DRAFT
January 2008

Charge to External Peer Reviewers for the Toxicological Review and IRIS Summary of Propionaldehyde

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review for a health assessment of propionaldehyde 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).

Peer review of this assessment is being sought to ensure that all available data relevant to the toxicological assessment of propionaldehyde have been appropriately and objectively evaluated. Below is a set of charge questions that address scientific issues in the assessment of propionaldehyde. Please provide detailed explanations for responses to the charge questions.

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 hazard?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of propionaldehyde.

3. Please discuss research that you think would be likely to increase the confidence in the database for propionaldehyde in future assessments.

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:

(A) Oral reference dose (RfD) for propionaldehyde

1. No oral RfD has been derived in the current draft assessment based on the lack of studies available that examine the effects of propionaldehyde administered via the oral route. Are there available studies missing from the draft document that might be useful for deriving an oral RfD or that should be considered in this decision?

(B) Inhalation reference concentration (RfC) for propionaldehyde

1. The current draft IRIS assessment for propionaldehyde uses a combined reproductive/developmental exposure study by Union Carbide (1993) as the principal study for the derivation of the RfC. Please comment on whether the selection of this study as the principal study has been scientifically justified. Has this study been 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. Is this study appropriate for use in this assessment?

2. Has the most appropriate critical effect (increase incidence of olfactory atrophy in male rats,) presented in Sections 4.3 and 4.5.2 of the Toxicological Review been selected? Is the rationale for this selection transparently and objectively described in the document? Please comment on whether the selection of this critical effect has been scientifically justified. Please comment on the choice of olfactory atrophy as the critical effect as opposed to other endpoints (e.g., vacuolization) and the rationale that this endpoint was chosen because it is on the continuum leading to overtly adverse effects such as cell death. Has the qualitative pathological relationship between effects observed been adequately and appropriately characterized? Please provide a detailed discussion. Please identify and provide the rationale for any other endpoints that should be used instead of increased incidence of olfactory atrophy in male rats to develop the RfC.

3. BMD methods were applied to incidence data on olfactory atrophy in male rats to derive the POD for the RfC. Please provide comments with regard to whether BMD modeling is the best approach for determining the POD. Has the BMD modeling been appropriately conducted and objectively and transparently described? Has the BMR selected for use in deriving the POD (i.e., 10% extra risk of olfactory atrophy) been scientifically justified? Please comment on EPA's decision to treat all cases of olfactory atrophy similarly, without consideration of the severity of the atrophy seen at different dose levels. Please provide a detailed discussion and any suggestions for consideration of severity in determining the POD including identifying and provide rationales for any alternative approaches for the determination of the POD and discussion of whether such approaches are preferred to EPA's approach considering the available data.

4. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfC. For instance, are they scientifically justified and transparently and objectively described in the document?

5. Please comment specifically on the database uncertainty factor of 3 applied in the RfC derivation. Please comment on the body of information regarding reproductive and developmental toxicity on propionaldehyde, the relevance of toxicity data on other aldehydes, and the relevance of toxicokinetic data regarding the likelihood of portal-of-entry effects as the critical effects in the determination of the database uncertainty factor. Please comment on whether the selection of the database uncertainty factor for the RfC has been scientifically justified. Has this selection been transparently and objectively described in the document?

(C) Carcinogenicity of propionaldehyde

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that *data are inadequate for an assessment of the human carcinogenic potential* of propionaldehyde Please comment on the scientific justification for the cancer weight of evidence characterization. In addition, has the Agency properly characterized the potential for concern for carcinogenicity of propionaldehyde based on the available data on propionaldehyde and other aldehydes?