

**EPA's Response to Selected Major Interagency Comments on the  
Interagency Science Consultation  
Draft IRIS Toxicological Review of 1,4-Dioxane (inhalation exposure route only)  
September 15, 2011**

**Purpose:** The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (Step 3 and Step 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Consultation step (Step 3) for the draft IRIS Toxicological Review of 1,4-Dioxane (inhalation exposure route only; dated May 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting for public comment and external peer review. The complete set of interagency comments is attached as an appendix to this document.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at [www.epa.gov/iris](http://www.epa.gov/iris).

**Topic #1: Selection of the Critical Effect for Derivation of the Reference Concentration (RfC)** – *CDC/ATSDR indicated agreement with the choice of principal study and critical effect (atrophy of the olfactory epithelium) for the derivation of the RfC. NIEHS/NTP also stated that they agreed with the derivation of the RfC. OMB commented that more clarity is needed regarding EPA's characterization of the level of adversity of the critical effect and that this effect should be described as a precursor effect, likely to occur early in the continuum of pathological events associated with the respiratory tract effects. DoD agreed with the choice of principal study, but disagreed with the selection of the critical effect, given the physiological differences between the respiratory systems of rodents and humans. DoD stated that the highly convoluted nasal turbinate system of the rodent results in greater deposition in the upper respiratory tract making the human relevance of the observed adverse effect uncertain. DoD also stated that this particular rat strain is highly sensitive to respiratory effects.*

**EPA Response:** Atrophy of the olfactory epithelium, a nasal lesion, was selected as the critical effect for the derivation of the RfC in the Interagency Science Consultation draft assessment. This critical effect is considered to be adverse and is biologically plausible and likely to be relevant to humans, as this nasal lesion occurs in cell types that are prevalent throughout the respiratory tract of both rats and humans. There are no data to indicate that atrophy of the olfactory epithelium is either a precursor effect. Indeed, both atrophy and respiratory metaplasia of the olfactory epithelium occurred at the same exposure concentration (50 ppm). In revising the assessment to more clearly indicate the consideration of adversity of the effects, EPA decided to select both types of nasal lesions (atrophy and respiratory metaplasia of the olfactory epithelium) as co-critical effects for the derivation of an RfC for 1,4-dioxane.

Further support for the use of rat nasal lesions as a critical effect is that a similar pattern of effects was observed in rats after both oral and inhalation exposure to 1,4-dioxane,

indicating that the nasal effects may also occur as a result of systemic circulation, independent of any differences in the inhalation physiology between rats and humans.

Text in Sections 5.2 and 5.2.1 of the Toxicological Review has been modified as a result of the designation of co-critical effects and External Peer Review charge question B2 has been modified to request comment on the selection of atrophy and respiratory metaplasia of the olfactory epithelium as critical effects.

**Topic #2: Application of Adjustment Factors for Duration and Dosimetry in the Derivation of the RfC** – *DoD recommended that a point of departure unadjusted for exposure duration should be used in the derivation of the RfC since metabolism of 1,4-dioxane is subject to saturation in rats. They indicated that the adjustment serves to artificially lower the exposure that would cause the effect, and that such an adjustment is not supported by biological considerations. OMB recommended that the RfC should be derived by application of both a dosimetric adjustment factor for portal-of-entry effects (Category 1) and effects from systemic acting gases (Category 3) for purposes of comparison. CDC/ATSDR indicated that EPA’s determination that 1,4-dioxane is a Category 3 gas was persuasive.*

**EPA Response:** A duration adjustment is used in the assessment to account for the non-continuous exposure protocol used in the principal study. Data to inform whether the parent compound or a metabolite is responsible for the effects observed following 1,4-dioxane exposure are not available. Therefore, it is unclear how information on metabolic saturation in rats would impact the duration adjustment.

The human equivalent concentration (HEC) for 1,4-dioxane was calculated by the application of the dosimetric adjustment factor (DAF) for systemic acting gases (i.e. Category 3 gases), in accordance with the EPA’s *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* ([U.S. EPA, 1994](#)). This conclusion was based upon a number of factors, including the low reactivity of 1,4-dioxane and the occurrence of systemic effects following oral and inhalation exposure to 1,4-dioxane. However, 1,4-dioxane is miscible in water and induces effects in portal-of-entry tissues, characteristics that are also indicative of a Category 1 gas. Therefore, in response to OMB comments, EPA has provided an alternative calculation of the HEC for 1,4-dioxane based on the application of the corresponding DAF for gases that act through the portal-of-entry (i.e., Category 1 gases). This additional analysis can be found in Appendix G of the Toxicological Review. The External Peer Review charge question B3 has been edited to request comment on these alternate methods for deriving the point of departure.

