Charge to External Reviewers for the
IRIS Toxicological Review of 1,4-Dioxane (inhalation route of exposure only)

September 2011

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the draft Toxicological Review of 1,4-Dioxane (inhalation route of exposure only) that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). The existing IRIS assessment for 1,4-dioxane (oral route of exposure only) was posted in 2010 and includes a reference dose (RfD), cancer descriptor, mode of action analysis for cancer, and an oral slope factor.

During the development of the *Toxicological Review of 1,4-Dioxane (oral route of exposure only)* that was posted on the IRIS database in 2010, new studies (Kasai et al., 2009; Kasai et al., 2008) regarding the toxicity of 1,4-dioxane via the inhalation route of exposure became available. These new studies have been merged with the previously posted assessment (U.S. EPA, 2010) resulting in a complete assessment of the health hazards associated with both the oral and inhalation routes of exposure to 1,4-dioxane. An evaluation of the data from the new studies resulted in the derivation of a reference concentration (RfC) and an inhalation unit risk (IUR) for 1,4-dioxane, and these toxicity values are now presented in the Toxicological Review. The sections of the Toxicological Review that have been impacted by the new inhalation studies are the focus of the current external peer review, and these sections can be identified by the red underlined text in the document. This external peer review is to evaluate only the data and qualitative and quantitative decisions relevant to the inhalation route of exposure. Although this external peer review is focused only on the sections of the Toxicological Review that were revised based on the new inhalation studies, the entire document is being provided to the external peer reviewers for completeness.

Charge Questions

Below is a set of charge questions that address scientific issues in the draft Toxicological Review of 1,4-Dioxane (inhalation route of exposure only). Please provide detailed explanations for responses to the charge questions. EPA will also consider reviewer comments on other major scientific issues specific to the hazard identification and dose-response assessment of 1,4-dioxane. Please identify and provide the rationale for approaches to resolve the issues where possible. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

(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 health effects from exposure to 1,4-dioxane via inhalation?

2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects from exposure to 1,4-dioxane via inhalation.

Chemical-Specific Charge Questions:

Please Note: An external peer review for 1,4-dioxane (oral route of exposure only) was completed in 2009. The conclusions of the peer review panel and EPA's responses can be found in Appendix A. This information, particularly regarding the cancer descriptor and cancer mode of action evaluation, may be useful for the review of the inhalation portion of the 1,4-dioxane assessment.

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

1. A 2-year inhalation bioassay in male rats (Kasai et al., 2009) was selected as the basis for the derivation of the RfC. Please comment on whether the selection of this study is scientifically supported and clearly described. If a different study is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

2. Atrophy and respiratory metaplasia of the olfactory epithelium in male rats were concluded by EPA to be adverse effects and were selected as co-critical effects for the derivation of the RfC. Please comment on whether the selection of these co-critical effects and their characterization is scientifically supported and clearly described. If a different health endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.

3. Benchmark dose (BMD) modeling methodology (U.S. EPA, 2000) was used to analyze the candidate endpoints identified for 1,4-dioxane. However, due to poor fit or substantial model uncertainty, BMD model results were inadequate for the following nasal lesions: atrophy (olfactory epithelium), respiratory metaplasia (olfactory epithelium), and sclerosis (lamina propria). Consequently, the NOAEL/LOAEL approach was used to identify the POD for derivation of the RfC. Please comment on whether this approach is scientifically supported and clearly described.

4. 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 U.S. EPA RfC methodology (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, since 1,4-dioxane is water soluble and induces effects in portal-of-entry tissues, an alternative calculation of the HEC for 1,4-dioxane based on the application of the corresponding DAF for portal-of-entry acting gases (i.e., Category 1) is provided in Appendix G. Please comment on EPA's conclusion that 1,4-dioxane is a Category 3 gas, and the resulting application of the corresponding dosimetric adjustment factor (DAF) in deriving the RfC. If a different approach is recommended in the derivation of the RfC, please identify this approach and provide scientific support for the proposed changes.

5. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the RfC. Are the UFs appropriate based on *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5; www.epa.gov/iris/backgrd.html) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

(C) Carcinogenicity of 1,4-dioxane and derivation of an inhalation unit risk (IUR) for 1,4-dioxane

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; Section 2.5; www.epa.gov/iris/backgrd.html), the draft IRIS assessment characterizes 1,4-dioxane as "likely to be carcinogenic to humans" by all routes of exposure. Please comment on whether this characterization of the human cancer potential of 1,4-dioxane is scientifically supported and clearly described.

2. The draft assessment concludes that there is insufficient information to identify the mode(s) of carcinogenic action for 1,4-dioxane. Please comment on whether this determination is appropriate and clearly described. If it is judged that a mode of action can be established for 1,4-dioxane, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

3. A two-year inhalation cancer bioassay in male rats (Kasai et al., 2009) was selected as the basis for the derivation of the inhalation unit risk (IUR). Please comment on whether the selection of this study is scientifically supported and clearly described. If a different study is recommended as the basis for the IUR, please indentify this study and provide scientific support for this choice.

4. 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 selected to serve as the basis for the derivation of the IUR. Please comment on whether this selection is scientifically supported and clearly described. If a different health endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

5. The IUR was derived based on multiple carcinogenic effects observed in rats exposed to 1,4-dioxane via inhalation. A Bayesian approach was used to estimate a $BMDL_{10}$ associated with the occurrence of these multiple tumors, and then a linear low-dose extrapolation from this POD was performed to derive the IUR. Additionally, for comparative purposes only, a total tumor analysis was performed with the draft BMDS (version 2.2Beta) MSCombo model that yielded similar results (See Appendix H). Please comment on whether these approaches for deriving the IUR have been clearly described and appropriately conducted?

Kasai, T; Saito, M; Senoh, H; Umeda, Y; Aiso, S; Ohbayashi, H; Nishizawa, T; Nagano, K; Fukushima, S. (2008). Thirteen-week inhalation toxicity of 1,4-dioxane in rats. Inhal Toxicol 20: 961-971. http://dx.doi.org/10.1080/08958370802105397.

Kasai, T; Kano, H; Umeda, Y; Sasaki, T; Ikawa, N; Nishizawa, T; Nagano, K; Arito, H; Nagashima, H; Fukushima, S. (2009). Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhal Toxicol 21: 889-897. http://dx.doi.org/10.1080/08958370802629610.

U.S. EPA. (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. (EPA/600/8-90/066F). pp. 409. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993.

U.S. EPA. (U.S. Environmental Protection Agency). (2000). Benchmark dose technical guidance document [external review draft]. (EPA/630/R-00/001). pp. 96. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/raf/publications/benchmark-dose-doc-draft.htm.

U.S. EPA. (U.S. Environmental Protection Agency). (2010). Toxicological review of 1,4-Dioxane (CAS No. 123-91-1) in support of summary information on the Integrated Risk Information System (IRIS). (EPA-635/R-09-005-F). pp. 319. Washington, DC. www.epa.gov/iris/toxreviews/0326tr.pdf.