Department of Defense (DoD) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of 1,4-Dioxane (dated May 2011)

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Department of Defense Comments on 14-dioxane inhalation_Toxicological Review_IASC draft_05-13-11.pdf					
Comments submitted by: Chemical Material Risk Management Directorate			Organization: Department of Defense	Date Submitted: 6/15/2011	
*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**	**Pages**	**Comment**	**Suggested Action, Revision and References (if necessary)**	***Category**
1	Global	92, 120, 133, 136	Typographical errors in sentences: beginning line 5, pg 92; line 2, page 120; lines 18 and 24 on pg 133; and in sentence beginning line 9, pg 136.	Please fix typographical and/or grammatical errors.	E
2	Global		As discussed further in specific comments below, DoD has found that there is sufficient information to support a nonlinear extrapolation for the carcinogenic potency of 1,4-dioxane, i.e., this chemical works as a promoter that most toxicologists would consider sufficient proof for nonlinearity at low doses. We suggest that 1,4-dioxane would be an excellent case to implement Section 3.3.4 of EPA's 2005 cancer guidelines. It this section titled Nonlinear "Extrapolation to Lower Doses" the guidelines state [emphasis added], "*Nonlinear extrapolation having a significant biological support may be presented in*	Per EPA's 2005 cancer guidelines, DoD suggests that EPA present both a linear and a nonlinear extrapolation for the carcinogenic effects of 1,4-dioxane.	S

			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. If the mode of action and other information can support chemical-specific modeling at low doses, it is preferable to default procedures.		
3	Global		We appreciate EPA's clear identification of the sections of the draft document that have been revised to include the inhalation pathway analysis and thus, are the focus of the current interagency review.	N/A	O
4	4.2.2.1.2	57	The magnitude of organ weight changes (the percent change compared to control) is not listed in the Kasai et al. 2008 summary, and as such, the biological significance of organ weight changes is indeterminable.	Recommend adding the percent organ weight change compared to controls from Kasai et al. 2008 in the study summary. EPA should also present the dose-related organ weight effects and magnitude of change in tabular format to increase clarity and ease comparisons between histopathologic effects and organ weight changes.	E
5	4.2.2.1.2	58	The DoD agrees with EPA that the endpoint "nuclear enlargement" is of uncertain toxicological significance. Therefore, it is unclear why EPA chose to utilize the Kasai et al. 2008 author-identified LOAEL of 100ppm based on "slight nuclear enlargement of nasal epithelium". This LOAEL is then carried forward throughout Section 4 in the summary discussions and comparison tables (e.g., Table 4-22).	EPA should identify their own LOAEL/NOAEL from Kasai et al. 2008. We recognize that this suggested revision will not impact the RfC derivation, however it is recommended that EPA consider the male vaculoic change in olfactory epithelium	S

				at 400ppm as the LOAEL from Kasai et al. 2008, instead of the nuclear enlargement of respiratory epithelium. Additionally, if EPA would move discussion and presentation of toxic endpoints that have been rejected as either not relevant or as not fitting criteria for goodness of fit for BMD modeling to an appendix the text would be more clear and succinct.	
6	4.2.2.2.2	61	EPA's treatment of the endpoint "nuclear enlargement of epithelial cells" is not transparently described. It would be beneficial for EPA to indicate within the Kasai et al. 2009 summary in Section 4.2.2.2. that they discount the effect that was identified by the study authors as the LOAEL (nuclear enlargement of nasal and respiratory epithelium) due to uncertain toxicological significance, and chose 50 ppm as the EPA-derived LOAEL for respiratory metaplasia and atrophy in the nasal olfactory epithelium. For clarity, EPA should list their toxicologic effect only as the LOAEL in Table 4-22.	Recommend adding a clarifying statement regarding EPA's decision to dismiss the nuclear enlargement of nasal and repiratory epithelium as "adverse" given the unclear toxicological relevance of this endpoint within the Kasai et al. 2009 study summary in Section 4.2.2.2. This should also be indicated in Table 4-22 as the EPA-derived LOAEL from Kasai et al. 2009.	S
7	4.6	83	Nasal and respiratory effects following inhalation of 1,4-dioxane have not been included in the general overview paragraph of the "Synthesis of Major Noncancer Effects."	Recommend adding nasal and respiratory effects and the Kasai et al. 2008 and 2009 citations to the overview	E