**Topic #3: Use of Linear Low-Dose Extrapolation for Cancer** – *DoD stated that there is sufficient information to support a non-linear extrapolation for the carcinogenic potency of 1,4-dioxane. They suggested that EPA implement Section 3.3.4 of EPA’s Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 2005) which states that: “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. If the mode of action and other information can support chemical-specific modeling at low doses, it is preferable to default procedures.” DoD stated 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 mode of action for 1,4-dioxane carcinogenicity; that 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. They indicated that the mode of action for 1,4-dioxane induced liver cancer involves sustained cytotoxicity followed by regenerative and unregulated cell growth, that liver cytotoxicity occurs only at doses above which metabolic detoxification pathways are saturated, and that the dose-response curve can be assumed to be nonlinear in the low-dose region.*

*OMB stated that it appears that data exist to support a non-linear mode of action as the Kasai studies show accumulation related to saturation at high doses. OMB indicated that on page 104 of the draft Toxicological Review a statement is made that data on key events is missing; however, it is not clear that this implies that there is not biological support for a non-linear mode of action and that EPA’s discussion could be strengthened and clarified.*

*NASA stated that when the previous oral assessment for 1,4-dioxane was subjected to external peer review, a number of the reviewers indicated that the mode of action for cancer could not be readily determined, but that the mode of action is likely to be non-linear. NASA suggested that in the absence of solid, defensible data that indicates a linear relationship, EPA should consider non-linear extrapolation for the estimation of cancer risks.*

*On the other hand, NIEHS/NTP stated that EPA should consider deletion of Tables 4-23 and 4-24 since there are no data available to support any of the mode of action assumptions presented in the assessment.*

**EPA Response:** When EPA evaluates whether the available data provide significant biological support for a mode of action for cancer the goal is to identify key events, and to have reasonable confidence in the sequence of events and how they relate to the development of tumors including information on the shape of the dose-response curve at low doses. It is EPA’s judgment that there are insufficient data to establish the shape of the dose response curve in the exposure-response curve at low doses based on the mode of action data for cancer effects following exposure to 1,4-dioxane, for both oral and inhalation routes of exposure; thus a default linear extrapolation was used.

1,4-Dioxane produces liver, nasal, kidney, peritoneal (mesotheliomas), mammary gland, Zymbal gland, and subcutis tumors in animal models. Several hypothesized mode(s) of action exist for liver and nasal tumors; however, they are not supported by data either in a temporal or dose-related manner. Specifically, tumors occur in some rodent models in the absence of data to support the hypothesized key events (i.e., cytotoxicity) such that the plausibility of these potential modes of action is questionable. In addition, studies evaluating the kinetics of 1,4-dioxane suggest that liver carcinogenicity may be related to the accumulation of the parent compound following metabolic saturation; however, the toxic moiety (i.e., parent compound and/or metabolite(s)) is unknown. Perhaps more importantly, there are no available data regarding any hypothesized carcinogenic MOA

for 1,4-dioxane-induced kidney, lung, peritoneal (mesotheliomas), mammary gland, Zymbal gland, and subcutis tumors.

In accordance with EPA's *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)), the absence of evidence for genotoxicity does not invoke the use of nonlinear low-dose extrapolation, nor does it define a mode of action. Furthermore, it is not clear what endpoints would be used for the presentation of a non-linear (presumed threshold) extrapolation as an alternate approach for liver and/or nasal tumors, nor is it evident as to how that approach would be scientifically supported or beneficial to risk assessors.

Although this review is focused on the inhalation route of exposure, interagency review comments received also discussed the previous external peer review comments on the oral assessment, particularly as they relate to the mode of action information and determination of low-dose extrapolation for 1,4-dioxane. In brief, the external peer reviewers of the oral assessment of 1,4-dioxane (see Appendix A of the 2010 Toxicological Review) had mixed opinions regarding the mode of action with 4 out of 8 reviewers indicating that the mode of action could not be defined, thereby supporting the linear low-dose extrapolation:

- three reviewers supported the conclusion that a mode of action could not be identified for any of the tumor sites;
- one reviewer commented that the mode of action is likely to be nonlinear but stated that there is inadequate evidence to support a specific mode of action hypothesis with any confidence, so that a default linear extrapolation is necessary;
- one reviewer stated this was outside of his area of expertise but indicated that the discussion was too superficial and suggested including consideration of the effect of various mode of action assumptions in the uncertainty discussions, as well as adding statements as to what the Agency would consider essential information to make a determination about a mode of action;
- one reviewer indicated that better presentation of the analysis was warranted; and
- two reviewers commented that even though the mode of action for 1,4-dioxane is not clear there is substantial evidence that it is non-genotoxic. One of these two reviewers also suggested that a nonlinear cancer model should be utilized.

