Hexavalent Chromium: Development of a Guidance Value Protective of Cancer

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Today’s Agenda

1. Overview of chromium’s guideline development process
2. Critical information to derive the health based value (HBV)
3. Derivation of the HBV for chromium in drinking water
4. Comparison of risk assessment approaches

Based on:


Approved March 2016; Available online
August 17, 2018
1. Chromium Guideline Development Process

Priority Setting

**Risk Assessment:**
- Independent contractor provided a review of all available science
- 2 senior evaluators conducted risk assessment
- Treatment & analytical considerations included

**Peer review (EPA, OEHHA, Summit Toxicology & internally)**
- F/P/T committee on drinking water (CDW) review, impact & approval
- Public consultation
- CDW review, impact considerations & approval

Extensive review process

**Publication**

CHE & HC approval
2. What is the critical information to derive a health based value (HBV) for chromium in drinking water?
Critical Information to Derive a HBV for Chromium

Toxic moiety: Cr(VI)
- No definitive evidence of toxicity from Cr(III) exposure
- Cr(VI) “carcinogenic to humans” (group 1) based on sufficient evidence for carcinogenicity in humans (lung cancer) & sufficient evidence in experimental animals (IARC 2012)

Hazard ID: Diffuse hyperplasia of the small intestine
- 0.4 & 0.8 mg Cr(VI)/kg bw/day diffuse epithelial hyperplasia of small intestine (SI) in mice & histiocytic cellular infiltration of SI of rats respectively (NTP 2008)
- ≥1.4 mg Cr(VI)/kg bw/day SI tumors in mice (NTP 2008)
- 2.1 mg Cr(VI)/kg bw/day oral mucosal tumors in rats
- Environmental Cr(VI) levels are >1,000-fold lower than lowest concentration (5 mg/L) in the two-year cancer bioassay (a concentration that was not carcinogenic to mice or rats).
Critical Information to Derive a HBV for Chromium- Cont’d

Kinetics: Supports a threshold approach
– Reduction, absorption & localization of chromium in the GI tract indicate several nonlinearities in Cr(VI) disposition.
– Depletion of reducing pools at high concentrations.
– Average Cr(VI) measurements (0.2–2 μg/L) in Canadian & US drinking water are within the reductive capacity of rodent & human gastric fluid.

MOA analysis: Supports a threshold approach & is relevant to humans
– A nonmutagenic MOA of cytotoxicity leading to chronic regenerative hyperplasia (not a mutagenic MOA).
Linear or Threshold Risk Assessment Approach?

Intestinal hyperplasia & tumours

MOA analysis for intestinal carcinogenesis (Thompson et al. 2013)
- Based on an established MOA framework (Boobis et al. 2006, Meek et al. 2003).
- Reviewed by seven peer reviewers with expertise in MOA analysis provided by a science advisory board convened by an independent group (TERA 2012, 2009).
Mode of Action of Cr(VI)-Induced Intestinal Tumors in Mice

Low [Cr(VI)]: -Cr (VI) is reduced to Cr(III) by gastric & intestinal lumen fluid/contents; -Cr(III) has minimal uptake relative to Cr(VI).

High [Cr(VI)]: the MOA has these key events:
1. Unreduced Cr(VI) is available for absorption into villus enterocytes (red circles),
2. Cr(VI) causes cytotoxicity in villus enterocytes that can lead to villus blunting,
3. Crypt hyperplasia (note lengthening of the crypt depth) occurs to regenerate lost villus enterocytes,
4. Increased cell replication increases the chance of spontaneous mutation in intestinal crypt stem cells (indicated by X).
→ Ultimately, chronic regenerative hyperplasia can lead to adenoma formation.
→ Based on analysis this MOA is relevant to humans.

(Moffat et al. 2018, JAWWA 110:5)
Chromium likely not directly interacting with DNA: Chromium localized to intact intestinal villi (terminally differentiated cells) but not the crypt (proliferating cells).

No genotoxicity in target tissues
  – in vivo assays of intestinal tissues.
  – no genotoxicity in the oral cavity of rats which develop tumours (180 mg/L).

Data do NOT fit the key characteristics for chemicals with a mutagenic MOA.

Data has strong tissue-relevant, dose-response & temporal concordance for a cytotoxic MOA.

Precedent: cytotoxic MOA for captan/folpet induced intestinal tumours.