				introduction paragraph to section 4.6.	
8	4.6.2	86-88	Section 4.6.2 "Synthesis of Major Noncancer Effects: Inhalation" is well written and objectively summarizes the available noncaner 1,4-dioxane inhalation data in sufficient detail, without overly repeatative information.	N/A	E
9	4.7 and 5.2	90-107, 115-123	The DoD believes that the available data strongly suggest a lack of genetic toxicity and a tumor promotion mechanism associated with tissue injury and subsequent regeneration as the MOA for 1,4-dioxane carcinogenicity. 1,4-Dioxane mediated hepatocyte cell proliferation has been demonstrated (Slott 1981; Goldsworthy 1991; Miyagawa 1999) and numerous mechanistic studies have also demonstrated the proliferation-potential of 1,4-dioxane. The MOA for 1,4-dioxane induced liver cancer involves sustained cytotoxicity followed by regenerative and unregulated cell growth. Furthermore, liver cytotoxicity occurs only at doses above which metabolic detoxification pathways are saturated. We believe that the dose-response curve can be assumed to be nonlinear in the low-dose region.	Recommend using a nonlinear approach for low dose extrapolation of cancer risk. At the very least, both approaches should be presented, and qualitatively and quantitatively compared. If EPA still asserts that the MOA information for liver tumor formation is insufficient to move from the default linear extrapolation methodology, it should be clearly stated as a scientific policy determination, and the quantitative impact of that decision presented.	S/M
10	4.7.1	90, line 21	The term "peritoneal" is properly used as an adjective as in "peritoneal tumor" or "pertioneal cavity"; when referring to the membrane organ itself, the term "peritoneum" should be used.	Change "peritoneal" to "peritoneum" on life 21 of page 90.	E
11	4.7.2	93, line 21	The single sentence paragraph on line 21 is out of place.	Recommend removing the	E

			The information regarding the tumor promoting potential of 1,4-dioxane should be expanded and added to the carcinogenic weight of evidence and/or MOA discussions.	sentence on page 93, line 21 and adding a summary of 1,4-dioxane's tumor promoting potential to the cancer weight of evidence or MOA sections (sections 4.7.1 or 4.7.3, respectively).	
12	4.7.2 and 4.7.3.2	92-93, 96	The negative hepatic and nasal effects from Torkelson et al. 1974 at 111ppm 1,4-dioxane for 2 years is not sufficiently discussed and should be more clearly presented for transparency and a more balanced weight of evidence analysis.	Recommend additional discussion regarding the negative findings of Torkelson et al. 1974. This study possibly provides a lower bound on tumorigenic effects and is important for the weight of evidence discussion.	S
13	4.7.3 Mode of Action, 5.4.4.2 and 5.5.1.1	92-100, 135 and 138	Canada's assessement of this chemical (*1,4-Dioxane Screening Assessment, Environment Canada, Health Canada, March 2010 (Chemical Abstracts Service Registry Number 123-91-1* that has already been peer reviewed*)* states: *"Based principally on the weight of evidence–based assessments of several international and other national agencies and available toxicological information, critical effects associated with exposure to 1,4-dioxane are tumorigenesis following oral and inhalation exposure, but not following dermal exposure; and other systemic effects, primarily liver and kidney damage, via all routes of exposure (i.e., oral, dermal and inhalation). The collective evidence indicates that 1,4-dioxane is not a mutagen and exhibits weak clastogenicity in some assays,*	We strongly suggest that EPA review the analysis by Canada and that it either (1) agree that the dose-response function has a threshold, i.e., is nonlinear at low doses per EPA's 2005 cancer guidelines terminology or (2) explain the flaws in the Canadian analysis. While recognizing that these governments operate under different legislation and guidance, DoD believes that transparency and clarity are better served if either analyses of the same data are consistent	S