In response to the interagency reviewer comments, text in Section 4.7 of the Toxicological Review has been modified to further clarify the available data related to the mode of action for cancer and EPA's rationale for the use of a linear approach for extrapolation of cancer risk. In addition, External Peer Review charge question C2 has been modified to specifically request that reviewers identify whether a mode of action can be established for 1,4-dioxane (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

Tables 4-23 and 4-24 have been retained in the Toxicological Review as they provide support for EPA's conclusions regarding the mode of action for 1,4-dioxane. These

tables provide an evaluation of the data that are available, as well as data that are lacking, to show temporal sequence and the dose-response relationship for the hypothesized key events for 1,4-dioxane-induced liver and nasal tumors – the two tumor types for which some mode of action data are available.

**Topic #4: Use of tumor incidence data in the Derivation of the Inhalation Unit Risk (IUR) –** *OMB commented that the rationale for combining hepatocellular adenomas and carcinomas is unclear given that there were only statistically significant increases in hepatocellular adenomas, not carcinomas. DoD stated that it is important to clearly differentiate between the statistically significant tumor incidence data in various organs/glands compared to controls from just a statistically significant dose-response trend. DoD also commented that the EPA’s 2005 Cancer Guidelines and previous cancer guidelines are very clear: adenomas or fibromas can be added to carcinomas, but these lesions alone should not be considered in the estimation of carcinogenic risk given that it is commonly understood that not all of these non-cancerous lesions will progress to cancer.*

**EPA Response:**

The incidence of adenomas and carcinomas within a dose group at a site or tissue in rodents are often combined based upon EPA’s *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005). This practice is based upon the hypothesis that adenomas may develop into carcinomas if exposure at the same dose was continued (McConnell et al., 1986). It is not clear that the cancer guidelines require subtypes of tumors to be statistically significantly elevated in order to be combined. In any case, the increased incidence of hepatocellular carcinomas both in male and female rats was statistically significant by trend test, which is generally more robust for analyzing dose-response trends than separate pairwise comparisons because it considers the entire data set simultaneously. In some cases, lack of statistical significance in a trend test may be followed with pairwise comparisons between control and higher dose responses. In this case, the increases in carcinomas, observed only at the high dose, were also statistically significantly elevated over control by pairwise comparisons. Accordingly, the incidences of hepatocellular adenomas and carcinomas were combined without double-counting as the incidence of either hepatocellular adenoma or carcinoma and utilized to calculate the IUR.

In accordance with EPA’s *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005), EPA utilized adenomas and fibromas in the absence of malignant neoplasms. Section 2.2 of the guidelines state that while the term “tumor” is defined as a malignant neoplasm or a combination of malignant and corresponding benign neoplasms, observations of only benign neoplasia may or may not have significance for evaluation. Therefore, the use of benign tumors in the absence of malignancy should be evaluated on a case-by-case basis. Given the multiplicity of tumors in the Kasai et al. (2009) study and an unknown MOA(s), the inclusion of benign tumors is scientifically justified.

In response to the reviewer comments, text in Section 5.4.2.2 of the Toxicological Review has been modified to further clarify the use of both statistically significant tumor incidence data and statistically significant dose-response trend tumor data. In addition,

clarifying text has been added to Section 5 regarding the use of benign tumors in the absence of malignancy, as appropriate. In addition, EPR Charge Question C4 requests comment on EPA's justification for selection of tumor data used in quantitative assessment.

**Topic #5: Use of the Multi-tumor Bayesian Analysis in Derivation of the Inhalation Unit Risk (IUR) –**

*DoD suggested that the Bayesian approach used by EPA to develop a combined estimate of cancer risk across several tumor sites “appears suboptimal” and recommended that a different type of Bayesian analysis be performed. The approach suggested involved a multistep process first analyzing “data of carcinogens alone and that the results of this analysis be updated by the combined cancers and non-neoplastic tumors.” The comment also suggested that EPA’s analysis was in conflict with the standard assumption in dose response modeling that risk increases (monotonically) with dose.*

**EPA Response:** EPA’s goal in the assessment is to conduct a statistical analysis to estimate the combined risk of different types of tumors resulting from exposure to a chemical. The analysis performed by EPA (using “diffuse priors”) is an application of a widely used statistical methodology that supports broad application of Bayesian statistical methods in data analysis (see for example, T. Ando in *Bayesian Model Selection and Statistical Modeling*; Chapman & Hall/CRC, 2010). The specific statistical procedure employed followed a peer-reviewed published methodology (Kopylev et al. 2009). The Bayesian analysis used in the draft assessment yielded a risk estimate that was closely similar to the value estimated using non-Bayesian statistical methods, confirming the reasonableness of these results. EPA also notes that its analysis conforms to the principle that response increases with dose since EPA’s modeling is based on application of the (monotonically increasing) multistage model. The External Peer Review charge question C5 requests comment on EPA’s methods for deriving an IUR.

