Department of Defense Comments on the Final Draft Toxicological Review of 1,4-Dioxane (CAS No. 123-91-1)					
Submitted by: Office of the Secretary of Defense, Chemical and Material Risk Management Directorate			organization: Department of Defense	Date Submitted: June 8, 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 or Global	Comment	Suggested Action, Revision and References (if necessary)	Category*
1	3. Toxicokinetics	6	The statement is made at this point in the document, and subsequently, that HEAA is the primary metabolite; however to our knowledge there has never been resolution in the literature of the question of dioxanone, the metabolite originally proposed by Woo's group.	We previously commented on this as a related issue during the first interagency review but do not believe the final draft text entirely resolves the issue. Text should reflect that this is an unresolved issue that potentially bears on the MOA question.	S
2	4. Hazard Identification	Table 4-14, Page 50; Table 5-5. Page 102	We observed several changes in data that are due to a change in the critical study to Kano 2009 after the external peer review. There were changes in the number of animals, the number of animals that had tumors, the doses given to the animals, and changes in both the statistical procedures and the goodness-of-fit calculations, but the cancer slope factor (page 107, line 21) remains exactly the same (to the two significant figures reported).	We believe such major changes in the critical data after completion of the interagency and external peer reviews suggest use of an additional external peer review to preclude a data quality challenge based on the fact that the original panel did not have accurate data at the time of their review. We further suggest (see comment # 3) that both the data reviewed by the external panel as well as the data on which EPA bases its analysis, be presented in the final report.In addition, we would like to discuss with EPA why the cancer potency estimates appear to be insensitive to changes in the data; and also believe that some clarification of this in the toxicological review would be useful.	S, M
3.	Section 4.2.1.2.6	Page 83, Table 4-18 Page 50, lines 5-18; Table 5-5. Page 102; Table 5-6, Page 103 Appendix A,	Lines 15-18 of page 50 state that "The tumor incidence data presented for male and female mice in Table 4-14 are based on reanalyzed sample data presented in Kano et al. (2009) that included lesions in animals that became moribund or died prior to the completion of the 2-year study." The body of the text should more clearly state that these data that were reanalyzed were from the JBRC 1998a studies and describe and discuss the procedure(s) used in greater detail. This information should also be included upfront in an "Executive Summary" section due to its importance.	We believe that the data reanalysis should be more fully explained and that EPA consider adding separate study tables (before and after reanalysis) to increase transparency and hopefully result in less confusion with portions of the text citing JBRC private communications with authors. The fact <u>that the external peer</u> <u>reviewers used one set of data and that the</u> <u>current analysis relies on significant changes</u> <u>made in data used to derive the proposed oral</u> <u>cancer slope factor (based on the liver female</u> <u>mouse data) should be obvious to all who wish</u>	S, M

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		Page A-2.	Based on the U.S. EPA "Response" given in Appendix A-2, which states " <i>Following external peer</i> <i>review (as noted above) Kano et al. (2009) was</i> <i>added to the assessment, which was an update and</i> <i>peer-reviewed published manuscript of the JBRC</i> (1998a) report." Page A- states, "Since the external <i>review, Kano et al. (2009) was published and this</i> <i>assessment was updated accordingly (previously</i> <i>JBRC (1998a)</i> " it appears that the external peer reviewers did not have an opportunity to review and evaluate the methodology Kano et al., 2009 followed for reanalysis of the mouse data, as given in this EPA draft final document. It is not clear if the female mouse data set changed after the reanalysis by Kano et al., 2009. This should be discussed further in the body of the text. Table 4-18 on page 83, entitled " <i>Temporal</i> <i>sequences and dose-response relationship for</i> <i>possible key events and liver tumors in rats and</i> <i>mice</i> " groups " <i>Kano et al., 2009; JBRC, 1998a—</i> <i>male F344/DuCrj rats</i> " combines studies together under one heading for liver tumor results. This method for presentation of liver tumor results does not help the reader see and understand how the data from the JBRC 1998a studies compares to the reanalyzed Kano et al. 2009 studies for positive responses at various doses, especially for the female mouse. This should be discussed further in the body of the text.	to use these data, not just those who have been through the various steps of the review process. The EPA draft document should clarify that the external peer reviewers did not have an opportunity to review and evaluate the methodology Kano et al., 2009 followed for reanalysis of the mouse data, as given in this U.S. EPA draft final document. We also recommend that EPA characterize their confidence in the reanalyzed female mouse data in consideration of the varying response for this critical effect between rats and mice and the gender differences reported.		
4	4.2.1.6	Page 47	We believe that the deleted portion of the text on page 47 (lines 1-4), <i>"in micesurvival was low in all male groups (31/50, 33/50, 25/50, 26/50 in control,</i>	Please consider adding back in similar text as was deleted between versions of the document. The external peer reviewers, as	S	

