



California's Public Health Goal for Hexavalent Chromium (2011)

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Overview

- Background
- History of hexavalent chromium (Cr VI) PHG and MCL
- Derivation of health protective concentration for noncancer effects
- Derivation of health protective concentration for cancer

California Safe Drinking Water Act of 1996

- Also known as the Calderon-Sher Safe Drinking Water Act of 1996
- Requires OEHHA to develop public health goals based exclusively on the protection of public health and provides special consideration for infants, children, pregnant women and their fetuses, and other sensitive subpopulations
- Requires the State Water Resources Control Board to develop Maximum Contaminant Levels (MCLs) as close to the PHG as is technologically and economically feasible

Public Health Goal

- Concentration of contaminant that provides protection against any known cancer and noncancer health effects associated with exposure to the chemical in question
 - For carcinogens, the PHG is established at a “one-in-one-million” risk level
 - For noncarcinogens, the PHG is set at a level that is not expected to cause any toxic effects, including birth defects and chronic illness
- For contaminants associated with both cancer and noncancer health effects, a health protective level will be established for both endpoints and the PHG will be set at the lower of the two levels

Chromium Toxicology Evaluation

- 1999: OEHHA establishes a PHG of 2.5 parts per billion (ppb) for total chromium, based on limited data on the carcinogenic effects of Cr VI in drinking water
- 2001: OEHHA withdraws total chromium PHG because of questions about the study used for developing the PHG
- 2000 and 2001: OEHHA and others petition NTP to study the carcinogenicity of Cr VI in drinking water; study is published in 2008
- 2001: California legislation requires a Cr VI MCL be established by 2004
- 2008 and 2010: External scientific peer review of draft Cr VI PHG
- 2009 and 2010: OEHHA releases draft Cr VI PHG for public comment
- 2011: OEHHA finalizes Cr VI PHG based on cancer by the oral route

Chromium Regulation in California

- 1977: California adopts US EPA's MCL of 50 ppb for total chromium
- 1991: US EPA raises the federal MCL to 100 ppb for total chromium; California retains the MCL of 50 ppb
- 2001: Senate Bill 351 requiring the adoption of a Cr VI MCL by 2004 is signed into law
- 2014: California MCL of 10 ppb for Cr VI is adopted
- 2017: Superior Court of Sacramento County issues a judgment to rescind the 2014 MCL because the MCL evaluation "failed to properly consider the economic feasibility of complying with the MCL."
- The science supporting the PHG and MCL was not challenged
- The MCL of 50 ppb for total chromium remains in place until a new MCL is adopted

Noncancer Critical Study

- NTP (2008): sodium dichromate dihydrate in drinking water for 2 years
- F344/N rats and B6C3F1 mice (50/sex/group)
- Male rats: 0, 0.2, 0.8, 2.1, or 5.9 mg/kg-day Cr VI
- Female rats: 0, 0.2, 0.9, 2.4, or 7.0 mg/kg-day Cr VI
- Male mice: 0, 0.38, 0.9, 2.4, or 5.9 mg/kg-day Cr VI
- Female mice: 0, 0.38, 1.4, 3.1, or 8.7 mg/kg-day Cr VI
- Critical effect: hepatotoxicity (chronic inflammation, fatty changes) in female rats
- LOAEL = 0.2 mg/kg-day

Noncancer Equation

$$C = \frac{ADD \times RSC}{DWI} = \text{mg/L}$$

where,

ADD = acceptable daily dose (point of departure/total uncertainty factor);

RSC = relative source contribution (proportion of exposure from drinking water;

DWI = daily water intake (L/day)

Health Protective Concentration for Noncancer Effects

$$\text{ADD} = \frac{0.2 \text{ mg/kg-day}}{1,000} = 0.0002 \text{ mg/kg-day}$$

(UFs: 10 for interspecies extrapolation, 10 intraspecies variability, 10 for LOAEL to NOAEL extrapolation)

$$C = \frac{0.0002 \text{ mg/kg-day} \times 0.8}{0.067 \text{ L/kg-day}} = 0.002 \text{ mg/L or 2 ppb}$$

(A 95th percentile water intake rate of 0.067 L/kg-day for a child 0 to <11 years of age is used)

Critical Study for Cancer

Tumors of the Small Intestine^a in Mice Exposed to Cr VI in Drinking Water for Two Years (NTP, 2008)

