

Centers for Disease Control and Prevention (CDC) / Agency for Toxic Substances and Disease Registry (ATSDR) Comments on the Interagency Science Discussion Draft IRIS Assessment of 1,4-Dioxane (Inhalation) (dated July 2013)

Date: July 24, 2013

Date: July 23, 2013

From: Centers for Disease Control and Prevention / Agency for Toxic Substances and Disease Registry

Subject: Comments on Toxicological Review of 1,4-dioxane

To: Environmental Protection Agency

We appreciate the opportunity to review and comment on the EPA's Toxicological Review of 1,4-dioxane. We previously reviewed the Charge to External Reviewers in June 2011. The comments below refer primarily to the Toxicological Review (Inhalation), with focus on changes made since the previous review in June 2011.

General comments

In our previous review of these documents, we noted the addition of studies by Kasai et al. (2008) and Kasai et al. (2009). These studies were thoroughly reviewed and incorporated in all of the relevant sections of the documents. 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 5, Line 4: Remove the hyphen between trichloro and ethane.

Page 5, Lines 7, 24 and 28 and page 144, Line 23: ATSDR's Toxicological profile for 1,4-dioxane has been finalized and should be cited as ATSDR 2012.

Page 63, Line 15: Delete "Acute and short term toxicity studies (all routes) are summarized in Table 4-18" from Section 4.4.1.2 because it was correctly noted in Section 4.4.1 on the same page (Line 5) that these studies are summarized in Table 4-22.

Page 64, Table 4-22 (and many other tables in the document): The text is centered in the columns, making it harder to read. We suggest aligning the data to the left of the columns.

Page 67, Line 25: Delete "However". The negative results using closed systems to prevent evaporation support the lack of genotoxicity.

Page 82, Line 3: Delete the word "after".

Page 89 Line 26: Add "of tumor promotion" between "No studies" and "have been conducted".

Page 91, Line 6 in Section 4.7.3.1.2: Delete "(Kasai et al., 2009)" after "nasal cavity" at the end of line 6.

Page 91, Line 6 in Section 4.7.3.2.1: Change reference to Table 4-18 to Table 4-22.

Page 134, Line 22: Change “OSF” to “oral CSF”.

Appendix B, Page B-1, Line 25: The name “Young et al.” appears to have been inadvertently deleted from the reference. It should read: (Young et al., 1978c,d; Young et al., 1977b).

Appendices B through G: Check agreement between identification of Tables and Figures in the text and the actual Table and Figures numbers in the legends of the Tables and Figures. They appear to be correct in the Redlined Draft, but not in the Clean Draft.

Inhalation RfC

The rationale and justification of selecting the Kasai et al. (2009) two-year study as the principal study and the critical effect are clear, reasonable and appropriate. ATSDR has finalized its updated Toxicological Profile for 1,4-Dioxane, which includes the Kasai et al. (2009) study for deriving a chronic inhalation Minimal Risk Level (MRL). EPA’s RfC of 0.03 mg/m³ is equivalent to 0.008 ppm. ATSDR’s chronic duration inhalation MRL of 0.03 ppm, based on the same study and POD, is equivalent to 0.1 mg/m³. This difference between the RfC and the MRL reflects EPA’s use of an additional uncertainty factor (UF) of 3 for data deficiencies (the lack of a multi-generation reproductive study). ATSDR did not include a UF for data deficiencies.

IUR for Cancer

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