

**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 mg/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 χ^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/m³, 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.