The suggestion of the above comment that a two stage Bayesian approach be implemented (first analyzing data on malignant tumors, then in a second step incorporating both malignant and non-malignant tumors) might be suitable for consideration in a research investigation; however, EPA does not see its advantage and is unsure whether it could be successfully implemented.

## **Appendix**

**National Institute of Environmental Health Sciences/National Toxicology Program (NTP) comments**

**Center for Disease Control/Agency for Toxic Substances and Disease Registry (ATSDR) comments**

**National Aeronautics and Space Administration (NASA) comments**

**Department of Defense (DoD) comments**

**Office of Management and Budget (OMB) comments**

**National Institute of Environmental Health Sciences/National Toxicology Program (NTP)  
Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of  
1,4-Dioxane (dated May 2011)**

Date: June 3, 2011

EPA has done an outstanding job in integrating recently published data on inhalation toxicology and carcinogenesis studies to the existing draft document prepared based on oral studies for 1,4-dioxane. The derivation of POD, uncertainty factors, RfC and IUR are all clearly and logically presented. The only comment we have is for EPA to consider deletion of Tables 4-23 and 4-24 since there is no data available for any of the mode-of-action assumptions.

Submitted by:  
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**Center for Disease Control/Agency for Toxic Substances and Disease Registry (ATSDR)  
Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of  
1,4-Dioxane (dated May 2011)**

Date: June 8, 2011

From: Agency for Toxic Substances and Disease Registry

Subject: Comments on EPA's Toxicological Review of 1,4-Dioxane (Inhalation)

To: Environmental Protection Agency

We appreciate the opportunity to review EPA's Toxicological Review of 1,4-Dioxane (Inhalation) and the Charge to External Reviewers. Overall, we found that the Charge to External Peer Reviewers is appropriate and reflects the recommendations and risk assessments in the IRIS Summary. Our comments below refer primarily to the Toxicological Review of 1,4-Dioxane (Inhalation).

**General**

The recent well-conducted studies by Kasai et al. (2008) and Kasai et al. (2009) were thoroughly reviewed and incorporated in all relevant sections. The Kasai et al. (2009) chronic study was appropriately used for the derivation of both the RfC for non-neoplastic effects and the Inhalation Unit Risk (IUR) for neoplastic effects.

**Minor comments**

Page 56, Line 24: The concentrations in ppm units were also expressed parenthetically in units of  $\text{mg}/\text{m}^3$ , but the converted concentrations were rounded off. ATSDR would not have rounded the concentrations.

Page 56, Line 26: What is "195044" in the Kasai reference?

Page 57, Line 23: The sentence: "Changes in hematological parameters were observed at 3,200 ppm...." should be changed to "Changes in hematological *and clinical chemistry* parameters..." as AST, ALT, glucose, and triglycerides are not hematological parameters.

Page 58, Table 4-15: Male, nuclear enlargement, nasal olfactory epithelium, 200 ppm, 5/10 needs a d superscript;  $p \leq 0.05$  by  $\chi^2$  test.

Page 58, Table 4-15: Male, vacuolic change; olfactory epithelium, 3200 ppm, should be 9/10.

Page 60, Line 27: The sentence "Measurement of hematological parameters..." should be changed to "Measurement of hematological parameters and clinical chemistry parameters..." See also Page 60 Line 35, and Page 61 Line 19.

Page 63, Table 4-17: For renal cell carcinoma, the 1250 ppm entry “4/50” should show a superscript, significantly different from control at  $p \leq .01$  for Peto test.

Page 87, Line 13: Change “severe” to “sensitive.”

Page 92, Lines 5 and 6: “Human studies of occupational exposure to 1,4-dioxane were inconclusive; in each case, the cohort size was limited and the number of reported cases *were of limited size* was small.” Should the words in italics be deleted?

