

Draft Charge to External Peer Reviewers for the IRIS Toxicological Review of 1,4-Dioxane May 2011

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment (inhalation route of exposure) of 1,4-dioxane that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). There is a current assessment on the IRIS database for the health effects associated with 1,4-dioxane exposure which was first available in 2010 that derived oral toxicity values only.

During the development of the 2010 *Toxicological Review of 1,4-Dioxane*, new studies ([Kasai, et al., 2009](#); [Kasai, et al., 2008](#)) regarding the toxicity of 1,4-dioxane through the inhalation route of exposure became available. These studies have been added to the previously posted assessment ([U.S. EPA, 2010](#)). An evaluation of the data and a draft reference concentration (RfC) and inhalation unit risk (IUR) have been derived and are presented in this document for review. Sections where the new inhalation studies have impacted the assessment are the focus of the current review and can be identified by the red underlined text in the document. This review is to evaluate only the data and qualitative and quantitative decisions relevant to the inhalation route of exposure. Although this review is focused only on sections that were revised based on the new inhalation studies, the entire document is being provided for completeness. Below are a set of charge questions that address scientific issues in the assessment of 1,4-dioxane (inhalation). Please provide detailed explanations for responses to the charge questions.

(A) General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly presented and synthesized the scientific evidence for noncancer and cancer hazards via the inhalation route of exposure?
2. Please identify any additional studies that would make a significant impact on the conclusions of the Toxicological Review.

Chemical-Specific Charge Questions:

(B) Inhalation reference concentration (RfC) for 1,4-dioxane

1. A chronic RfC for 1,4-dioxane has been derived from a 2-year inhalation bioassay ([Kasai, et al., 2009](#)) in male rats. Please comment on whether the selection of this study as the principal study is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.
2. Atrophy of the olfactory epithelium was selected as the critical effect. Please comment on whether the rationale for the selection of this critical effect is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. A LOAEL based upon the observation of atrophy of the olfactory epithelium was used as the point of departure (POD) for the RfC. Please provide comments with regard to whether the LOAEL approach is the best approach for determining the POD. Please identify and provide rationales for any alternative approaches for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.
4. Please comment on the rationale for the selection of the uncertainty factors applied to the POD for the derivation of the RfC. Are the UFs scientifically supported and clearly described? If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s).

(C) Inhalation carcinogenicity of 1,4-dioxane

Please Note: An external peer review for 1,4-dioxane (oral assessment) was completed in 2009. The conclusions of this panel can be found in Appendix A and provide informative information, especially regarding the cancer descriptor and cancer mode of action evaluation, that may be useful for the review of the 1,4-dioxane (inhalation assessment).

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that 1,4-dioxane is *likely to be carcinogenic to humans*. Please comment on whether the cancer weight of evidence characterization is scientifically justified and clearly described.
2. Several hypothesized MOAs were evaluated within the Toxicological Review and EPA reached the conclusion that a MOA(s) could not be supported for any tumor types observed in animal models. Please comment on whether the weight of the scientific evidence supports this conclusion and whether the analysis is clearly described.
3. A two-year inhalation cancer bioassay ([Kasai, et al., 2009](#)) was selected for the derivation of an inhalation unit risk (IUR). Please comment on whether the selection of this study for quantification is scientifically justified and clearly described. Please identify and provide the rationale for any other studies that should be selected.
4. Data on the incidence of hepatocellular adenomas and carcinomas, nasal cavity squamous cell carcinoma, renal cell carcinoma, peritoneal mesothelioma, mammary gland fibroadenoma, Zymbal gland adenoma, and subcutis fibroma were used to estimate the inhalation unit risk. Please comment on whether this selection is scientifically justified and clearly described. Please identify and provide the rationale for any other endpoints that should be selected to serve as the basis for the quantitative cancer assessment.
5. The inhalation unit risk was calculated based on multiple carcinogenic effects of 1,4-dioxane observed in rats via the inhalation route. A Bayesian analysis was performed to estimate a BMDL₁₀ associated with the occurrence of multiple tumors, and then a linear low-dose extrapolation was applied. Please comment on this modeling

approach. In addition, an alternative modeling approach has been included in Appendix G. Has the modeling been appropriately conducted and clearly described?