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Use of dose-dependent absorption into target tissues to more accurately predict cancer risk at low oral doses of hexavalent chromium

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ABSTRACT

The mouse dose at the lowest water concentration used in the National Toxicology Program hexavalent chromium (CrVI) drinking water study (NTP, 2008) is about 74,500 times higher than the approximate human dose corresponding to the 35-city geometric mean reported in EWG (2010) and over 1000 times higher than that based on the highest reported tap water concentration. With experimental and environmental doses differing greatly, it is a regulatory challenge to extrapolate high-dose results to environmental doses orders of magnitude lower in a meaningful and toxicologically predictive manner. This seems particularly true for the low-dose extrapolation of results for oral CrVI-induced carcinogenesis since dose-dependent differences in the dose fraction absorbed by mouse target tissues are apparent (Kirman et al., 2012). These data can be used for a straightforward adjustment of the USEPA (2010) draft oral slope factor (SFo) to be more predictive of risk at environmentally-relevant doses. More specifically, the evaluation of observed and modeled differences in the fraction of dose absorbed by target tissues at the point-of-departure for the draft SFo calculation versus lower doses suggests that the draft SFo be divided by a dose-specific adjustment factor of at least an order of magnitude to be less over-predictive of risk at more environmentally-relevant doses.

1. Introduction

In recent years, there has been a great deal of scientific debate and new research regarding exactly how and under what conditions CrVI is likely to induce cancer following oral exposure (e.g., Thompson et al., 2011a; McCarroll et al., 2010; USEPA, 2010). Some significant topics of debate concern issues relevant to the mode of action (MOA) and whether the excess risk observed at very high mouse oral doses of CrVI would be expected to extrapolate downward to significantly lower, truly environmentally-relevant human doses in a linear manner or if a nonlinear/threshold dose–response should be expected at such low doses. Such topics include the roles of mutagenicity and chronic hyperplasia in CrVI-induced carcinogenicity in target tissues, if the MOA and/or gastrointestinal (GI) extracellular reductive capacity likely impart a nonlinear/threshold character to the dose–response, and the potential that mouse oral doses in NTP (2008) exceeded the extracellular CrVI reductive capacity of the stomach/GI tract.

As part of the CrVI MOA research project (e.g., Thompson et al., 2011a), Proctor et al. (2012) report that stomach reducing capacity was likely exceeded at doses causing cancer in the mouse small intestine, and indicate that physiologically-based toxicokinetic (PBTK) models are necessary to account for competing kinetic rates in extrapolating target tissue dose for the purpose of risk assessment. If extracellular CrVI reductive capacity is exceeded at high drinking water concentrations such as those inducing cancer of the small intestine in NTP (2008), increased tissue uptake would be anticipated compared to lower doses (Thompson et al., 2011b). In other words, dose-dependent changes in the fraction of dose absorbed would be expected at doses which exceed stomach/GI extracellular CrVI reductive capacity compared to those that do not, with a higher dose fraction absorbed at doses exceeding reductive capacity.

In this study, tissue concentration data collected at various doses as part of the CrVI MOA research project (including some doses lower than those used in NTP, 2008) are evaluated to:

(1) quantify differences in the dose fraction absorbed at relevant doses; and
(2) derive factors based on dose-dependent changes in target tissue absorption that may be used to adjust the draft oral slope factor (SFo) to be more predictive of risk at lower, more environmentally-relevant doses.

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Table 1
Total chromium target tissue concentrations in B6C3F1 mice.[a]