Page 102, Lines 24 - 27: The following sentence is not exactly correct: “A comparison of 13-week and 2-year studies conducted in F344/DuCrj rats could not be conducted since the tumorigenic concentration of 1,4-dioxane was different from the concentration which produced nasal toxicities by 13 weeks of exposure.” In the 13-week study, nasal toxicity occurred at all exposure concentrations from 100 to 3200 ppm, and the 1250 ppm concentration at which the nasal tumors were seen in the 2-year study fall within the concentrations of 800 and 1600 ppm in the 13-week study. Furthermore, on page 117, line 15 and 16, it is noted that the range of exposure concentrations in the 2-year study was based on the results of the subchronic study. We therefore suggest that you delete the sentence.

Page 104, Line 27: The statement “Nasal cavity tumors have been reported in the absence of cell proliferation (Kasai, et al., 2009) and hyperplasia” seems questionable. On page 894 of the Kasai et al. (2009) study, the study authors state that “squamous cell hyperplasia in the nasal cavity...were observed in the 1250 ppm-exposed group. The squamous cell hyperplasia occurred primarily on the nasoturbinate septum, and had...proliferation of basal cells resembling an early stage of squamous cell carcinoma.”

### **Inhalation RfC**

The rationale and justification for selecting the Kasai et al. (2009) 2-year study as the principal study and the critical effect are clear, reasonable and appropriate. ATSDR is in the process of finalizing its updated Toxicological Profile for 1,4-Dioxane Draft for Public Comment, which will include the Kasai et al. (2009) study for consideration in deriving a chronic inhalation Minimal Risk Level (MRL). EPA’s analysis will be helpful in ATSDR’s deliberations. EPA’s proposed RfC of 0.03 mg/m<sup>3</sup>, which is equivalent to 0.008 ppm, was derived by converting the point of departure (POD) to a human equivalent concentration (HEC), considering 1,4-dioxane as category 3 gas. ATSDR’s proposed intermediate duration inhalation MRL is 0.006 ppm, based on the Kasai et al (2008) 13-week study, but it was derived from a HEC that was calculated by considering 1,4-dioxane as a category 1 gas. EPA’s discussion for considering 1,4-dioxane as a category 3 gas is persuasive and will be considered as ATSDR revises the Toxicological Profile.

### **IUR for Cancer**

The rationale, justification and analysis of the principal study and tumor data are clear, reasonable and appropriate.

## **National Aeronautics and Space Administration (NASA) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of 1,4-Dioxane (dated May 2011)**

Date: June 13, 2011

NASA thanks EPA for the opportunity to review and comment on the updated draft assessment for 1,4-Dioxane. Upon review, we have the following comments and issues and request EPA consider addressing the identified issues, prior to submitting this updated draft for peer review.

### Global Issues:

- This updated draft (which now includes proposed RfD and RfC levels) demonstrates the verbosity and lack of ready transparency with a lengthy discussion of the literature but limited clarity on the chosen studies and assumptions. NASA has noted this issue in previous draft assessments and this concern was also identified as a systemic concern in the most recent NAS review on formaldehyde. EPA is encouraged to implement the guidance provided by the NAS to ensure clear presentation of EPA's application of studies in the development of its assessments.
- As this draft was previously subjected to peer review (for the RfD only), NASA encourages a complete peer review to determine if EPA adequately addressed the previous peer review issues and also to consider the new data and study forming the basis of the proposed RfC. Inclusion of new studies (Kano et al, 2009) is a significant change but without peer review, there is no way to know if this significant new addition addresses the peer review issue or raises questions or incompatibilities with the use of Kasai, 2008 and 2008 to estimate the RfC.
- The reader finds it difficult to determine if EPA was responsive to the initial peer review. Redline strikeouts indicate new language for the proposed RfC but little clarification of efforts to address outstanding scientific issues identified during the first peer review.

### Specific Issues:

- The draft lacks clarity and discussion on the Kano et al, 2009 study and its relationship (and clarification of) the JBRC 1998a study. It appears that two different data sets were used to make conclusions between the two drafts. NASA questions that use of different data requires significant clarification by EPA and also full peer review.
- As noted in the previous interagency review, use of the Kociba study remains problematic, especially as EPA characterizes its decision to use Kociba as the basis of the RfD as it was "the most sensitive". The updated draft lacks clear discussion of why Kociba was chosen and question what is meant by "sensitivity" and its relevance in this draft. EPA is encouraged to clarify its choice of Kociba and any issues or inconsistencies found when comparing the Kociba and Kasai studies that are the basis for the proposed RfD and RfC respectively.

