

**Draft Charge to External Reviewers for the IRIS Toxicological Review of Vanadium Pentoxide  
July 2011**

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment 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). An existing IRIS assessment for vanadium pentoxide, which includes an oral reference dose (RfD), was posted on IRIS in 1987.

The current draft health assessment includes an RfD, an RfC and carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of vanadium pentoxide. 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 presented and synthesized the scientific evidence for noncancer and cancer hazard?
2. Please identify any additional studies that would be likely to make a significant impact on the conclusions of the Toxicological Review.

**Chemical-Specific Charge Questions:**

**(A) Oral Reference Dose (RfD) for Vanadium Pentoxide**

1. A chronic RfD for vanadium pentoxide has been derived from the subchronic oral dietary study (Mountain et al., 1953) in Wistar 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. Decreased red blood cells in male Wistar 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. The NOAEL/LOAEL approach with dosimetric adjustments for calculating the human equivalent dose was used to derive the POD. 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. If changes to a UF are proposed, please identify and provide a rationale(s).

### **(B) Inhalation Reference Concentration (RfC) for Vanadium Pentoxide**

1. A two-year bioassay of vanadium pentoxide in F344 rats (NTP, 2002) was selected as the basis for the derivation of the RfC. 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. Laryngeal lesions in female F344 rats were 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. Benchmark dose (BMD) modeling was conducted on the incidence of laryngeal lesions in female F344 rats in conjunction with dosimetric adjustments for calculating the human equivalent concentration to derive the point of departure (POD). Has this approach been appropriately conducted and clearly described? Is the benchmark response (BMR) selected for use in deriving the POD (i.e. A 10% extra risk of incidence of laryngeal 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 RfC. Are the UFs scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

### **(C) Carcinogenicity of Vanadium Pentoxide**

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* ([www.epa.gov/iris/backgrd.html](http://www.epa.gov/iris/backgrd.html)), vanadium pentoxide is "likely to be carcinogenic to humans" by the inhalation route of exposure. Is the cancer weight of evidence characterization scientifically supported and clearly described?

2. EPA has concluded that the available data do not support any specific mode of action for vanadium pentoxide-induced lung tumors in mice. Please comment on whether this determination is scientifically supported and clearly described. Please comment on data available for vanadium pentoxide that may support an alternative mode of action.

#### *Oral Slope Factor (OSF)*

3. An OSF was not derived due to lack of available studies to characterize the carcinogenic potential of vanadium pentoxide administered via ingestion. Is the rationale for not deriving an OSF scientifically supported and clearly described? Please identify and provide rationale for any studies that should be selected as the principal study.

*Inhalation Unit Risk (IUR)*

4. A two-year bioassay of vanadium pentoxide in B6C3F1 mice (NTP, 2002) was selected for the derivation of an IUR. 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 selected for quantitation.
5. The incidence of respiratory tumors 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. Please identify and provide the rationale for any other endpoints that should be selected to serve as the basis for the IUR.
6. The IUR was calculated by low-dose linear extrapolation from the POD (i.e., the lower 95% confidence limit on the concentration associated with 71% extra risk of respiratory tumors). Has the modeling been appropriately conducted and clearly described?