Tumor Type	Hexavalent Chromium Concentration (mg/kg-day)				
	Male Mice				
	0	0.38	0.9	2.4	5.9
Adenomas or Carcinomas	1/49 ^b	3/49	2/49	7/50*	20/48**
	Female Mice				
	0	0.38	1.4	3.1	8.7
Adenomas or Carcinomas	1/44	1/45	4/47	17/45**	22/49**

^a Includes duodenum, jejunum, and ileum

^b Number of animals with tumors/number of animals at risk (alive at the time of the first occurrence of tumor, day 451, and if tissue was not missing)

*, ** Statistically significant (p<0.05, p<0.0001) Fisher's Exact Test

Cancer Slope Factor Derivation

- Analysis of in vivo genotoxicity studies support a genotoxic/mutagenic mode of action (MOA) for Cr VI carcinogenicity
- Genotoxic effects in distant tissues (e.g., bone marrow, liver, brain) have been observed in rodents chronically administered Cr VI by gavage at doses (1-2.5 mg/kg-day) not likely to overwhelm the reductive capacities of the stomach, intestines, and blood
- OEHHA's standard approach for carcinogens operating via a genotoxic or mutagenic MOA, consistent with US EPA's *Guidelines for Carcinogen Risk Assessment*, is to apply a linearized multistage model to derive a cancer slope factor

Cancer Slope Factor Derivation

Rationale for not considering a cytotoxicity/regenerative hyperplasia MOA in CSF derivation:

Endpoint (Duodenum)	0 mg/kg-d	0.4 mg/kg-d	0.9 mg/kg-d	2.4 mg/kg-d	5.9 mg/kg-d
Diffuse Hyperplasia	0/50	11/50 (2.0)	18/50 (1.6)	42/50 (2.1)	32/50 (2.1)
Adenomas/Carcinomas	1/49	3/49	2/49	7/50	20/48

Diffuse hyperplasia reported by Stout et al. (2009);

Mean severity shown in parentheses: 1, minimal; 2, mild; 3, moderate; 4, marked

- Incidence and severity of hyperplasia are not concordant with tumor incidence
- 10/32 treated male mice with neoplasms had no hyperplasia in any small intestinal segment
- Rats developed oral tumors in the absence of cytotoxicity/hyperplasia
- If more than one MOA is viable, OEHHA would default to the MOA that results in the more health protective CSF

Other Toxicity Considerations

- OEHHA's evaluation of a Chinese cancer study in humans drinking Cr VI contaminated water concluded that the data are consistent with increased stomach cancer risk in people (*Epidemiology* 2008; 19(1):12-23)
 - [A later OEHHA meta-analysis of studies on occupationally inhaled Cr VI (*Occup Environ Med* 2015; 72:151-159) similarly found elevated summary relative risks for stomach cancer]
- Linos et al. (*Environ Health* 2011; 10:50) examined the relationship between Cr VI in drinking water and organ specific cancer mortality in Greece and found a statistically significant increase in primary liver cancer mortality in exposed populations

Dose-Response Analysis

- US EPA's BMDS Multistage-Cancer model estimated the 95% lower confidence limit of the dose associated with a 10% incidence of tumors (BMDL₁₀) as 1.2 mg/kg-day
- This was converted to a human dose based on allometric scaling of body weight to the ³/₄ power (time-averaged body weight of male mouse from NTP (2008) is 0.050 kg and human body weight is 70 kg):
$$1.2 \text{ mg/kg-day}_{\text{mouse}} \times (0.050 \text{ kg}/70 \text{ kg})^{1/4} = 0.196 \text{ mg/kg-day}_{\text{human}}$$
- CSF = tumor response/BMDL₁₀ = 0.1/0.196 = 0.5 (mg/kg-day)⁻¹

Cancer Equation

$$C = \frac{R}{P_o \times (\sum_j [ASF_j \times d_j \times cons^{i/o}_j])}$$

where:

R = a default risk level of one-in-one-million, or 10^{-6} ;

P_o = oral cancer potency, in mg/kg-day;

\sum_j = sum of contributions at each age range;

ASF_j = age sensitivity factors for the 3rd trimester + infants, children and adults;

d_j = duration of exposure factors for the 3rd trimester + infants, children and adult life stages;

$cons^{i/o}_j$ = equivalent water exposure values for each age range

Health Protective Concentrations

- **Cancer**
 - **0.02 ppb**
 - Cancer in mouse small intestine
 - Oral potency of 0.5 (mg/kg-day)⁻¹
- **Noncancer**
 - **2 ppb**
 - Liver damage (chronic inflammation and fatty changes) in female rats
 - LOAEL of 0.2 mg/kg-day

Cancer endpoint is more protective