EPA's Response to Selected Interagency Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Vanadium Pentoxide

September 30, 2011

Purpose:

The Integrated Risk Information System (IRIS) assessment development process of May 2009, includes two steps (Step 3 and 6) where White House offices and other federal agencies can comment on draft assessments. The following are EPA's responses to selected major interagency review comments received during the Interagency Science Consultation step (Step 3) for the draft IRIS Toxicological Review of Vanadium Pentoxide (dated July 2011). All interagency comments provided were taken into consideration in revising the draft assessment prior to posting for public comment and external peer review. The complete set of interagency comments is attached as an appendix to this document.

For a complete description of the IRIS process, including Interagency Science Consultation, visit the IRIS website at www.epa.gov/iris.

July 2011 Interagency Science Consultation Draft IRIS Assessment—Selected Comments and Responses:

Topic #1: Clarification regarding the equation used to determine human equivalent oral doses from data in laboratory animal species for derivation of the RfD -*NTP requested clarification on the use of the following equation to determine the dosimetric adjustment factor (DAF): DAF = $(BW_a^{1/4}/BW_h^{1/4})$ when the discussion focused on the use of body weight $^{3/4}$ scaling, not body weight$^{1/4}$ scaling.*

> **EPA Response:** In EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011), the Agency endorses body weight scaling to the ¾ power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. A body of literature exists that generally supports an allometric relationship between $BW^{3/4}$ and various physiological and biochemical processes, mostly related to kinetics, for a number of compounds across a reasonable number and range of species. Therefore, it is assumed that in general, an equal biological effect is obtained in an animal and a human when the

dose of a chemical (in mg) is expressed relative to body weight to the ¾ power (i.e., $BW^{3/4}$); represented by the following equation:

$$[mg_H / BW_H^{3/4}] = [mg_A / BW_A^{3/4}]$$

where the subscripts "H" and "A" refer to human and animal, respectively. $BW^{3/4}$ also can be represented as $[BW^{1/1} / BW^{1/4}]$, and this representation can then be substituted into the above equation:

$$[mg_H / (BW_H^{1/1} / BW_H^{1/4})] = [mg_A / (BW_A^{1/1} / BW_A^{1/4})]$$

Solving this equation for $[mg_H / BW_H]$, the human dose, yields the following:

$$[mg_H / BW_H] = [mg_A / BW_A] \times [BW_A / BW_H]^{1/4}$$

Thus, to convert an animal dose (in mg/kg) to a toxicologically equivalent human dose (in mg/kg) using $BW^{3/4}$ scaling, you multiply the animal dose by $[BW_A / BW_H]^{1/4}$, also known as the dosimetric adjustment factor or DAF, and this is what is represented in the DAF equation in the text of the Toxicological Review (Section 5.1.2).

Topic #2: Clarification of the discussion of the NTP (2002) study-*NTP included several comments requesting clarification in the discussion of the 16 day, 13 week, and 2 year exposure studies reported in NTP (2002). For example, NTP requested that EPA note in the text that the historical databases referenced for comparison were different for males and females (e.g., databases for female rats fed NIH-07 diets versus male rats fed NTP-2000 diets). NTP suggested that the presentation of the respiratory tumor data following exposure to vanadium pentoxide for 2 years shown in the tables should also be included in the text. NTP also requested clarification related to the reporting of the data from the 16 day study (i.e., presentation of results following 13 and 16 day exposures).*

EPA Response: EPA has revised the text in the Toxicological Review to clarify which databases of historical controls were utilized for comparison with the NTP (2002) data. Additionally, EPA has included the tumor incidence data for both male and female rats exposed to vanadium pentoxide for 2 years in the text as requested by NTP. With regard to the 16 day study, NTP (2002) conducted three separate experiments utilizing a 16 day exposure to vanadium pentoxide, including the following: (1) an experiment in which male

rats and female mice were assessed for pulmonary inflammation and systemic immunotoxicity following exposure to 0, 4, 8, and 16 mg/m^3 vanadium pentoxide for 16 days; (2) an experiment in which five male and five female mice were exposed by inhalation to vanadium pentoxide for 6 hours per day, 5 days a week for 16 days at concentrations of 0, 2, 4, 8, 16, or 32 mg/m^3; and (3) an experiment where an additional group of female mice were exposed to 0, 2, 4, or 8 mg/m^3 for 6 hours per day, 5 days per week for 16 days and evaluated for nonneoplastic lung lesions on days 6 and 13. EPA augmented the Toxicological Review to clarify the presentation of the results of the 16 day studies.