- The lack of studies (only four are mentioned) for the development of an RfC raises significant concerns that the updated draft's proposed RfC is premature and not supported by scientific literature. The Kasai 2008 and 2009 studies were chosen as the foundation of the RfC development. EPA, by its own admission, states that the lack of any corroborating evidence in other studies for the Kasai result. EPA further notes the weakness in reliance on this one study but setting UFs of 1000 with significant levels of uncertainty in all categories. NASA requests EPA re-consider issuing a draft RfC, based on such limited evidence. We also request an in-depth discussion of how EPA will address peer review responses, should this very limited base (one study) source for the proposed RfC be identified as an outstanding issue.
- The previous interagency review and the peer reviewers of the proposed RfD requested EPA consider non-linear extrapolation. A number of commenters indicated that the Mode of Action (MOA) could not be readily determined but the MOA was likely to be non-linear. EPA's response in the updated draft is to dismiss the peer reviewers input. NASA requests EPA re-visit this issue, in light of the peer reviewers input and the lack of solid, defensible data that indicates a linear relationship. This remains a significant issue and the updated draft needs clarifying language to clearly state EPA's evaluation. Again, the draft text should contain this clarifying language and be subject to peer review again.

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

Date: June 15, 2011

<p align="center"><b>Department of Defense Comments on 14-dioxane inhalation_Toxicological Review_IASC draft_05-13-11.pdf</b></p>					
<p>Comments submitted by: Chemical Material Risk Management Directorate</p>		<p>Organization: Department of Defense</p>		<p>Date Submitted: 6/15/2011</p>	
<p>*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.</p>					
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], " <u>Nonlinear extrapolation having a significant biological support may be presented in</u>	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

			<i>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.</i>		
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 vacuoloid change in olfactory epithelium	S

				<p>at 400ppm as the LOAEL from Kasai et al. 2008, instead of the nuclear enlargement of respiratory epithelium.</p> <p>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.</p>	
6	4.2.2.2. 2	61	<p>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.</p>	<p>Recommend adding a clarifying statement regarding EPA's decision to dismiss the nuclear enlargement of nasal and respiratory 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.</p>	S
7	4.6	83	<p>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."</p>	<p>Recommend adding nasal and respiratory effects and the Kasai et al. 2008 and 2009 citations to the overview</p>	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 noncancer 1,4-dioxane inhalation data in sufficient detail, without overly repetitive information.	N/A	E
9	4.7 and 5.2	90-107, 115-123	<p>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.</p> <p>We believe that the dose-response curve can be assumed to be nonlinear in the low-dose region.</p>	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 "peritoneal cavity"; when referring to the membrane organ itself, the term "peritoneum" should be used.	Change "peritoneal" to "peritoneum" on line 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 assessment of this chemical ( <i>1,4-Dioxane Screening Assessment, Environment Canada, Health Canada, March 2010 (Chemical Abstracts Service Registry Number 123-91-1</i> that has already been peer reviewed) states:  <i>“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,</i>	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

			<p><i>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, <u>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.</u></i> [emphasis added] (URL: <a href="http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1.cfm">http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1.cfm</a>)</p>	<p>or if differences are clearly described so that stakeholders are not required to infer them.</p>	
14	4.7.3	94, lines 23-26	<p>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.</p>	<p>If the writer intended to say that toxicity of metabolites has not been ruled out, that should be stated more clearly.</p>	E
15	4.7.3.2.2	96, line 29	<p>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.</p>	<p>Recommend clarifying the sentence on line 29, page 96 regarding Nannelli et al. 2005's assessment of reactive metabolites.</p>	E
16	4.7.3.5 and 5.5.1	103, 138	<p>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.</p>	<p>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"</p>	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 Princip al Studies	117, lines 25;28; 118, Table 5-5	<p>Page 117 of the U.S. EPA draft states that “<i>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.</i>”</p> <p>This section states: “<i>The candidate endpoints included centrilobular necrosis of the liver, spongiosis hepatitis, 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).</i>”</p> <p>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&lt;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</p>	<p>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.</p>	S/M

			significant.		
18	5.2.1; Table 5-8 footnote c, Table 5-10 footnote e	117 lines 3-5, 128, 130	<p>Page 117 states that [emphasis added] <i>“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.”</i></p> <p>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, <i>“... 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.”</i>[emphasis added]</p> <p>Table 5-10 on page 130, footnote “e”, states, <i>“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.”</i> [emphasis added]</p>	<p>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</p> <p>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.</p>	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.	<p>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 <math>4 \times 10^{-1}</math> mg/m<sup>3</sup>.</p> <p>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.</p>	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 drunk 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 Dose Metric 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 Toxicological Profile for 1,4-Dioxane, ATSDR states that <i>“the use of a nonlinear approach to low dose</i>	Similar to other comments above, DoD suggests that EPA	S

