National Institute for Occupational Safety and Health (NIOSH) Comments on the Interagency Science Discussion Draft IRIS Assessment of 1,4-Dioxane (Inhalation) (dated June 2013)

Date: July 25, 2013

Informal Comments on the Final Draft Toxicological Review and IRIS Summary on 1,4-Dioxane (inhalation)

July 19, 2013

The National Institute for Occupational Safety and Health (NIOSH) thanks the U.S. Environmental Protection Agency (EPA) for the opportunity to comment on the final draft Toxicological Review and IRIS Summary on 1,4-Dioxane (inhalation) with a focus on the EPA's responses to the external peer review recommendations and public comments pertaining to the inhalation route of exposure.

1,4-Dioxane is used as a solvent for a wide range of products and its reaction products are used in the manufacture of insecticides, herbicides, plasticizers, and monomers. 1,4-Dioxane is also a contaminant of some ingredients used in the manufacture of personal care products and cosmetics. Human exposures involve both the oral and inhalation routes. The present weight of evidence supports 1,4-dioxane as a toxicant and carcinogen in multiple organ systems in animals; however, the mode of action, toxic/carcinogenic moiety, role of metabolism, and dose-response relationship at the low dose range of 1,4-dioxane remain unclear.

<u>Comments</u>

1. Overall, the Toxicological Review and IRIS Summary are logical, clear, and concise. The tables and figures are appropriate and easy to follow. No additional peer-reviewed studies from the primary literature are suggested to be considered in the assessment. The choices of the studies, the critical effects, the methods of assessments, the selection of uncertainty factors, and the use of a default linear dose-response relationship at the low dose range were based on best information available, scientific soundness, and the EPA polices and guidelines.

2. The revised version of the draft Toxicological Review and IRIS summary (inhalation) has synthesized and addressed most of the comments from the external reviewers and public reviews clearly and logically. The responses reflect relevant facts, the science, and EPA policies.

3. The issue about the toxicological significance of nuclear enlargement and whether it should be used as a critical effect needs to be clearly addressed in the revision, particularly:

a. Page 82, lines 9—11 state “In both studies, … however, the toxicological significance of nuclear enlargement is uncertain”. This statement needs to be expanded to explain why it is uncertain.
b. Page 109, lines 3—6 state “Furthermore, … is largely unknown”. This statement appears to indicate that (a) nuclear enlargement has only been reported by JBRC and (b) no information on the nature, severity, and significance of this observation exists in the literature. Both could be misleading because nuclear enlargement was: (1) observed in different tissues after treatment with several carcinogens such as nitrosamines; (2) found to be associated with some nuclear events such as DNA ploidy, and (3) suggested to be related to alteration of the “background” within which subsequent events in carcinogenesis occur [Clawson et al. 1992].
c. Appendix A has less explanation on this issue than the text. Rather than stating “no information” or “unknown”, clarify these facts and indicate that nuclear enlargement has been found to be associated with exposure to certain carcinogens and possibly related to early carcinogenic effects of the carcinogens in the literature; however, its toxicological/carcinogenic significance has not been conclusively determined.

Editorial comments (all page 82)

a. line 3, “vapor after concentrations”: a typo or a specific term?
b. 2nd and 3rd paragraphs: the description about GST-P positive cell foci needs to be straight forward.
c. last paragraph: “Kidney effects were reported less frequently in these inhalation studies and were generally observed …”; clarify whether the kidney effects were compared between inhalation and oral studies.

Reference

Clawson GA, Blankenship LJ, Rhame JG, Wilkinson DS [1992]. Nuclear enlargement induced by hepatocarcinogens alters ploidy. Cancer Res 52(5):1304-1308.