Draft Charge to External Reviewers for the IRIS Toxicological Review of Dichloromethane
December 2009

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of dichloromethane 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). An existing IRIS assessment of dichloromethane was posted to the database in 1987; the cancer assessment was updated in 1990.

The current draft health assessment includes a chronic reference dose (RfD) and reference concentration (RfC) and a carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of dichloromethane. Please provide detailed explanations for responses to the charge questions.

General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazard?

2. Please identify any additional studies that would make a significant impact on the conclusions of the Toxicological Review and should be considered in the assessment of the noncancer and cancer health effects of dichloromethane.

Chemical-Specific Charge Questions:

(A) PBTK Modeling

1. A rat PBTK model was used for calculating the internal dosimetry for the RfC and RfD . EPA evaluated several versions of previously published rat PBTK models and selected the Andersen et al. (1991) model for use in these calculations.
    a. Does the chosen model adequately represent the toxicokinetics? Was the model applied properly? Are the model assumptions and parameters clearly presented and scientifically supported? Are the uncertainties in the model structure appropriately considered and discussed?
    b. The internal dose metric used in the RfD and RfC derivations was based on total hepatic metabolism through the CYP2E1 pathway. Because the metric is a rate of metabolism, and the clearance of metabolites is expected to be slower in the human compared with the rat (assuming clearance scales as $BW^{3/4}$), the rat internal dose metric is adjusted by dividing by a pharmacokinetic scaling factor to obtain a human-equivalent internal dose.
        ? Are the choices of dose metric and toxicokinetic scaling factor appropriate? Is the rationale for these choices transparently and objectively described?

2. The mouse PBTK model used in deriving the cancer toxicity values was based on the

published work of Marino et al. (2006).

a. Does the chosen model adequately represent the toxicokinetics? Was the model applied properly? Are the model assumptions and parameters clearly presented and scientifically supported? Are the uncertainties in the model structure appropriately considered and discussed?
b. Please comment on the application of the metabolism-based dose metrics in the PBTK modeling for the cancer quantitation. Specifically, please comment on the scientific rationale in choosing the tissue-specific GST-metabolite dose metric and the application of a toxicokinetic scaling factor to account for potential clearance rate differences between humans and animals

3. For the RfD and RfC derivations, a human PBTK model (David et al., 2006) was used to estimate human equivalent doses from internal rat liver doses. For the derivation of cancer toxicity values, the human PBTK model was used to calculate the distribution of human internal dose metrics of dichloromethane metabolized via the tissue-specific (i.e. liver or lung) GST pathway per unit volume of tissue.
   a. Is the rationale for the human parameter estimates scientifically justified and transparently and objectively described? Have the modifications in the model parameters accounted for population variability and parameter uncertainty in estimating human equivalent doses? Are these modifications scientifically supported?
   b. Do these parameter values represent the optimal choice, given the current state of knowledge? Are the uncertainties in these parameters appropriately considered and discussed?

(B). Noncancer Toxicity of Dichloromethane

Oral reference dose (RfD) for dichloromethane

1. A chronic RfD for dichloromethane has been derived from a 2-year oral (drinking water) study in the rat (Serota et al., 1986a). Please comment on whether the selection of this study as the principal study is scientifically justified.

2. An increase in the incidence of nonneoplastic liver lesions (foci/areas of alteration) was selected as the critical effect for the RfD. Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Benchmark dose (BMD) modeling methods were applied to the nonneoplastic liver lesion data to derive the point of departure (POD) for the RfD. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., a 10% increase in incidence of liver lesions) scientifically justified?

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfD. If changes to a UF are proposed, please identify and provide

a rationale(s).

Inhalation reference concentration (RfC) for dichloromethane

5. A chronic RfC for dichloromethane has been derived from a 2-year inhalation bioassay in rats (Nitschke et al., 1988a). Please comment on whether the selection of this study as the principal study is scientifically justified.

6. Hepatic vacuolation was selected as the critical effect for the RfC. Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

7. BMD methods were applied to incidence data for hepatic vacuolation to derive the POD for the RfC. Has the BMD modeling been appropriately conducted? Is the BMR selected for use in deriving the POD (i.e., a 10% increase in incidence of hepatic vacuolation) scientifically justified?

8. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the RfC. If changes to a UF are proposed, please identify and provide a rationale(s).

(C) Carcinogenicity of Dichloromethane

1. Under the EPA's 2005 Guidelines for Carcinogen Risk Assessment (www.epa.gov/iris/backgr-d.htm), dichloromethane is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified and clearly described?

2. A mutagenic mode of carcinogenic action is proposed for dichloromethane. Please comment on whether the weight of the scientific evidence supports this conclusion. Please comment on whether the analysis is scientifically justified and clearly described. Please comment on data available for dichloromethane that may support an alternative mode of action.

Quantitative cancer assessment - oral exposure

3. A two-year drinking water study (Serota et al., 1986b) was selected for the derivation of an oral slope factor (OSF) for dichloromethane. Please comment on whether the selection of this study for quantification is scientifically justified.

4. The OSF was calculated by linear extrapolation from the POD (lower 95% confidence limit on the dose associated with 10% extra risk for mouse liver tumors). The OSF is based on the analysis of the most sensitive of the subgroups, the GST-T1 +/+ genotype, using mean internal dose predictions for that subgroup. Please comment on the adequacy of this approach, including the choice of tumors and the manner in which the modeling was conducted.

Quantitative cancer assessment - inhalation exposure

5. A two-year cancer bioassay (NTP, 1986) was selected for the derivation of an inhalation unit risk (IUR) for dichloromethane. Please comment on whether the selection of this study for quantification is scientifically justified.

6. The IUR was calculated by linear extrapolation from the POD (using a BMR of 10% extra risk for mouse liver and lung tumors) and by determining the upper bound on the combined central tendency IURs for male lung and liver tumors. The IUR is based on the analysis of the most sensitive of the subgroups, the GST-T1 +/+ genotype, using mean internal dose predictions for that subgroup. Please comment on the adequacy of this approach, including the choice of tumors and the manner in which the modeling was conducted