Draft Charge to External Reviewers for the IRIS Toxicological Review of n-Butanol
June 2011

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of n-butanol 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 n-butanol which includes a chronic reference dose (RfD) was posted to the database in 1990.

The current draft health assessment includes an RfD and reference concentration (RfC). Below is a set of charge questions that address scientific issues in the assessment of n-butanol. Please provide detailed explanations for responses to the charge questions. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

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 hazard of n-butanol.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for n-butanol

1. A chronic RfD for n-butanol has been derived from the oral drinking water developmental toxicity study (Sitarek et al., 1994) in Wistar IMP:DAK rats. 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. Visceral malformations in litters from female Wistar IMP:DAK rats were selected as the critical effect. 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 methods were applied to the litter visceral malformation data to derive the point of departure (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 visceral malformations in litters) 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. If changes to a UF are proposed, please identify and provide a rationale(s).

(B) Inhalation reference concentration (RfC) for n-butanol

1. A chronic RfC for n-butanol has been derived from a 90 days inhalation in rats (Korsak et al., 1994). 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. Impaired neurobehavioral function in male Wistar rats 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.

3. The NOAEL/LOAEL approach was used to derive the POD for the RfC. Please comment on whether this approach is scientifically supported and clearly described.

4. PBPK modeling was used to extrapolate the POD from rats to humans. Please comment on whether the PBPK modeling for interspecies extrapolation has been appropriately conducted and clearly described. Are the model assumptions, parameter values, and selection of dose metrics scientifically supported?

5. 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 n-butanol

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgrd.html), there is *inadequate information to assess the carcinogenic potential* of n-butanol. Is the cancer weight of evidence characterization scientifically supported and clearly described?

2. EPA did not derive a quantitative estimate of the carcinogenic potential of n-butanol. Do the data support an estimation of a cancer slope factor for n-butanol? If a quantitative estimate is proposed, please identify the data set and a description of the method that should be used.