Charge to External Reviewers
for the Toxicological Review of 1,4-Dioxane

May 2009

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment 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 1988.

The draft health assessment includes a chronic Reference Dose (RfD) and a carcinogenicity assessment. An inhalation Reference Concentration (RfC) and inhalation unit risk (IUR) were not derived in this assessment. EPA will evaluate the recently published 1,4-dioxane inhalation data for the potential to derive an RfC and IUR in a separate document to follow this assessment. Below are a set of charge questions that address scientific issues in the current assessment of 1,4-dioxane. 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 accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazards?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of 1,4-dioxane.

3. Please discuss research that you think would be likely to increase confidence in the database for future assessments of 1,4-dioxane.

4. Please comment on the identification and characterization of sources of uncertainty in Sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

Chemical-Specific Charge Questions:
(B) Oral reference dose (RfD) for 1,4-dioxane

1. A chronic RfD for 1,4-dioxane has been derived from a 2-year drinking water study (Kociba et al., 1974) in rats and mice. Please comment on whether the selection of this study as the principal study has been scientifically justified. Has the selection of this study been transparently and objectively described in the document? Are the criteria and rationale for this selection transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Degenerative liver and kidney effects were selected as the critical effect. Please comment on whether the rationale for the selection of this critical effect has been scientifically justified. Are the criteria and rationale for this selection transparently and objectively described in the document? Please provide a detailed explanation. Please comment on whether EPA's rationale regarding adversity of the critical effect for the RfD has been adequately and transparently described and is scientifically supported by the available data. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Kociba et al. (1974) derived a NOAEL based upon the observation of degenerative liver and kidney effects and these data were utilized to derive the point of departure (POD) for the RfD. Please provide comments with regard to whether the NOAEL approach is the best approach for determining the POD. Has the approach been appropriately conducted and objectively and transparently described? 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. EPA evaluated the PBPK and empirical models available to describe kinetics following inhalation of 1,4-dioxane (Reitz et al., 1990; Young et al, 1978, 1977). EPA concluded that the use of existing, revised, and recalibrated PBPK models for 1,4-dioxane were not superior to default approaches for the dose-extrapolation between species. Please comment on whether EPA's rationale regarding the decision to not utilize existing or revised PBPK models has been adequately and transparently described and is supported by the available data. Please identify and provide the rationale for any alternative approaches that should be considered or preferred to the approach presented in the toxicological review.

5. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfD. For instance, are they scientifically justified and transparently and objectively described in the document? If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s). Please comment specifically on the following uncertainty factors:

    - An interspecies uncertainty factor of 10 was used to account for uncertainties in extrapolating from laboratory animals to humans because a PBPK model to support interspecies extrapolation was not suitable.
    - An intraspecies (human variability) uncertainty factor of 10 was applied in deriving the RfD because the available information on the variability in human response to 1,4-dioxane is considered insufficient to move away from the default uncertainty factor of 10.
    - A database uncertainty factor of 3 was used to account for lack of adequate reproductive toxicity data for 1,4-dioxane, and in particular absence of a multigeneration reproductive toxicity study.

    Has the rationale for the selection of these uncertainty factors been transparently and objectively described in the document? Please comment on whether the application of these uncertainty factors has been scientifically justified.

(C) Carcinogenicity of 1,4-dioxane

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 the cancer weight of evidence characterization. Has the scientific justification for the weight of evidence descriptor been sufficiently, transparently and objectively described? Do the available data for both liver tumors in rats and mice and nasal, mammary, and peritoneal tumors in rats support the conclusion that 1,4-dioxane is a likely human carcinogen?

2. Evidence indicating the mode of action of carcinogenicity of 1,4-dioxane was considered. 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. Please comment on whether the rationale for this conclusion has been transparently and objectively described. Please comment on data available for 1,4-dioxane that may provide significant biological support for a MOA beyond what has been described in the Toxicological Review. Considerations should include the scientific support regarding the plausibility for the hypothesized MOA(s), and the characterization of uncertainty regarding the MOA(s).

3. A two-year drinking water cancer bioassay (JBRC, 1998a) was selected as the principal study for the development of an oral slope factor (OSF). Please comment on the appropriateness of the selection of the principal study. Has the rationale for this choice been transparently and objectively described?

4. Combined liver tumors (adenomas and carcinomas) in female Cjr:BDF_1 mice from the JBRC (1998a) study were chosen as the most sensitive species and gender for the derivation of the final OSF. Please comment on the appropriateness of the selections of species and gender. Please comment on whether the rationale for these selections is scientifically justified. Has the rationale for these choices been transparently and objectively described?

5. Has the scientific justification for deriving a quantitative cancer assessment been transparently and objectively described? Regarding liver cancer, a linear low-dose extrapolation approach was utilized to derive the OSF. Please provide detailed comments on whether this approach to dose-response assessment is scientifically sound, appropriately conducted, and objectively and transparently described in the document. Please identify and provide the rationale for any alternative approaches for the determination of the OSF and discuss whether such approaches are preferred to EPA's approach.