Draft Charge to External Reviewers for the Toxicological Review of Dichloromethane
March 2010

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

The current draft health assessment includes a chronic reference dose (RfD), 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 and objectively represented and 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.

Chemical-Specific Charge Questions:
(A) PBPK Modeling

1. A rat PBPK model was used for calculating the internal dosimetry for the RfD and RfC. EPA evaluated several versions of previously published rat PBPK models and modified the Andersen et al. (1991) model for use in the reference value calculations.

> a. Does the chosen model with EPA's modifications 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?
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> b. The internal dose metric used in the RfD and RfC derivations was based on total hepatic metabolism via the CYP2E1 pathway. Because the metric is a rate of metabolism, and the clearance of metabolites is generally 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 toxicokinetic scaling factor to obtain a human-equivalent internal dose. Are the choices of dose metric and toxicokinetic scaling factor appropriate and scientifically supported? Is the rationale for these choices clearly described? Are the uncertainties in the dose metric selection and calculations appropriately considered and discussed?

2. The mouse PBPK model used in deriving the cancer risk estimates 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. The internal dose metric used in the cancer quantitation was based on tissue-specific GST metabolism. To account for potential clearance rate differences, the mouse internal dose metric was adjusted by dividing by a toxicokinetic scaling factor to obtain a human-equivalent internal dose. Are the choices of dose metric and toxicokinetic scaling factor appropriate and scientifically supported? Is the rationale for these choices clearly described? Are the uncertainties in the dose metric selection and calculations appropriately considered and discussed?

3. A probabilistic human PBPK model (David et al., 2006) was used to estimate a distribution of human equivalent doses and concentrations for the points of departure (PODs) for the RfD and RfC, respectively. The 1st percentile of these distributions was selected to represent the most sensitive portion of the population. For the derivation of the oral and inhalation cancer risk estimates, the probabilistic human PBPK model was used to calculate the distribution of human internal doses (mg dichloromethane metabolized via the tissue-specific GST pathway per unit volume of tissue) that would be expected from a 1 mg/kg-day oral dose or a 1 µg/m^3 inhalation concentration. This distribution of human internal doses was used with the tumor risk factor to generate a distribution of oral slope factors or inhalation unit risks.

a. Does the chosen model adequately represent the toxicokinetics? Was the model applied properly? Are the model assumptions clearly presented and scientifically supported? Are the uncertainties in the model appropriately considered and discussed?

b. EPA modified the parameter distributions in the published David et al. model. Does the set of model parameter distributions adequately account for population variability and parameter uncertainty in estimating human equivalent doses? Are the human parameter values and distributions clearly presented and scientifically supported?

(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 supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. An increase in the incidence of 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 supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

3. Benchmark dose (BMD) modeling was applied to the incidence data for liver lesions to derive the POD for the RfD. Has the BMD modeling been appropriately conducted and clearly described? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., a 10% increase in incidence of liver lesions) scientifically supported and clearly described?

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfD. Are the UFs scientifically supported and clearly described in the document? Please provide a detailed explanation. If changes to an UF are proposed, please identify and provide a rationale.

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 supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

6. An increase in the incidence of hepatic vacuolation was selected as the critical effect for the RfC. Please comment on whether the selection of this critical effect is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

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

8. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the RfC. Are the UFs scientifically supported and clearly described in the document? Please provide a detailed explanation. If changes to an UF are proposed, please identify and provide a rationale.

(C) Carcinogenicity of Dichloromethane

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

2. A mutagenic mode of carcinogenic action is proposed for dichloromethane. Please comment on whether this determination is scientifically supported 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 2-year drinking water study in mice (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 quantitation is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be considered.

4. The OSF was calculated by linear extrapolation from the POD (lower 95% confidence limit on the dose associated with 10% extra risk for liver tumors in male mice). The OSF is based on an analysis of the most sensitive of the human subgroups, the GST-T1 +/+ genotype, using mean internal dose predictions for that subgroup. Please comment on whether this approach is scientifically supported and clearly described. Has the modeling been appropriately conducted and clearly described?

Quantitative cancer assessment - inhalation exposure

5. A 2-year cancer bioassay in mice (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 quantitation is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be considered.

6. The IUR was calculated by linear extrapolation from the POD (lower 95% confidence limit on the dose associated with 10% extra risk for lung or liver tumors in male mice) taking into consideration total cancer risk by determining the upper bound on the combined risk for male lung and liver tumors. The IUR is also based on the analysis of the most sensitive of the human subgroups, the GST-T1 +/+ genotype, using mean internal dose predictions for that subgroup. Please comment on whether this approach is scientifically supported and clearly described. Has the modeling been appropriately conducted and clearly described?