	Assessment 5.4.1.1 Choice of Study Data		<i>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.”</i> <a href="http://www.atsdr.cdc.gov/toxprofiles/tp187-c2.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp187-c2.pdf</a>	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	<p>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]: <i>hepatomas, nasal squamous cell carcinomas, renal cell carcinomas, peritoneal mesotheliomas, mammary gland fibroadenomas, Zymbal gland adenomas, and subcutis fibromas (Kasai, et al., 2009).</i>”</p> <p>It is very important to clearly differentiate between the <u>statistically significant tumor incidence</u> [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.”</p> <p>The authors of the Kasai et al. 2-year inhalation “principal” study of 1,4-dioxane in air (2009) reported</p>	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

		<p>that [emphasis added] “...repeated inhalation exposure to 1,4-dioxane vapor for 2 yr was found to produce a dose-dependent and <u>statistically significant increase</u> [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 <u>increased incidences were not statistically significant compared with the concurrent, matched controls by Fisher’s exact test.</u>”</p> <p>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 “<u>Dose-dependent and significant increases in incidences</u> [emphasis added] of nasal squamous cell carcinomas and hepatocellular adenomas were observed primarily in the 1250 ppm (4500 mg/m<sup>3</sup>) exposed rats and a significantly increased incidence of peritoneal mesotheliomas was observed at 250 ppm (900 mg/m<sup>3</sup>) and above. The incidences of renal cell carcinomas, fibroadenomas in the mammary gland and adenomas in the Zymbal gland also increased with dose, <u>but were not statistically significant.</u> [emphasis added] (<a href="http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1.cfm">http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1.cfm</a>)</p>	<p>strong evidence of carcinogenicity, especially when sites with statistically significant increases are reported in the same analysis.</p> <p>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.</p> <p>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</p>	
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				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 fibromas 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

			<p>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.</p>	<p>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.</p>	
28	5.4.2.2 Inhalation Data	130, Table 5-10	<p>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.</p> <p>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.</p>	<p>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.</p>	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 diffuse 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

	<p>n Method s</p>		<p>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.</p>	<p>suggests that this new procedure undergo a separate, external peer review by experts in statistics.</p>	
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## Office of Management and Budget (OMB) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of 1,4-Dioxane (dated May 2011)

Date: June 16, 2011

### General Science Comments:

- While we recognize that EPA staff are trying to provide clarity, we suggest either revising or dropping the fact sheet. The RfC derivation as described in the tox review does not fully track with the fact sheet. For example, in reading the Fact Sheet, we were confused as to why EPA was treating Kasai 2009 as a subchronic study. It may be easiest to just drop the Fact Sheet.
- It seems that EPA is proposing an RfC which is in the range of background level. According to HSDB, the average value of 1,4 dioxane in US air was 1.029 ppb. Rough calculations tell us that this is equivalent to about  $4 \times 10^{-3}$  mg/m<sup>3</sup>, which is less than an order of magnitude away from the proposed RfC. Considering the closeness of the values, and what may be known about ranges of background exposures, it would be helpful to ensure that the RfC is plausible and that the incidences of nasal lesions expected can be predicted by current exposures. In particular, we recognize that rats are obligate nose breathers while humans are not. It is not clear how EPA has taken this into account when considering the relevance of the RfC to humans. We note that EPA applies an UF of 3x for interspecies comparison but this implies that humans would be more sensitive, not less sensitive to a similar dose.
- Similar to the comment above, what would be the expected cancer risks at current background US levels (1ppb or about 4ug/m<sup>3</sup>) and is this consistent with cancer incidence data? Similarly, do we expect the same risks from 1,4 dioxane as we do from other compounds with a similarly low IUR? Discussion of this in the cancer section would be helpful.
- While 1,4 dioxane is not a chemical of great broad concern, if EPA is going to propose an RfC and IUR that is within the range of background exposures, EPA may want consider a more robust SAB or NAS review (compared to a contractor run panel review) to assure that the scientific underpinnings of the values are scientifically sound.
- In discussing the mode of action (MOA) for nasal tumors, as per page 95, it appears that data exist to support a non-linear mode of action as the Kasai studies show accumulation related to saturation at high doses. We recognize that data gaps exist, could this MOA still be considered plausible and having significant biological support as per EPA cancer guidelines? Page 104 states that data on key events is missing, however it is not clear that this implies that there is not biological support for a non-linear MOA. EPA's discussion could be strengthened and clarified here.
- It is not clear why EPA uses and presents data only for the male rats from Kasai 2009. Page 117 discusses that no mesotheliomas were seen in female rats exposed via drinking water, however it is unclear why female data, relating to the RfC and nasal effects should not be considered and presented. If Kasai 2009 evaluated female rats (page 117 implies that it did), we suggest including this discussion and considering the effects seen in females.