Appendix
Comments on the Interagency Science Consultation Draft
IRIS Toxicological Review of Vanadium Pentoxide

National Institute of Environmental Health Sciences/National Toxicology Program Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Vanadium Pentoxide (dated July 2011)

NIEHS/NTP
VANADIUM PENTOXIDE IRIS COMMENTS
August 1, 2011

Page 6 – When discussing NTP exposures prior to blood collection for vanadium analysis, consider changing to …16 days or 2 years, as blood collection was part of a 16 day study (will provide consistency with toxicity results)

Page 46 – When describing increases in neoplasms for rats exposed to vanadium pentoxide, please note that the historical control databases referenced were different for males and females. For females, a larger database in rats fed NIH-07 diet (which was used prior to NTP-2000 diet) was used as the historical control database. In addition, there was one lung tumor in each of the 1 and 2 mg/m3 groups, compared to 3 at 0.5 mg/m3 and none in controls.

Page 47 – particle size is listed for mouse chronic (and prechronic) studies but not chronic/prechronic rat studies. The particle size is the same for both studies and should be listed as such.

Page 59 – when referring to "short term" inhalation studies in animals, please consider including the duration. In addition, it appears that increases in relative lung weight were observed in the short term NTP inhalation study.

Page 59 – It is unclear why 13-day and 16-day exposures are described. For example, the text indicates that non-neoplastic lesions were observed in the 13-day and 16-day (are these referring to the 16-day and 16-day special study animals?) studies. However, histopathology was not performed on the special study animals, so it is unclear which data are being described. In the last sentence of the last full paragraph, a 3 month study is mentioned and in the next sentence a 13-day study is mentioned. Are these referring to

the same study (13-weeks/3-monts vs. 13-days)? Interestingly, on the next page, the 16-day special studies are described. Please clarify.

Page 84- in the second paragraph, it is indicated that exposure caused tumors… in mice, while "some evidence" was used to describe the level of evidence in male mice and female mice were not mentioned. Please consider standardizing the descriptions to either use or omit the NTP levels of evidence and a description of what the levels of evidence were based on (ex. Clear/statistically significant increases; some/increased over historical controls; equivocal/increased only at low dose and over a larger historical control database with a different diet…).

Page 89 – it is unclear what study is being referred relative to neurotoxic effects (the NTP studies were described in the previous sentence).

Page 90 – similar to page 59, it is unclear why decreased lung weights are mentioned. Increased lung weights were observed.

Page 102 – The sentence in the middle of the second full paragraph ("…both sexes at all doses, with 50% of the male mice…") is unclear. Was the intent to indicate that the deaths in males were due to increased tumors?

Page 103 – The sentence "Thus, the increased tumor incidence in rats equivocal overall,…" is incorrect. The male and female rat studies were two separate studies. In males, there was some evidence of carcinogenic activity while in females there was equivocal evidence.

Page 108 – It is unclear why in the DAF equation, body weights are raised to the ¼ and not the ¾ power.

Page 133 – 13 day exposure is mentioned again (see previous comments). In addition, the rat strain is the F344/N.

Agency for Toxic Substances and Disease Registry (ATSDR) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of Vanadium Pentoxide (dated July 2011)

Date: August 2, 2011

From: Agency for Toxic Substances and Disease Registry

Subject: Comments on EPA's Toxicological Review of Vanadium Pentoxide

To: Environmental Protection Agency

We appreciate the opportunity to review EPA's Toxicological Review of Vanadium Pentoxide. Overall, we found the draft IRIS Toxicological Review and fact sheet well-written and concise. Studies of support within the document are sufficiently synthesized in a scientific manner to present the overall assessment of this substance as it relates to environmental health. The authors did a good job of stacking the evidence for the specific exposure and leading the reader to appropriate conclusions about vanadium pentoxide.

One minor editorial comment: On Page 14, last sentence under Oral Exposure: there should be a comma after hair"…but not hair, is a sensitive…"