			but not others, at high exposure levels often associated with cytotoxicity. Consideration of the available information regarding genotoxicity, and conclusions of other agencies, indicate that 1,4-dioxane is not likely to be genotoxic. Accordingly, although the mode of induction of tumors is not fully elucidated, the tumors observed are not considered to have resulted from direct interaction with genetic material. Therefore a threshold approach is used to characterize risk to human health." [emphasis added] (URL: http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1.cfm)	or if differences are clearly described so that stakeholders are not required to infer them.	
14	4.7.3	94, lines 23-26	There is a logical disconnect in this sentence: Kociba's paper suggested hepatotoxicity is "the result of accumulation of parent compound, however non in vivo or in vitro assays have examined the toxicity of metabolites resulting from 1,4-dioxane synthesis to support this hypothesis." The meaning is unclear. The second part of the sentence appears to be unrelated to the first part.	If the writer intended to say that toxicity of metabolites has not been ruled out, that should be stated more clearly.	E
15	4.7.3.2.2	96, line 29	As stated, it is unclear whether the Nannelli et al. 2005 study evaluated possible reactive intermediates and did not have sufficient information, or conversely, if they did not assess possible reactive intermediates.	Recommend clarifying the sentence on line 29, page 96 regarding Nannelli et al. 2005's assessment of reactive metabolites.	E
16	4.7.3.5 and 5.5.1	103, 138	As discussed for the noncancer evaluation, the human relevance of the observed carcinogenic nasal effects in rodents is uncertain. The brief mention of this uncertainty in Section 5.5.1.3, pg 130 is insufficient.	Recommend additional language within the "Nasal Cavity" Section of 4.7.3.5 "Biological Plausibility and Coherence" and within Section 5.5.1 "Sources of Uncertainty"	S

				regarding the uncertain human relevance of rodent nasal effects due to differences in the physiology of respiratory systems.	
17	5.2.1 Choice of Principal Studies	117, lines 25;28; 118, Table 5-5	Page 117 of the U.S. EPA draft states that "*All systemic and portal-of-entry nonneoplastic lesions from the Kasai et al. (2009) study that were statistically increased at the low- or mid- exposure* concentration (50 or 250 ppm) compared to controls, [emphasis added] *or the lesions that demonstrated a dose-response relationship in the absence of statistical significance* [emphasis added] *were considered candidates for the critical effect."* This section states: "*The candidate endpoints included centrilobular necrosis of the liver, spongiosis hepatis, squamous cell metaplasia of nasal respiratory epithelium, squamous cell hyperplasia of nasal respiratory epithelium, respiratory metaplasia of nasal olfactory epithelium, sclerosis in lamina propria of nasal cavity, and two degenerative nasal lesions, that is, atrophy of nasal olfactory epithelium* [emphasis added] *and hydropic change in the lamina propria (Table 5-5)."* Lesions that demonstrated a dose-response relationship in the absence of statistical significance should not be considered as candidates for the critical effect due to the lack of robustness and greater amount of uncertainty associated with these data. We do note that Kasai et al., 2009 reported $p<0.01$ by Fisher's exact test for atrophy; olfactory epithelium (this effect in 40/50 male rats at 50 ppb of 1,4-dioxane via inhalation), which is statistically	We recommend that the text differentiate between those non-neoplastic lesions whose increases were statistically significant at various exposure concentrations and those that just demonstrated a dose-response relationship in the absence of statistical significance. We recommend that the latter should not be considered as candidates for the critical effect due to the lack of robustness and greater amount of uncertainty associated with these data sets.	S/M

			significant.		
18	5.2.1;Table 5-8 footnote c, Table 5-10 footnote e	117 lines 3-5, 128, 130	Page 117 states that [emphasis added] **"***Because Fairley et al. (1934) did not present the statistics of the dose response data*, [emphasis added] *neither study was sufficient to characterize the inhalation risks of 1,4-dioxane."* The lack of reporting on the statistics of the dose response as policy reason for eliminating the Fairley et al. data appears to be applied inconsistently. Neither the statistical analysis nor the incidence data of hepatocellular adenoma or carcinoma for the Kasai (2008) study were published in a peer reviewed journal. Table 5-8, footnote "c" states that, "…. *For Kasai et al. (2009) incidence data was provided via personal communication from Dr. Tatsuya Kasai to Dr. Reeder Sams on 12/23/2008 (2008). Statistics were not reported*."[emphasis added] Table 5-10 on page 130, footnote "e", states, *"Provided via personal communication from Dr. Tatsuya Kasai to Dr. Reeder Sams on 12/23/2008 (2008). Statistics were not reported for these data by study authors*, so statistical analyses were conducted by EPA. [emphasis added]	For both clarity and transparency, we strongly recommend that EPA either apply its policies in a consistent manner or provide the rationale as to why these datasets appeared to be treated differently, i.e., why EPA did not reject the Kasai study but did reject the Fairley study; why EPA chose to contact Dr. Kasai but not Dr. Fairley, and why EPA chose to perform its own statistical analysis on the Kasai data but not on the Fairley data Furthermore, for other chemicals, EPA has stated that they will not use unpublished data. We suggest that EPA also provide stronger justification for using unpublished data that can not be easily verified and that has not been externally peer reviewed. Alternatively, if this is a change in EPA policy, it should be so stated.	S/M
19	5.2.2	120	It is unclear why sclerosis of the lamina propria is excluded as a potential critical effect (line 1-2).	Recommend explicit justification for excluding	E

