Charge to External Reviewers for the IRIS Toxicological Review of Vanadium Pentoxide

September 2011

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the draft Toxicological Review of Vanadium Pentoxide 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 vanadium pentoxide includes an oral reference dose (RfD) posted in 1987. The external review draft Toxicological Review of Vanadium Pentoxide 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 Vanadium Pentoxide. 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 vanadium pentoxide. Please identify and provide the rationale for approaches to resolve these 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 vanadium pentoxide?

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 vanadium pentoxide.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for vanadium pentoxide

1. A subchronic oral dietary study in Wistar rats (Mountain et al., 1953) 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. A decrease in red blood cell count in male 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. The NOAEL/LOAEL approach was used in conjunction with dosimetric adjustments for calculating the human equivalent dose (HED) to identify the POD for derivation of the RfD. Please comment on whether this approach is 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 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 vanadium pentoxide

1. A two-year inhalation bioassay of vanadium pentoxide in F344/N rats (NTP, 2002) 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. An increase in laryngeal inflammation in female F344/N rats was concluded by EPA to be an adverse effect and was selected as the critical effect for 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. Benchmark dose (BMD) modeling was conducted using the incidence of laryngeal inflammation in female F344/N rats in conjunction with dosimetric adjustments for calculating the human equivalent concentration (HEC) to estimate the point of departure (POD) for derivation of the RfC. Has the modeling been appropriately conducted and clearly described based on EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000)? Is 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 laryngeal inflammation) supported and clearly described?

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 vanadium pentoxide

1. Under the EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005; www.epa.gov/iris/backgrd.html), the draft Toxicological Review of Vanadium Pentoxide characterizes vanadium pentoxide as "likely to be carcinogenic to humans" by the inhalation route of exposure. Please comment on whether this characterization of the human cancer potential of vanadium pentoxide is scientifically supported and clearly described.

2. The draft Toxicological Review of Vanadium Pentoxide concludes that there is insufficient information to identify the mode(s) of carcinogenic action. Please comment on whether this determination is appropriate and clearly described. If it is judged that a mode of action can be established for vanadium pentoxide, please identify the mode of action and its scientific support (i.e., studies that support the key events, and specific data available to inform the shape of the exposure-response curve at low doses).

Oral Slope Factor (OSF)

3. The draft Toxicological Review of Vanadium Pentoxide did not derive an OSF due to lack of available studies. Are there available data to support the derivation of an OSF for vanadium pentoxide? If so, please identify these data.

Inhalation Unit Risk (IUR)

4. A two-year inhalation bioassay of vanadium pentoxide in B6C3F1 mice (NTP, 2002) was selected as the basis for the derivation of the inhalation unit risk (IUR). 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 IUR, please indentify this study and provide scientific support for this choice.

5. The incidence of alveolar/bronchiolar adenomas or carcinomas in B6C3F1 male mice was selected to serve as the basis for the quantitative inhalation cancer assessment. Please comment on whether this selection is scientifically supported and clearly described. If a different cancer endpoint is recommended for deriving the IUR, please identify this endpoint and provide scientific support for this choice.

6. Benchmark dose (BMD) modeling was conducted using the incidence of alveolar/bronchiolar adenomas or carcinomas in male B6C3F1 mice in conjunction with dosimetric adjustments for calculating the human equivalent concentration (HEC) to estimate the point of departure (POD). A linear low-dose extrapolation from this POD was performed to derive the IUR. Has the modeling been appropriately conducted and clearly described based on EPA's draft *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000)? Has the choice of the benchmark response (BMR) for use in deriving the POD (i.e., a BMR of 71% extra risk of the incidence of alveolar/bronchiolar adenomas or carcinomas in male mice) been supported and clearly described?