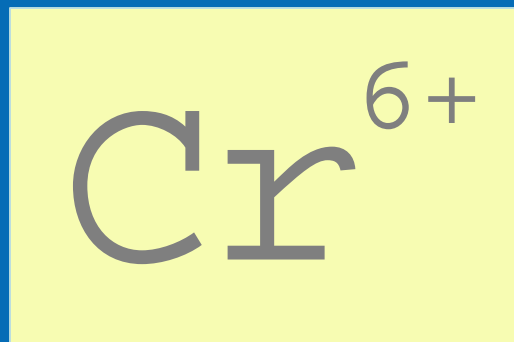


Preliminary Materials for the IRIS Assessment of Hexavalent Chromium

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- 1998** **Cr(VI) Toxicological Review posted to the IRIS database**
- *Known human carcinogen* by inhalation; *not classifiable* by ingestion
 - Includes RfD, RfC, and IUR; no OSF
- 2008** **NTP 2-yr bioassay of Cr(VI) in drinking water**
- *Clear evidence* of carcinogenic activity
 - Oral cavity tumors in male and female rats
 - Small intestinal tumors in male and female mice
 - Prompts EPA program offices and regions to nominate Cr(VI) for reassessment by IRIS
 - Focus on oral exposure

2010 External Peer Review draft of the IRIS assessment (oral exposure only) is posted

2011 External Peer Review meeting on the 2010 draft assessment

- ACC presents research plans during public comment period
- Several panelists recommend waiting for ACC-funded studies to be completed

IRIS assessment of Cr(VI): Timeline

- 2013** IRIS conducts a workshop on issues regarding gastrointestinal reduction, absorption, and transit of ingested Cr(VI) in rodents and humans, including susceptible subpopulations
- 2014** IRIS releases the first of two preliminary packages for Cr(VI)
– Scope of assessment expanded to include both oral and inhalation exposures

Cr(VI) gut reduction workshop webinar (Sept. 2013)

- Facilitated discussion among experts from industry, academia, government, and the public
 - Panelists included principal investigators of Cr(VI) studies
 - Discussions on gastrointestinal metabolism, physiology, and variability
- Discussions emphasized many unknowns regarding Cr(VI) uptake and reduction
 - Uncertainty in uptake transporters, variability of GI motility and gastric acid secretion
- Physiologically-based pharmacokinetic (PBPK) modeling is possible for the GI tract (*although challenging*)

Bimonthly Meetings for Cr(VI)

Preliminary Package for Cr(VI), Part 1 (today)

- Science issues related to:
 - Problem formulation
 - Evidence from experimental animal studies

Preliminary Package for Cr(VI), Part 2 (future bimonthly meeting)

- Science issues related to:
 - Evidence from human studies
 - Toxicokinetic studies
 - Mechanistic studies

Cr(VI) Science Issues for the June IRIS Bimonthly Meeting

- Cancer classification by inhalation
- Noncancer hazards to be considered
- Susceptibility of mice to gastrointestinal toxicity
- Utility of subchronic histopathological data
- Database for reproductive and developmental effects
- Relation between anemia and oral tumors in rats



Science issue 1: Cancer classification by inhalation

In 1998, EPA classified hexavalent chromium as a "known human carcinogen by the inhalation route of exposure." The same conclusion has been reached by other federal, state, and international health agencies.

This assessment plans to adopt this conclusion and focus its review of the lung cancer evidence on identifying studies that might improve the quantitative dose-response analysis.

Science issue 2: Noncancer hazards

Based on the hazards identified in recent reviews by other federal, state, and international health agencies and on an examination of the more recently published studies, this assessment plans to focus its review on the potential for the following effects:

- Respiratory
- Gastrointestinal
- Immunological
- Hematological
- Hepatic
- Reproductive
- Developmental

Science issue 3: Species differences

Diffuse epithelial hyperplasia of the duodenum was observed in the 2-year NTP drinking water bioassay at 5 ppm (0.4 mg/kg-day). Analogous effects were not observed in rats, suggesting that mice may be more susceptible to gastrointestinal toxicity.

- What toxicokinetic or toxicodynamic factors might explain the susceptibility of mice to gastrointestinal toxicity?
- Are other effects in mice secondary to gastrointestinal toxicity?

Science issue 4: Subchronic data

A subchronic (90-day) study in rodents observed histopathological effects in the intestinal crypts and villi at high drinking water concentrations, but not at lower concentrations.

To what extent can these subchronic toxicological data inform the effects of chronic exposure to hexavalent chromium?

Science issue 5: Reproductive and developmental effects

NTP studies did not observe treatment-related reproductive effects in male or female rats or mice. Other studies have observed reproductive as well as developmental effects in rats and mice, but often at doses exceeding those found to induce gastrointestinal tract effects or maternal toxicity. Methodological or record-keeping anomalies have been identified for some studies.

EPA is seeking public discussion of the overall quality of the database for reproductive and developmental effects.

Science issue 6: Anemia and oral tumors

The 2-year NTP drinking water bioassay observed squamous cell carcinomas of the oral mucosa in male and female rats, but not in mice. Hematological effects were observed at a higher incidence in rats than mice in the NTP 2-year study.

It has been suggested that oral tumors are secondary to, or may be exacerbated by, anemia.

EPA is seeking public discussion on the occurrence of anemia and its possible relationship to oral tumors.