				sclerosis of the lamina propria as a potential critical effect for RfC derivation.	
20	5.2.2	120	We agree with the choice of Kasai et al. 2009 as the principal study for the derivation of the RfC, however we disagree with the choice of any nasal effect for the critical effect. Given the physiologic differences between the respiratory systems of rodents and humans, the uncertainty in the biological plausibility of nasal and respiratory effects from 1,4-dioxane exposure in humans needs to be considered. The more highly convoluted nasal turbinate system of a rodent results in greater deposition in the upper respiratory track; the human relevance of observed adverse effects in that area is uncertain. Furthermore, it seems that this particular rat strain is highly sensitive to respiratory effects, as noted by the high rate of effects in control animals.	Recommend use of centrilobular necrosis in the liver from Kasai et al. 2009 as the critical effect. Use of the BMD-derived POD from centrilobular necrosis in the liver would result in a composite UF of 100 (no UF LOAEL-to-NOAEL is needed) and an RfC of 0.4 of 4 x 10-1 mg/m3. If EPA elects to maintain olfactory epithelial atrophy as the critical effect, the uncertainty regarding the human relevance of this endpoint needs to be clearly described and added to Section 5.3.	S/M
21	5.2.3, 5.4.3.2	p.119, lines 3ff., p133, lines 1-3 119	Adjustment for the exposure duration appears to be based on application of default procedures rather than consideration of the data. Adjustments to dosage are being made by scaling the actual dose to a 24-hour, 7 day/week exposure. However, since it is known that metabolism of dioxane by rats is subject to saturation, it is questionable whether or not this procedure adequately reflects a chronic exposure. The endpoints of interest are	We recommend that the actual exposure, rather than the averaged exposure be used for RfC calculations. If not, we recommend that EPA describe why this adjustment is appropriate in this case for inhalation exposure and	S/M

			(1) at the point of exposure and (2) most likely to be influenced by the peak exposure, not the average exposure. Application of this procedure assumes that the system obeys Haber's Law and that only the AUC matters. It is possible that during the actual exposure period, metabolic processing capacity is exceeded, and it is known that neoplasms are more likely to occur in rats where metabolic capability has been exceeded. The adjustment serves to artificially lower the exposure that would cause the effect, an adjustment that is not supported by biological considerations.	damage to the respiratory epithelium.	
22	5.2.3	121, lines 8-9	EPA should acknowledge that the respiratory tract effects observed after oral exposure to 1,4-dioxane could still be considered portal-of-entry effects given that the 1,4-dioxane was administered via drinking water, which could have been aspirated when drank by the rodents.	Recommend clarifying language that the respiratory tract effects seen in rodents administered 1,4-dioxane via drinking water may or may not be systemic effects due to possible aspiration of water and direct contact of 1,4-dioxane with respiratory tissue.	S
23	5.2.3 Exposure Duration and Dosimetric Adjustments	121	Though justified for assessing systemic toxicity, the adjustment for absorption of the chemical appears unjustifiable for point-of-contact toxicity.	Recommend that EPA should either not perform this adjustment or provide specific justification for its use for point-of-contact effects.	S/M
24	5.4 Cancer	125	In the Toxicoligical Profile for 1,4-Dioxane, ATSDR a states that *"the use of a nonlinear approach to low dose*	Similar to other comments above, DoD suggests that EPA	S

