

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

September 2011

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the draft Toxicological Review 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). The existing IRIS assessment for n-butanol includes a chronic reference dose (RfD) posted in 1987 and a cancer assessment posted in 1991. The external review draft Toxicological Review of n-Butanol includes an RfD, a reference concentration (RfC), and a cancer assessment.

Charge Questions

Below is a set of charge questions that address scientific issues in the draft Toxicological Review of n-Butanol. Please provide detailed explanations for responses to the charge questions. EPA will also consider reviewer comments on other major scientific issues specific to the hazard identification and dose-response assessment of n-butanol. Please identify and provide the rationale for approaches to resolve the issues where possible. 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 presented and synthesized the scientific evidence for noncancer and cancer health effects of n-butanol?
2. Please identify any additional peer-reviewed studies from the primary literature that should be considered in the assessment of noncancer and cancer health effects of n-butanol.

Chemical-Specific Charge Questions:

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

1. An oral drinking water developmental toxicity study in Wistar rats (Sitarek et al., 1994) was selected as the basis for the derivation of the RfD. Please comment on whether the selection of this study is scientifically supported and clearly described. If a different study is recommended as the basis for the RfD, please identify this study and provide scientific support for this choice.
2. Dilation of the lateral ventricle and/or the third ventricle of the brain in offspring of female Wistar rats was concluded by EPA to be an adverse effect and was selected as the critical effect for the RfD. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different endpoint is recommended as the critical effect for deriving the RfD, please identify this effect and provide

scientific support for this choice.

3. Benchmark dose (BMD) modeling was conducted using the incidence of litters with dilation of the lateral ventricle and/or the third ventricle of the brain to estimate the point of departure (POD) for derivation of the RfD. Has the modeling been appropriately conducted and clearly described, based on EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000b)? Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR of 10% extra risk of the incidence of litters with any offspring showing dilation of lateral ventricle and/or third ventricle of the brain in the absence of nested offspring data) been 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 appropriate based on the recommendations described in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

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

1. A 90-day subchronic inhalation study in Wistar rats (Korsak et al., 1994) was selected as the basis for the derivation of the RfC. Please comment on whether the selection of this study is scientifically supported and clearly described. If a different study is recommended as the basis for the RfC, please identify this study and provide scientific support for this choice.

2. Decreased rotorod performance in male Wistar rats was concluded by EPA to be an adverse effect and was selected as the critical effect for the derivation of the RfC. Please comment on whether the selection of this critical effect and its characterization is scientifically supported and clearly described. If a different endpoint is recommended as the critical effect for deriving the RfC, please identify this effect and provide scientific support for this choice.

3. The NOAEL/LOAEL approach was used in conjunction with dosimetric adjustments for calculating a human equivalent concentration (HEC), using a rat and human PBPK model (Teeguarden et al., 2005), to identify the POD for derivation of the RfC. Please comment on whether this approach is scientifically supported and clearly described.

- a) Does the selected PBPK model with EPA's modifications adequately describe the toxicokinetics of n-butanol? Was the PBPK modeling appropriately utilized and clearly described? Are the model assumptions and parameters scientifically supported and clearly described? Are the uncertainties in the model structure adequately characterized and discussed?
- b) The internal dose metric selected for use in the derivation of the RfC was the area under the curve (AUC) for n-butanol concentration in arterial blood corresponding to the NOAEL for decreased rotorod performance in a 90-day subchronic rat study (Korsak et al., 1994). Please comment on whether the selection of this dose metric is scientifically supported and clearly described. If a different dose metric is recommended for deriving

the RfC, please identify this metric and provide scientific support for this choice. Are the uncertainties in the selected dose metric adequately characterized and discussed?

4. Please comment on the rationale for the selection of the UFs applied to the POD for the derivation of the RfC. Are the UFs appropriate based on the recommendations described in *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5) and clearly described? If changes to the selected UFs are proposed, please identify and provide scientific support for the proposed changes.

(C) Carcinogenicity of n-butanol

1. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a; www.epa.gov/iris/backgrd.html), the draft Toxicological Review of n-Butanol concludes that there is "inadequate information to assess the carcinogenic potential" of n-butanol. Please comment on whether this characterization of the human cancer potential for n-butanol is scientifically supported and clearly described.

2. The draft Toxicological Review of n-Butanol did not derive a quantitative cancer risk estimate for n-butanol due to lack of available studies. Are there available data to support the derivation of a quantitative cancer risk estimate for n-butanol? If so, please identify these data.