

## **Charge to External Reviewers for the IRIS Toxicological Assessment of the RfC and Inhalation Cancer Assessment for 1,4-Dichlorobenzene**

### **Background**

The Toxicological Review of Dichlorobenzenes (DCBs), including the 1,2-, 1,3-, and 1,4-isomers, was subject to an external peer review in February 2004. Revisions to the health assessment were made in response to external peer review comments, which are summarized in Appendix A of the Toxicological Review. The February 2004 external peer review identified a 2-year inhalation toxicity study of 1,4-DCB (Japan Bioassay Research Center [JBRC], 1995) that was subsequently published in the peer-reviewed literature by Aiso et al. (2005). The JBRC study was used as the basis for deriving a revised inhalation reference concentration (RfC) and an inhalation cancer assessment for 1,4-DCB.

The scope of the current external peer review is limited to analyses of dose-response data from the JBRC inhalation study of 1,4-DCB that were not included in the February 2004 external peer review draft. The charge questions below specifically address the revised inhalation RfC and the inhalation cancer assessment for 1,4-DCB. Please provide detailed responses to these charge questions.

### **Charge Questions – Derivation of the RfC for 1,4-DCB**

1. The principal study used to derive the RfC is the JBRC 2-year inhalation bioassay (Aiso et al., 2005). Is this study the most appropriate selection for the principal study (i.e., the best study upon which to determine the point of departure)? Has the rationale for this choice been transparently and objectively described?
2. The endpoints considered as possible critical effects were eosinophilic changes of the olfactory epithelium in rats and mineralization of the testes in male mice. Please comment on the biological significance of these two endpoints. Was the most appropriate critical effect (eosinophilic changes of the olfactory epithelium) selected as the critical effect? Has the rationale and justification for selection of this critical effect been transparently described? Is the selection of the critical effect scientifically justified?
3. Inhalation dosimetry methods were used in the calculation of the human equivalent concentration (HEC) based on U.S. EPA (1994). Is the explanation for dosimetry choices in the derivation of the RfC scientifically justified and transparently described?
4. Benchmark dose (BMD) modeling was used to derive the point of departure for determining the RfC. In the absence of information on the level of response to consider adverse, 10% extra risk was used according to the U.S. EPA Benchmark Dose Guidance (U.S. EPA, 2000) as the benchmark response for the dichotomous

data sets. Was the correct benchmark response chosen? Was the BMD modeling accurately and transparently described?

5. Have the uncertainties in the derivation of the 1,4-DCB RfC been adequately characterized? Does the Toxicological Review provide a transparent explanation for the selection of uncertainty factors? Are the uncertainty factors scientifically justified?

### **Charge Questions – Inhalation Cancer Assessment for 1,4-DCB**

1. The principal study used as the basis for the quantitative inhalation cancer assessment is the JBRC 2-year inhalation bioassay (Aiso et al., 2005). Is this study the most appropriate selection for the principal study (i.e., the best study upon which to determine the point of departure)? Has the rationale for this choice been transparently and objectively described?
2. An inhalation unit risk was derived using BMD modeling to define the point of departure followed by linear low-dose extrapolation below the point of departure.
  - (a) Has support for the use of a linear low-dose extrapolation been objectively and transparently presented?
  - (b) The inhalation unit risk is based on the summed risks of developing liver carcinomas and hepatic histiocytic sarcomas (male mice) or hepatocellular adenomas/carcinomas and bronchoalveolar adenomas/carcinomas (female mice). Have the most appropriate data sets been chosen for derivation of the inhalation unit risk? Has the modeling been accurately and transparently described?
3. Inhalation dosimetry methods were used in the calculation of the human equivalent concentration (HEC) based on U.S. EPA (1994). Is the explanation for dosimetry choices in the derivation of the inhalation unit risk scientifically justified and transparently described?
4. Have the sources of uncertainty been adequately and transparently described?
5. It is EPA's judgment that there is insufficient evidence to establish a mode of action for mouse liver tumors, and thus a linear low-dose extrapolation model was used for the quantitative dose-response assessment. There is evidence, however, that suggests that sustained mitogenic stimulation and proliferation of hepatocytes may be involved in the induction of mouse liver tumors, and that this cell proliferation may be a threshold response. Based on what is known about the mode of action, does the science support EPA developing a nonlinear dose-response model as well to help characterize the cancer dose-response? If so, please provide us with advice on conducting such a nonlinear analysis.