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Hexavalent Chromium
Oral Reference Dose

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Executive Summary

Background

In recent years, a great deal of new research has been conducted specifically to generate data to better inform the mode of action (MOA) analysis for hexavalent chromium-induced carcinogenesis due to chronic oral exposure and to improve the extrapolation of rodent oral study results to humans (e.g., Thompson et al. 2011a, 2011b, 2012a, 2012b, 2012c, 2013a; Kirman et al. 2012, 2013; Proctor et al. 2012; Kopec et al. 2012a, 2012b; O'Brien et al. 2013; Suh et al. 2014; Thompson et al. 2015a, 2015b, 2015c). These research project data have been thoroughly evaluated to gain critical scientific understanding and insight into key areas of carcinogenic dose-response assessment for hexavalent chromium (CrVI) such as:

- The carcinogenic MOA (i.e., key events) operating in relevant rodent studies (e.g., NTP 2008);
- CrVI toxicokinetics following oral exposure (e.g., dose-dependent differences in target tissue absorption); and
- Data-informed, biologically-plausible expectations about potential low-dose risk.

The current, significantly greater scientific understanding of these issues (especially considering the previous lack of sufficient relevant data and understanding just 5-6 years ago) is of paramount importance considering the substantial regulatory challenge of extrapolating high oral dose results from laboratory animal studies to environmentally-relevant human doses that are orders of magnitude lower in a meaningful, toxicologically-predictive manner (e.g., the mouse dose at the lowest water concentration used in NTP 2008 is about 74,000 times higher than the approximate human dose corresponding to the 35-city geometric mean drinking water concentration reported in EWG 2010).

TCEQ Scientific, Peer-Reviewed Publications

In addition to the numerous studies published as part of the CrVI MOA research project, TCEQ staff have independently and critically evaluated the relevant published study data (and supplemental data) and its implications for the carcinogenic dose-response assessment of oral exposure to CrVI. As part of that scientific endeavor, three manuscripts have been published in a scientific peer-reviewed journal (Haney 2015a, 2015b, 2015c). The last of these scientific, open-access articles (Haney 2015c) considers both the non-linear, non-threshold approach as well as the threshold (i.e., reference dose) approach prior to conducting a weight-of-evidence (WOE) analysis of available MOA data. The WOE indicates that cytotoxicity-induced regenerative hyperplasia is indubitably the most scientifically well-supported MOA. Health Canada (2015) concurs that confidence in a cytotoxic MOA is high (and evidence for a mutagenic MOA is weak). More specifically, compensatory crypt enterocyte hyperplasia induced by chronic villous toxicity should be considered as a required (but not always sufficient) key event in CrVI-induced intestinal tumorigenesis. Consequently, the reference dose (RfD) approach is the most

scientifically-defensible approach based on the WOE of available MOA information and analyses conducted for the most scientifically-supported MOA and should be adopted for assessing the potential intestinal carcinogenicity of oral exposure to CrVI (Haney 2015c).

RfD Derivation

The RfD derived in Haney (2015c) will be adopted by the TCEQ. The RfD of 0.0031 mg CrVI/kg-day was derived to protect against cytotoxicity-induced regenerative hyperplasia as a key precursor carcinogenic MOA event. Briefly, the duodenum was selected as the critical mouse target tissue for benchmark dose (BMD) analysis since diffuse hyperplasia has a strong, well-defined dose-response relationship in the mouse duodenum. This is consistent with both significant tissue absorption of CrVI by the duodenum and the duodenum as the most tumorigenically responsive tissue. The incidence of diffuse hyperplasia in the duodenum of female mice was used for BMD modeling since: (1) Statistical analyses did not reveal differences between male and female mice in hyperplastic or tumorigenic response to CrVI exposure (Thompson et al. 2013b); (2) The dose-response for diffuse hyperplasia in female mice is strong and more monotonic than that in male mice (see Tables C4 and D4 of NTP 2008); and (3) Importantly, the water concentrations used in NTP (2008) for female mice correspond to those used in Kirman et al. (2012) to determine added chromium (Cr) concentrations in mouse target tissues due to CrVI oral exposure, which is a useful internal dose metric for BMD modeling. Accordingly, the incidence of diffuse hyperplasia in the duodenum of female mice from NTP (2008) along with the duodenum tissue concentrations (added mg Cr/kg tissue) reported in Kirman et al. (2012) were used for BMD modeling. A benchmark response (BMR) of 10% was used so that the BMD and 95% lower confidence limit on the BMD (BMDL) would be calculated at a BMR that did not extrapolate farther than necessary below the range of the data.

The Log-Logistic and Dichotomous-Hill models provided adequate and almost identical fits to the mouse data with a goodness-of-fit p value >0.1, lowest Akaike Information Criterion, and scaled residuals <|2|. The mouse BMD_{10} value was 1.83 added mg Cr/kg tissue for both models using mean added mg Cr/kg tissue as the internal dose metric. The average mouse $BMDL_{10}$ of 1.39 added mg Cr/kg tissue (based on individual model values of 1.37 and 1.41 added mg Cr/kg tissue) was used as the point of departure (POD) for diffuse hyperplasia in the duodenum for derivation of the RfD.

The mouse POD of 1.39 added mg Cr/kg duodenum tissue was converted to a corresponding oral dose based on the relationship between duodenum tissue concentration (mean mg Cr/kg tissue) and oral dose (mg CrVI/kg-day) that was modeled previously (Haney 2015a). The POD falls between two of the tissue concentrations modeled, and is similar to one of the modeled concentrations (1.5 mg Cr/kg tissue) where the estimated and observed values showed excellent agreement (i.e., the scaled residual was 0.421, well below |2|), which increases confidence in the oral exposure estimate corresponding to the target tissue dose POD. A mouse oral dose of 0.31 mg CrVI/kg-day was estimated to correspond to the POD duodenum tissue concentration. Note that the application of an animal-to-human uncertainty factor (UF_A) to this mouse POD

ultimately results in a value (0.031 mg/kg-day) that is below the lower end of the range of average human equivalent doses (HED values of 0.05-0.1mg/kg-day) cited in a recent USEPA CrVI PBPK study (Sasso and Schlosser 2015), practically identical to the more conservative HED of 0.028 mg/kg-day (pH = 5) based on a similar evaluation (e.g., using the $BMDL_{10}$ for diffuse epithelial hyperplasia), and is 4.5-fold lower than the HED of 0.14 mg/kg-day (pH = 2.5) based on the similar evaluation (see Table 1 of Sasso and Schlosser 2015).

Dividing this mouse oral POD (0.31 mg CrVI/kg-day) by the same uncertainty factors (UF_A=10, UF_H=10, UF_D=1) as used in USEPA (2010) results in an RfD of 0.0031 mg CrVI/kg-day.

RfD = 3.1E-03 mg CrVI/kg-day

Comparison of TCEQ RfD with Other Published RfDs

The TCEQ-derived RfD is somewhat more conservative than, but shows remarkable agreement with, a previously published RfD (0.006 mg CrVI/kg-day; Thompson et al. 2013b) as well as Health Canada's Tolerable Daily Intake (TDI of 0.0044 mg CrVI/kg-day; Health Canada 2015). It also happens to correspond to the approximate human dose at the federal MCL for Cr (e.g., 0.1 mg/L × 2.5 L/day × 1/80 kg = 0.0031 mg/kg-day), and is considered protective of both the potential carcinogenic and noncarcinogenic effects of oral CrVI exposure. Additional details pertaining to the RfD derivation may be found in the open access article (Haney 2015c).

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