Charge to External Reviewers for the
Toxicological Review of Hexavalent Chromium
September 2010

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of hexavalent chromium 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 hexavalent chromium, which includes a chronic oral reference dose (RfD), a chronic inhalation reference concentration (RfC), and a carcinogenicity assessment, was posted on IRIS in 1998.

The current draft health assessment includes a reassessment of the noncancer and cancer health effects associated with the oral route of exposure (i.e., an RfD and oral slope factor) and a mode of action analysis for cancer. Below is a set of charge questions that address scientific issues in the assessment of hexavalent chromium. 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 make a significant impact on the conclusions of the Toxicological Review.

Chemical-Specific Charge Questions:

(A) Oral Reference Dose (RfD) for Hexavalent Chromium

1. A two-year drinking water study of sodium dichromate dihydrate in rats and mice (NTP, 2008) was selected as the basis for the derivation of the RfD. 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. Diffuse epithelial hyperplasia in the duodenum of female mice was selected as the critical effect for the RfD. 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 applied to the incidence of diffuse epithelial hyperplasia in the duodenum of female mice 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 the incidence of

diffuse epithelial hyperplasia) 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 scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

(B) Carcinogenicity of Hexavalent Chromium

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

2. A mutagenic mode of carcinogenic action by all routes of exposure is proposed as the primary mode of action for hexavalent chromium. Please comment on whether this determination is scientifically supported and clearly described. Please comment on data available for hexavalent chromium that may support an alternative primary mode of action.

3. A two-year drinking water study in rats and mice (NTP, 2008) was selected for the derivation of an oral slope factor. Please comment on whether the selection of this study for quantification is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be considered.

4. The incidence of adenomas and carcinomas combined in the small intestine of male mice from the NTP (2008) two-year drinking water study were selected to serve as the basis for the quantitative 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 quantitative cancer assessment.

5. The oral slope factor was calculated by linear extrapolation from the POD (i.e., the lower 95% confidence limit on the dose associated with 10% extra risk of tumors of the small intestine in male mice). Has the modeling been appropriately conducted and clearly described?