help resolve the discrepancies between the unpublished and published versions of the McCauley et al study.	In Appendix A it seems relevant to note Longstreths's qualifying statements on use of the McCauley study. Also please clarify whether the EPA authors were able to contact Dr. McCauley, as recommended, to verify data and help resolve discrepancies noted between the unpublished and published versions of the McCauley et al. (1990, 1995) study.	S

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6	Sections 5 and 6	Sections 5.1.1.1-5.1.1.3, 6.1, 6.2, and Appendix B. Tables B-3 and B-4	EPA presented both relative liver and kidney weight increases as potential candidates for the critical effect for cis-1,2-DCE. Because the BMDL10 of 5.1 mg/kg-day based on male rat data is more sensitive than the BMDL10 values based on liver weight data, increased relative kidney weight in male rats was selected as the critical effect. The cited sections and Appendix B were revised to reflect this change. The cited Tables present the goodness-of-fit statistics and BMD and BMDL estimates for all continuous models fit to these data for male and female rats, respectively.	We believe that presenting both relative liver and kidney weight increases as potential candidates for the critical effect for cis-1,2-DCE and using BMD modeling methodology to determine candidate points of departure (PODs) for these two different endpoints lends transparency to the document. This allowed comparisons to be made and provided overall completeness. However, as stated earlier, we would like to discuss the level of review of the new modeling. We understand that the changes were initiated by external peer review comments, but would also like to discuss what EPA believes is appropriate in circumstances when there are major changes/additions to a Toxicological Review post-external review.	
7	4.2.1.2.1	Pages 20-23; Table 4-2	Page 22 states for cis-1,2-DCE -that *"Absolute kidney weights in female rats were increased by 3, 16, 17, and 17% compared to the control at doses of 32, 97, 291 and 872 mg/kg-day, respectively, but were not statistically significant. In male rats increases in absolute kidney weight of 9, 17, 7 and*	We recommend that EPA further discuss whether the body weight to kidney weight relationships are the same or have changed with increased dosing and provide additional support that this is a valid comparison. We also believe that the range of experimental	S

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			14% for the 32, 97, 291 and 872 mg/kg-day dose groups, respectively, were not statistically significantly elevated compared to the control nor dose related (McCauley et al., 1990). Statistically significant increases in relative kidney weights (as a ratio of kidney weight to body weight) were recorded in male rats in all dose groups (14, 19, 19, and 27% at 32, 97, 291, and 872 mg/kg-day, respectively) (Table 4-1)." As histopathological findings for the kidney were negative, the critical study authors concluded that the increases in relative kidney weights may be due at least in part to decreased body weight gain. EPA authors disagree with these conclusions, but it seems that the body weight to kidney weight relationships may not be the same in these two groups.	accuracy within the variability range of the weight measurement relative to the control kidney weight variability range should be compared and discussed for completeness. Also, it would be worth noting and presenting the reasoning that an external reviewer stated in their recommendation that it was more applicable to compare the change in absolute weights relative to dose increases with control weight, and not relative male critical organ weight changes compared to control.	
8	EPA August 2009 IAR Draft		The previous version of this draft (August 2009) stated the following concerning the cis-1,2DCE*: "Increased relative kidney weight was less consistently observed by McCauley et al. (1990, 1995). In male rats, statistically significant increases in relative kidney weight were observed at all doses in the 90-day study but not in the 14-*	This excerpt from the 2009 EPA draft supports the above comments concerning the weight of evidence for the kidney data used for the critical effect selected in 2010 draft for the cis-1,2-DCE RfD.	E

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			day study. In female rats, relative kidney weights were not statistically elevated following 90 days of exposure, but were elevated in the highest two concentration groups following 14 days of exposure. The absence of compound-related histopathological changes in the kidney in the McCauley et al. (1990, 1995) study raises questions about the biological significance of the relative kidney weight findings. BUN and creatinine, two clinical chemistry parameters that are indicators of kidney function (generally renal dysfunction), did not provide supporting evidence for functional damage to the kidney (McCauley et al., 1990, 1995). In the 90-day study, BUN and creatinine were only marginally decreased (although statistically significant) in high-dose (872 mg/kg-day) male rats; values in treated females were similar to controls."		