Drinking water concentration (mg SDD/L)	Dose (mg Cr/kg-day)	Body weight[b] (g)	Total daily dose[c] (mg Cr/day)	Duodenum tissue concentration (mean mg Cr/kg tissue)	±SD	95% UCL[d] (mg Cr/kg tissue)	95% LCL[e] (mg Cr/kg tissue)	Jejunum tissue concentration (mean mg Cr/kg tissue)	±SD	95% UCL (mg Cr/kg tissue)	95% LCL (mg Cr/kg tissue)	Ileum tissue concentration (mean mg Cr/kg tissue)	±SD	95% UCL (mg Cr/kg tissue)	95% LCL (mg Cr/kg tissue)
0	0	25.8	0	0.017	0.007	0.022	0.012	0.046	0.044	0.078	0.014	0.020	0.01	0.027	0.013
0.3[f]	0.024	26.4	0.001	0.056	0.015	0.067	0.045	0.034	0.021	0.049	0.019	0.014	0.000	0.014	0.014
4	0.32	25.9	0.008	1.5	0.27	1.7	1.3	0.11	0.052	0.15	0.07	0.042	0.03	0.066	0.018
14	1.1	26.3	0.029	***7.3***	0.78	7.9	6.7	0.33	0.29	0.54	0.12	0.13	0.03	0.15	0.11
60	4.6	25.3	0.116	***33.5***	5.0	37.2	29.8	***4.7***	3.3	7.1	2.3	***0.92***	1.0	1.66	0.18
170	11.6	24.9	0.289	***42.4***	12.4	51.5	33.3	***21.6***	14.8	32.5	10.7	***1.8***	1.1	2.6	1.0
520	30.9	23.3	0.720	***60.9***	14.1	71.3	50.5	***13.9***	6.9	19.0	8.8	***2.3***	0.86	2.9	1.7

[a] Drinking water and tissue data taken from Table 3 of Kirman et al. (2012), who reported ***bold italicized*** values as significantly different than controls ($p < 0.05$).
[b] Body weight data from Table S2 of Thompson et al. (2011b).
[c] Calculated as mg Cr/kg-day × body weight in kilograms.
[d] 95%UCL = mean + (1.645 × SE) where SE = SD/n^0.5 and $n = 5$.
[e] 95%LCL = mean − (1.645 × SE) where SE = SD/n^0.5 and $n = 5$.
[f] Corresponds to the federal MCL of 0.1 mg Cr/L; MW of Cr_2/MW of SDD ≈ 104/298 ≈ 0.35 as conversion factor to convert SDD concentrations to Cr.

Table 2
Added chromium target tissue concentrations in B6C3F1 mice.[a]

Drinking water dose (mg Cr/kg-day)	Body weight[b](g)	Total daily dose[c] (mg Cr/day)	Duodenum tissue concentration (mean added mg Cr/kg tissue)	±SD	95% UCL[d] (added mg Cr/kg tissue)	95% LCL[e] (added mg Cr/kg tissue)	Jejunum tissue concentration (mean added mg Cr/kg tissue)	±SD	95% UCL (added mg Cr/kg tissue)	95% LCL (added mg Cr/kg tissue)	Ileum tissue concentration (mean added mg Cr/kg tissue)	±SD	95% UCL (added mg Cr/kg tissue)	95% LCL (added mg Cr/kg tissue)
0.024	26.4	0.001	0.039	0.015	0.050	0.028	0	0.021	0	0	0	0.000	0	0
0.32	25.9	0.008	1.5	0.3	1.7	1.3	0.068	0.052	5.78E−05	1.62E−05	0.021	0.033	0.045	−0.003
1.1	26.3	0.029	7.2	0.8	7.8	6.6	0.28	0.29	2.72E−04	3.68E−05	0.11	0.03	0.13	0.09
4.6	25.3	0.116	33.5	5.0	37.2	29.8	4.7	3.3	3.79E−03	1.21E−03	0.9	1.0	1.6	0.16
11.6	24.9	0.289	42.4	12.4	51.5	33.3	21.5	14.8	1.69E−02	5.55E−03	1.8	1.1	2.6	1.0
30.9	23.3	0.720	60.9	14.1	71.3	50.5	13.8	6.9	9.24E−03	4.27E−03	2.3	0.9	3.0	1.6

[a] Drinking water doses and added Cr (over background) tissue data taken from Table 8 of Kirman et al. (2012) with background shown as zero added.
[b] Body weight data from Table S2 of Thompson et al. (2011b).
[c] Calculated as mg Cr/kg-day × body weight in kilograms.
[d] 95%UCL = mean + (1.645 × SE) where SE = SD/n^0.5 and $n = 5$.
[e] 95%LCL = mean − (1.645 × SE) where SE = SD/n^0.5 and $n = 5$.