Draft Charge to External Reviewers for the IRIS Toxicological Review of Methanol
October, 2009

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of methanol 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 methanol exposure which was first available in 1988.

The draft health assessment includes a chronic reference dose (RfD), chronic reference concentration (RfC) and a carcinogenicity assessment. Below are a set of charge questions that address scientific issues in the assessment of methanol. 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 clearly 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 methanol.

Chemical-Specific Charge Questions:

(B) Inhalation reference concentration (RfC) for methanol

1. A chronic RfC for methanol has been derived from an inhalation study of the developmental effects from exposing rat dams and pups to methanol during gestation and lactation (NEDO, 1987). Reference values from mouse (Rogers et al., 1993) and monkey (Burbacher et al., 1999; 2004) developmental studies, were also derived and discussed, but were not chosen for the RfC. Please comment on whether the selection of the principal study has been scientifically justified.

2. Brain weight reduction at 6 weeks postnatal reported in the NEDO (1987) developmental rat study was selected as the critical effect. Please comment on whether the rationale for the selection of this critical effect has been scientifically justified. Please identify and provide the rationale for any other endpoints (e.g., other reproductive and developmental effects reported in mouse and monkey studies) that should be considered in the selection of the critical effect.

3. A PBPK model developed by EPA was used to convert the point of departure (POD) to a human equivalent concentration (HEC). The methanol PBPK model developed by EPA and used for the derivation of PODs and HECs estimates internal dose levels

due to exogenous exposure (i.e., above background). Background methanol levels were subtracted from the PK data in developing the PBPK models. The underlying assumption is that noncancer and cancer risk from methanol exposure are due to increases in the levels of methanol or its metabolites above background.

- Please comment on the scientific justification for the subtraction of methanol background levels in the PBPK model development.
- Please comment on the adequacy of the dose-metric extrapolation based on a PBPK model for non-pregnant adults (i.e., no fetal compartment) for predicting risks associated with fetal/neonatal brain concentrations of methanol.
- EPA assumes that there is limited methanol metabolism in the fetus because of limited alcohol dehydrogenase (ADH) activity in the human fetus, and limited catalase and ADH activity in fetal rodents. Please comment on the validity of this assumption given the lack of data regarding potential alternate metabolic pathways in the fetus.
- Please comment on the adequacy of the rat to human extrapolation approach for in-utero and neonatal lactational and inhalation exposures.

4. Benchmark dose modeling of decreased pup brain weight relative to maternal internal methanol doses predicted by the PBPK model was used to derive the point of departure (POD) for the RfC. Has the BMD/PBPK approach been appropriately conducted? Has adequate justification been provided for the selected internal dose metric, area under the curve (AUC) for methanol in the blood of dams? Please identify and provide the rationale for any alternative approaches for the determination of the POD, including choice of another dose metric (e.g., total metabolized methanol), and discuss whether such approaches are preferred to EPA's approach.

5. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. It is assumed that these UFs account for variability in methanol dosimetry among human newborns following gestational and lactational exposure, and for uncertainty regarding the ratio of newborn-dose to maternal-dose in humans. Please comment on these assumptions and on the scientific justification for the selected UFs.

(C) Oral reference dose (RfD) for methanol

1. EPA concluded that the oral RfD should be derived from the more extensive inhalation database given the paucity of oral toxicity data. Please comment on whether the rationale for this approach has been scientifically justified and clearly explained. Please identify and provide the rationale for any alternative approaches for the determining the RfD and discuss whether such approaches are preferred to EPA's approach.

2. A PBPK model was used to derive the RfD via a route-to-route extrapolation of the POD from the NEDO (1987) study used for the derivation of the RfC. Please comment on whether the rationale for this approach has been scientifically justified. Has adequate justification been provided for the selected internal dose metric, AUC for methanol in the blood of dams? Is the PBPK model suitable for extrapolation to oral exposures for the fetal and neonatal endpoints? Please provide a detailed explanation.

3. EPA applied the same uncertainty factors to the POD for the derivation of the RfD as were applied for the derivation of the RfC. Please comment on the rationale for the selection of the UFs applied

(D) Carcinogenicity of methanol

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

2. EPA has determined that the mode of action of the carcinogenicity of methanol is not known. Has the discussion of the mode(s) of carcinogenic action been accurately and clearly described?

3. A lifetime drinking water cancer bioassay in SD rats (Soffritti et al., 2002) was selected for the derivation of an oral slope factor. Please comment on the scientific justification for the selection of this study. Have the strengths and limitations of the study been adequately characterized? There are two main issues associated with the use of the European Ramazzini Foundation (ERF) bioassay results. One issue is the differences in protocol used by the ERF compared to more generally used study protocols such as those used by the National Toxicology Program. Another issue concerns the possibility of *Mycoplasma pulmonis* infection in the test animals. Please comment on whether these issues have been adequately and clearly described and addressed.

4. Specific to the cancer assessment, EPA has chosen to model the total amount of methanol cleared by metabolic processes as an approximate measure of formaldehyde production (i.e., total metabolized methanol) from exposure to methanol. In part, this is due the difficulty in determining levels of formaldehyde in the blood. The metric of formaldehyde production is uncertain because metabolic processes may differ between species. Are there alternative approaches to estimate formaldehyde production from methanol metabolism that would be preferred and, if so, please provide the rationale and a detailed explanation of how an alternative formaldehyde dose metric could be implemented in the PBPK model.

5. The oral cancer slope factor (OSF) was calculated by linear extrapolation from the POD (lower 95% confidence limit on the dose associated with 10% extra risk for lymphomas). PBPK model estimates of total metabolized methanol/day were used to establish the POD and extrapolate to a human equivalent oral dose. Please comment on the adequacy of this approach, including the choice of endpoint and the manner in which the modeling was conducted.

6. A two-year inhalation cancer bioassay in F344 rats (NEDO et al., 2002) was selected for the development of an inhalation unit risk (IUR). Please comment on whether the selection of this study is scientifically justified. Have the strengths and limitations of the study been adequately characterized?

7. The inhalation unit risk was calculated by linear extrapolation from the POD (lower 95% confidence limit on the dose associated with 10% extra risk for pheochromocytomas). PBPK model estimates of total metabolized methanol/day were used to establish the POD and extrapolate to a human equivalent inhalation concentration. Please comment on the adequacy of this approach, including the choice of endpoint and the manner in which the modeling was conducted.