	Assessment 5.4.1.1 Choice of Study Data		*extrapolation might be considered based on the observation that liver toxicity, which some have suggested may be required for tumor development, occurs only at doses above which the metabolism of 1, 4-dioxane is saturated."* http://www.atsdr.cdc.gov/toxprofiles/tp187-c2.pdf	either use a nonlinear extrapolation from the point of departure or explain why it disagrees with ATSDR's analysis.	
25	5.4.2,Table 5-8,5-10,5-13,5-14,5.5, A.11	127 lines 6-13, 128 line 1, 130, 136-142	According to the text on pages 127-128, "*…1,4-dioxane produced a statistically significant increase in incidence and/*or a statistically significant dose-response trend for the following tumor types[emphasis added]**:** *hepatomas, nasal squamous cell carcinomas, renal cell carcinomas, peritoneal mesotheliomas, mammary gland fibroadenomas, Zymbal gland adenomas, and subcutis fibromas (Kasai, et al., 2009)."* It is very important to clearly differentiate between the statistically significant tumor incidence [emphasis added] data in various organs/glands compared to controls out of the group of 50 male rats) from just "a statistically significant dose-response trend [emphasis added]**.**" They should not carry the same weight of evidence for carcinogenicity, from inhalation exposure. It is crucial that renal cell carcinomas, mammary gland fibroadenomas, and Zymbal gland adenomas data not be used to derive the "Bayesian Total Tumor Analysis" (Table 5-13, page 136) as if they were of the same importance (same robustness). We believe that this does not represent use of "sound science." The authors of the Kasai et al. 2-year inhalation "principal" study of 1,4-dioxane in air (2009) reported	We strongly recommend that U.S. EPA not use renal cell carcinomas, mammary gland fibroadenomas, or Zymbal gland adenomas data to derive the "Bayesian Total Tumor Analysis". At a minimum, as mentioned in another comments, only sites that have some carcinomas should be included in any quantitative or qualitative analysis of carcinogenicity, according to EPA's cancer guidelines. We firmly believe that the statistically significant tumor incidence should be distinguished from data that only showed a statistically significant dose -response trend. We also recommend that those tumors that increased with dose but did not exhibit statistical significance be distinguished as not having	S/M

			that [emphasis added] *"…repeated inhalation exposure to 1,4-dioxane vapor for 2 yr was found to produce a dose-dependent and statistically significant increase* [emphasis added] *in the incidences of nasal squamous cell carcinomas, hepatocellular adenomas, and peritoneal mesotheliomas, as indicated by Peto's test and Fisher's exact test, respectively. In addition, the dose dependently increased tumor incidences were recognized in renal cell carcinomas, mammary gland fibroadenomas, and Zymbal gland adenomas, although those increased incidences were not statistically significant compared with the concurrent, matched controls by Fisher's exact test."* Also confirming these findings, the 2010 Canadian 1,4-dioxane health assessment (which was externally peer reviewed) reported that the 2-year Kasai et al. (2009) "key" rat study found "*Dose-dependent and significant increases in incidences* [emphasis added] *of nasal squamous cell carcinomas and hepatocellular adenomas were observed primarily in the 1250 ppm (4500 mg/m^3) exposed rats and a significantly increased incidence of peritoneal mesotheliomas was observed at 250 ppm (900 mg/m^3) and above. The incidences of renal cell carcinomas, fibroadenomas in the mammary gland and adenomas in the Zymbal gland also increased with dose, but were not statistically significant.* [emphasis added] (http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1.cfm)	strong evidence of carcinogenicty, especially when sites with statistically significant increases are reported in the same analysis. If EPA decides nonetheless to continue to include them in their evaluation, sites that do not have a statistically significant increase in carcinomas should not carry the same weight in the Bayesian analysis. We do not believe these data have sufficient weight of evidence for carcinogenicity and will result in an inaccurate, scientifically unjustifiable, and highly inflated inhalation unit risk estimate. Weighted Bayesian analyses are a standard practice of this form of meta-analysis, and should be used in a case such as this when data are of significant and obvious difference in quality. Most statisticians	