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			<i>low-, mid-, and high-dose groups, respectfully)</i> <i>and particularly low in high-dose females</i> " provided valuable information that is not as insightful as in the replaced text, which now states <i>"In the mouse study, survival rates did not differ between the control male mice and the 1,4-dioxane dosed mice.</i> " Since data from the female and not the male mice were used to derive the oral cancer slope factor (CSF) and the mortality decreased with dose ingested, the fact that only 31/50 of the male controls survived the two-year study becomes less important.	 well as any other interested parties should be aware of the low levels of survival of the animals in the key studies. Readers should also be aware of the possible effects on the power and statistical significance of subtracting this high background from the resulting tumors, i.e., the increase in cancer potency. Address these findings in the uncertainty section. 	
5	Section 5.4.1	Table 5-5, page 102.	Changing the reference for the oral cancer slope factor in this final draft document is not clear. We tried to compare the Fisher rat liver dosing data from the JBRC 1998 studies (2 year) with the Kano et al., 2009 data given on Table 5.5 on page 102 of this draft final. We noted that the doses for the rat in mg/kg-day (Fisher male for example) do not agree with the data in Table 5-5 on page 102, although 50 animals were used for each dose in both; however, the female mouse incidence of liver tumors dosing data do agree from Table 4-14 to Table 5-5, again, with 50 groups of mice at each dose reported for both Tables.	Please see comments 2 and 3 above.	S, M.
6	5.4.3.1.	Pages 103- 106; Table 5-7, Page 104. A-11 (lines 1- 2)	The following comments and recommendations refer to allometric scaling, including use of BW3/4. Page 103 (lines 8-10) state that "Human equivalent doses (HEDs) were extrapolated from the administered animal doses using a BW scaling factor (BW ^{0.75}), the results are show in Table 5-7 on page 104. The 1,4-dioxane was administered via drinking water and in some cases be assumed to be allometrically scaled.	We recommend that EPA discuss the impact of using the default uncertainty factor of 10 for interspecies extrapolation as opposed to reducing it to 3 for dynamics since kinetics is already addressed by using BW^3/4 scaling. <u>The text should either clarify why the</u> <u>uncertainty factor of 10 was necessary or</u> <u>clarify that allometric scaling was not</u> <u>accounted for twice.</u>	S, M

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			The subject of allometric scaling extrapolation factors was addressed during the 2009 external peer review (Dr. Harvey Clewell III, Versar, Inc. 9 September 2009, "Draft Final Reviewer Comments External Peer Review A Meeting on the Toxicological Review of 1,4-Dioxane (CASRN 123- 91-1) prepared for EPA), where Dr. Clewell asked why an uncertainty factor of 10 was used for interspecies extrapolation, instead of a BW^3/4 default extrapolation factor for scaling for kinetics and a factor of three for dynamics, as this appears to be EPA's preferred default approach. U.S. EPA's response to this reviewer's question is given on page A-11 (lines 1-2): "Body weight scaling based on body surface [sic] for noncancer endpoints is not standard practice within the Agency and the default was implemented in this assessment." We believe that an RfD for another chemical has utilized the approach and we aware of near-final guidance advocating this method and don't believe that the EPA response given in Appendix A fully characterizes the Agency position on this issue.	The rationale for rejection of the reviewer's suggestion is not clear; EPA has a draft document that harmonizes the approach between carcinogens and noncarcinogens and we believe we have seen this performed for other chemicals. Please consider revising with a more complete response		
7	Section 5.1.1	Page 89	The selection of the study by Kociba et al. (1974) as the principal study remains lacking in technical objectivity and transparency. Quantitative incidence of adverse effects is not provided and therefore statistical evaluation cannot be conducted to demonstrate the technical strength of the POD upon which the RfD is calculated. We understand that principal study selection is at EPA's discretion, but wanted to be on record once more that we disagree the choice. Kano et al. (2008), is the technically	If possible at this late stage, a detailed analysis of the strengths and weaknesses of the Kociba et al (1974) and the Kano et al. (2008) serving as the principal study should be considered to improve the transparency of the selection process.	S, M	

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8	5.4.3.2. Extrapolation Method(s)	105; line 21 ff	superior investigation, as the principal study. During the interagency review, DoD well as other agencies urged EPA to consider nonlinear low dose extrapolation since the data indicated it may be justified. In the external peer review almost all of EPA's external peer reviewers' expressed the opinion that, while there were insufficient data to determine a mode of action (MOA), there were ample data to suggest that the MOA would be nonlinear. Therefore, the statement that "EPA concluded that the available information and data are insufficient to establish significant biological support for a non-linear approach." appears to be in conflict with that of its external experts, which could be acknowledged more completely. EPA cited part of its 2005 cancer guidelines, but did not provide the review panel with the following in Section 3.3.4. "Nonlinear Extrapolation to Lower Doses": "A nonlinear extrapolation method can be used for cases with sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses but with not enough data to support a toxicodynamic model that may be either nonlinear or linear at low doses. Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency's mode of action framework."	From the external peer reviewers' comments, as recorded in the report on EPA's web site, it is apparent that many of the reviewers would have liked to see a nonlinear extrapolation in addition to the linear extrapolation. Please add this analysis to the document as suggested by several of the external reviewers as well as interagency reviewers. Some of the external reviewers seemed to be under the impression that this was not allowed by EPA's cancer guidelines unless an MOA could be determined. To prevent any suggestion of biasing the panel, we recommend that, in the future, the external peer reviewers be given the section of EPA's cancer guidelines cited in this comment, so they can officially opine as to whether they think there is sufficient biological support absent an MOA determination for a nonlinear extrapolation to be provided also.	S, M	