- More clarity is needed regarding EPA's determination of the level of adversity of the nasal lesions (atrophy of the olfactory epithelium) throughout the RfC discussions. As per page 120, throughout the document and in the charge, EPA should clarify that this is a precursor effect, likely to occur early in the continuum of pathological events associated with the respiratory tract.
- EPA states that the BMD modeling resulted in a poor fit for the RfC. However when we look at Appendix F, many of the p values for fit, were  $>0.1$  and thus wouldn't they be considered to have a good fit (for example, see page F-14 where this is the criteria as defined by EPA)? EPA clearly states that if the p value is  $<0.1$ , then there is a lack of fit. However in most tables in Appendix F, the p value is greater. Additionally, it is unclear what model uncertainty EPA refers to (page 118) when discounting use of some of the BMD values.
- As the RfC is based upon effects in the nasal epithelium, it is not clear why EPA is saying there is a lack of clarity regarding whether or not these are portal of entry effects. It would be helpful to run the analysis treating 1,4 dioxane as a Category 1 gas to see what impact this has on the RfC. Presenting this information to the public and peer reviewers will help them to understand the impact of EPA's decision. A charge question on this determination would also be helpful.
- EPA uses an uncertainty factor of 10x to account for use of a LOAEL. Since the effects seen are minimal and early in the continuum, it is not clear why a full 10x factor is needed. Further justification of this choice would be helpful for peer reviewers and public commenters.
- To support the choice of 3x for the database uncertainty factor, it would be helpful to provide more discussion of the doses used in the oral prenatal development study to see if effects would be predicted at the point of departure used for the RfC. Even a back of the envelope calculation, taking kinetics into account, would be helpful.
- It is not clear why EPA has medium confidence in the RfC. There are three orders of magnitude of uncertainty, including uncertainties in four different areas. We suggest that the confidence in this derivation should be considered low.
- Page 130 shows that there were no statistically significant increases in hepatocellular carcinomas. Thus it is unclear why EPA has combined hepatocellular adenomas and carcinomas to look at combined impact. It is obvious that this will be driven by the statistically significant adenomas, seen only at high doses. Further rationale for combining these tumors is needed. If EPA had evaluated hepatocellular adenomas only, what would the IUR have been? This information should be presented in Table 5-13 and should be discussed. Similarly, it is not clear why EPA is calculating IUR estimates for cancer endpoints that were not statistically significant. We suggest adding a charge question on this.

#### **Editorial Comments (with Scientific Impacts):**

- Page 56, and elsewhere, when referring to Kasai, et al, it is important to always be clear about whether the reference is to the 2008 or 2009 study.

- Page 57, lines 17-28, it may be helpful to present this information in a table.
- Page 139, line 26-28, this discussion should mention that rats are obligate nose breathers while humans are not. The impacts of this on the RfC should be discussed.
- Page 142, table 5-14, please revise this to reflect the uncertainties in the RfC.

**Comments on the Draft Charge:**

[Note: some suggestions for charge questions are provided in comments in the above sections. Many of those comments have not been reiterated here, but should be considered as equally important.]

- It would be helpful if paragraph 2 of the charge discussed current background exposure levels in the context of the proposed RfC and IUR. This will also help to frame the issue of whether we are seeing results in the general population consistent with the final values EPA proposes.
- Please add a question asking reviewers about how they would interpret the proposed RfC and IUR in the context of known background levels.
- General Questions 2: It is unclear how reviewers will be able to tell if additional studies “would have a significant impact on the conclusions.” Suggest reframing this to simply ask about relevant studies and then EPA can conduct further evaluation to determine if the studies will have a significant impact.
- In B2, EPA calls ‘atrophy of the olfactory epithelium’ a critical effect. Please clarify for reviewers that this is precursor effect and not adverse. Suggest also taking comment on EPA’s determination of it as being a precursor effect.
- In section B, please have separate questions taking comment on EPA’s use of the dosimetric adjustment factor, the HEC calculation, as well as the determination to treat 1,4 dioxane as a category 3 gas (not solely with portal of entry effects) for the purpose of deriving the RfC. Similarly, if they are relevant, these questions should also be added to section C.
- In section C, please add the following specific questions:
  - Ask reviewers to comment on EPA’s approach of combining hepatocellular adenomas and carcinomas.
  - Ask reviewers to comment on EPA’s decision to calculate a combined IUR using tumor endpoints that were not statistically significant.
  - Please ask reviewers to comment on whether or not each of the endpoints used in the IUR is relevant to humans and should be part of the combined IUR calculation.