				would recommend that the Bayesian analysis be performed twice: once with only the highest quality data and once with all of the data appropriately weighted for quality. Comparison of the results provides an indication of the effect of the lower quality data on the results, from which a decision about their inclusion can be made from data rather than inference.	
26	5.4.1.2 Inhalation Study/ Data	128, Table 5-8	The incidence of subcutis fibroma in Table 5-8 decreases from 9/50 at 250 ppm to 5/50 at 1,250 ppm. This lack of an increased response at the highest dose tested is not mentioned in the text and is not fully described in the table's footnote. We believe the responses are not biologically relevant and should be more fully described.	Since the decrease in tumors at increasing doses is not due to an asymptotic approach of 100% response. The biological significance of this non-monotonic increase in the dose-response function needs to be justified. EPA should discuss the lack of an increase with increasing dose of this effect though the effect at 250 ppm was found to be statistically elevated.	S
27	5.4.2.2 Inhalation Data	129 - 130	EPA's 2005 and previous cancer guidelines are very clear: adenomas or firbromas can be added to the carcinomas, <u>but these lesions alone are not considered in the estimation of carcinogenic risk.</u> Therefore, all of EPA's cancer risk that depend on use of doses for which	While it is acceptable practice to combine these tumor types, we strongly recommend that EPA analyze the appropriate data with carcinomas alone and	S/M

			there were only adenomas or fibromas, which we believe are the estimations on which EPA has relied for its analysis of the IUR, should be recalculated without these lesions. Moreover, it is also commonly understood that not all of these non-cancerous lesions will progress to cancer.	with those doses where carcinomas and adenomas or fibromas were added. This analysis will serve as a useful quantitative measure of the uncertainty of the risk estimate.	
28	5.4.2.2 Inhalation Data	130, Table 5-10	Combined tumor endpoint data are rarely reported and must be obtained from the original data. The combined liver tumors (adenomas and carcinomas) and peritoneal mesotheliomas are by far the most common neoplastic lesions at high doses. The combined effect of the tumors can only be estimated by reviewers if it is shown which of the 3 or 4 rats with liver tumors at 250 ppm are also among the 14 rats with peritoneal mesotheliomas, and if any of the 21 to 23 rats with liver tumors at 1250 ppm are also among the 41 rats with peritoneal mesotheliomas, and how many rats have both types. Without these data, it is not possible to independently review that the appropriate data have been combined, i.e., that the number of tumors that were assigned to any dose did not exceed the number of tumor-bearing animals at that dosage. The use of unpublished data in Toxicological Review that have not been externally peer reviewed impedes the transparency of their analysis. Without these data, neither we nor the external reviewers of a panel organized by EPA can appropriately review and validate the procedures used.	Please supply the data discussed in the comment in order to allow a full review by external reviewers and to increase the transparency of the document.	S

29	5.4.4.2. Inhalation Unit Risk	136, Table 5-13	As mentioned above, this analysis appears to include some tumor sites for which there are not any carcinomas. This is contrary to EPA's 2005 and 1986 cancer guidelines	The quantitative and qualitative analyses of carcinogenesis should only include sites for which some dose-related cancers have been observed. Sites for which only non-neoplastic tumors were observed cannot be included in the analysis, unless EPA justifies this departure from its guidance and standard procedures.	S
30	Appendix F	F-13, F-14; Table F-2	The text states that the lowest AIC value was used to select the Dichotomous Hill model. Yet this model has an AIC of 130.404 and the Log-logistic model has an AIC of 129.465	EPA should use the log-logistic model or change its explanation of the choice of model.	S
31	Appendix G	Global	Although EPA does not provide printouts for all of the models, we believe that, in some cases, EPA is comparing AICs for models with different degrees of freedom. If this is true, such comparisons are not valid, as the AIC depends on the degrees of freedom.	We would like verification that the models being compared have the same degrees of freedom and assume other reviewers and stakeholders would as well. Please add the printouts for all of the models or include more information on the modeling parameters.	S
32	G.3. Multitumor Analysis Using Bayesia	G-61	The Bayesian approach used by EPA appears suboptimal. Given the available data, it would seem reasonable to optimize the value of Bayesian analysis, i.e., its ability to update the priors with new data. We recommend that, if EPA chooses to start with a defuse prior (which is problematic, given that the models in the	We recommend that EPA consider procedures that optimize the Bayesian approach for combining data by minimizing the effect of choice of initial prior. DoD also	S

	n Methods		BMD software require a monotonically increasing function) that the first posterior be based on the data of carcinogens alone and that the results of this analysis be updated by the combined cancers and non-neoplastic tumors. By using the process twice, the choice of initial prior will be less significant. Similarly, the individual sites could be used separately and combined.	suggests that this new procedure undergo a separate, external peer review by experts in statistics.	