Thus, the weight of evidence supports a cytotoxic MOA for Cr(VI)

(Moffat et al. 2018, JAWWA 110:5)
3. Derivation of the Health Based Value (HBV) for Chromium in Drinking Water

**Toxic moiety:** Cr(VI)  
**Key effect:** SI hyperplasia is protective of cancer & non-cancer effects  
**Approach:** Threshold approach is appropriate for risk assessment

\[
HBV = \frac{(POD/UF) \times AF}{WC} = \frac{0.0022 \text{ mg/kg bw/d} \times 70 \text{ kg} \times 0.5}{1.5 \text{ L}} = 0.05 \text{ mg/L}
\]

**Point of Departure (POD):** human equivalent dose (HED) 0.054 mg/kg bw per day (BMDL01 & PBPK modeling).  
**Uncertainty Factor (UF) 25:**  
- × 2.5 for interspecies variability (PBPK models for kinetic differences);  
- × 10 for intraspecies variability.  
**Body Weight (BW) 70kg:** Average adult Canadian body weight.  
**Allocation factor (AF) 0.5:** Based on exposure analysis; refers to the contribution of drinking water to the estimated total daily intake for Canadians.  
**Water Consumption (WC) 1.5 L:** is the daily average volume of drinking water ingested by an adult. Dermal & inhalation exposure during bathing/showering are NOT significant.
### 4. Risk Assessment of Total Chromium in Drinking Water

*Internationally regulated values 50-100 µg/L*

<table>
<thead>
<tr>
<th>Source</th>
<th>Key Endpoint / Modeling Parameters</th>
<th>Approach</th>
<th>Point of Departure mg/kg bw/day</th>
<th>Uncertainty Factors (UFs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada 2015</td>
<td>Diffuse epithelial hyperplasia (NTP 2008); modeled duodenum and jejunum of male and female mice</td>
<td>Threshold based on MOA analysis; used rodent and human PBPK models to convert internal mouse dose to human equivalent dose (Thompson et al. 2014, Kirman et al. 2013, Kirman et al. 2012); allocation factor 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>For BMRs of 10, 5, and 1%, BMDLs are 0.14, 0.11, and 0.054, respectively</td>
<td>25 (UF&lt;sub&gt;H&lt;/sub&gt;10, UF&lt;sub&gt;D&lt;/sub&gt; not necessary)</td>
</tr>
<tr>
<td>Haney 2015, TCEQ 2015</td>
<td>Diffuse epithelial hyperplasia (NTP 2008); modeled duodenum of female mice only</td>
<td>Threshold based on MOA analysis; duodenal doses in mice were obtained from experimental data (Kirman et al. 2012) and used for BMD modeling</td>
<td>BMR 10%: BMDL 0.31</td>
<td>100 (UF&lt;sub&gt;H&lt;/sub&gt;10, UF&lt;sub&gt;D&lt;/sub&gt; 1)</td>
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<tr>
<td>Thompson et al. 2018</td>
<td>Diffuse epithelial hyperplasia (NTP 2008); modeled duodenum and ileum of male and female mice</td>
<td>Threshold based on MOA analysis; used rodent and human PBPK models to convert internal mouse dose to human equivalent dose (Kirman et al. 2017)</td>
<td>BMR 5%: BMDL 0.02</td>
<td>21.6 (EF&lt;sub&gt;AD&lt;/sub&gt; 3, EF&lt;sub&gt;HK&lt;/sub&gt; 2.4, UF&lt;sub&gt;D&lt;/sub&gt; not necessary&lt;sup&gt;b&lt;/sup&gt;)</td>
</tr>
<tr>
<td>IPCS 2013, ATSDR 2012</td>
<td>Diffuse epithelial hyperplasia (NTP 2008); modeled duodenum of female mice only</td>
<td>Threshold; MOA uncertain</td>
<td>BMR 10%: BMDL 0.094</td>
<td>100 (UF&lt;sub&gt;H&lt;/sub&gt;10, UF&lt;sub&gt;D&lt;/sub&gt; not used&lt;sup&gt;b&lt;/sup&gt;)</td>
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<tr>
<td>WHO 1996</td>
<td>Carcinogenicity by the inhalation route</td>
<td>Linear; carcinogenicity by the inhalation route (provisional)</td>
<td></td>
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</tr>
</tbody>
</table>

*Note:*

- UF<sub>H</sub>10, UF<sub>D</sub> not necessary<sup>b</sup> indicates that the uncertainty factor is not used.
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(Moffat et al. 2018, JAWWA 110:5)
Acknowledgments

Health Canada
(Approved: 2016; Web posting: Aug. 17, 2018)

Science: Michelle Deveau, Richard Carrier, Michele Giddings
Policy: Veronique Morisset, Anne Vezina
Treatment: Nadia Martinova, France Lemieux

Federal-Provincial-Territorial committee on drinking water

Journal AWWA
(Moffat et al. 2018,110:5)

Chad Seidel - Corona Environmental Consulting
Chad Thompson - ToxStrategies
Thank you

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Water quality mailing list