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Proposed Health-Protective Concentration for the Noncancer Effects of Hexavalent Chromium in Drinking Water

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Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Prepared by

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PREFACE

Public Health Goal (PHG) technical support documents provide information on health effects from contaminants in California drinking water. PHGs are developed for chemical contaminants based on the best available data in the scientific literature and using the most current principles, practices, and methods used by public health professionals. These documents and the analyses contained therein provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

Under the California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365), the Office of Environmental Health Hazard Assessment (OEHHA) develops PHGs for drinking water contaminants in California based exclusively on public health considerations. OEHHA periodically reviews PHGs and revises them as necessary based on the occurrence of the respective chemicals in California drinking water supplies and the availability of new scientific data. In October 2016, OEHHA initiated the PHG update for Cr(VI), and provided interested parties the opportunity to submit information for OEHHA to consider. A second data call-in was announced in March 2023.

If a chemical has been identified as a human or animal carcinogen, health-protective water concentrations are determined for both cancer and noncancer effects and the lowest value is selected as the PHG. This document presents the proposed updated noncancer health-protective concentration for hexavalent chromium, a known human carcinogen. A separate document for the derivation of a health-protective concentration based on cancer will be released at a later date. Once cancer and noncancer health- protective concentrations are determined, the lowest value will be selected as the PHG.

PHGs published by OEHHA are for use by the State Water Resources Control Board (SWRCB) in establishing primary drinking water standards (California Maximum Contaminant Levels, or CA MCLs). Whereas PHGs are based solely on scientific and public health considerations, MCLs adopted by SWRCB consider economic factors and technological feasibility. State law requires that MCLs be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. Thus, a PHG represents a health-protective level for a contaminant that SWRCB and California's public water systems aim to achieve if it is feasible to do so. However, a PHG is not a boundary line between a "safe" and "unsafe" level of a contaminant, and drinking water can still be considered acceptable for public consumption even if it contains contaminants at levels exceeding the PHG.

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SUMMARY

This draft document presents an update of the noncancer health-protective concentration (HPC) for hexavalent chromium, or Cr(VI). For carcinogens, OEHHA derives HPCs for both cancer and noncancer effects, and the lower of the two values is selected as the PHG. The proposed updated HPC for noncancer effects is 5 parts per billion (ppb) and is based on chronic liver toxicity in female rats exposed to Cr(VI) in drinking water for two years in a study by the National Toxicology Program (NTP, 2008a). The updated dose- response assessment leading to this value includes toxicokinetic adjustments and benchmark dose modeling. Updated drinking water intake rates are also incorporated into the derivation of the draft noncancer HPC. This draft HPC updates the noncancer HPC of 2 ppb published in 2011, which was also based on chronic liver toxicity in female rats in the NTP study (OEHHA, 2011).

INTRODUCTION

The Office of Environmental Health Hazard Assessment (OEHHA) performs health risk assessments and develops Public Health Goals (PHGs) for drinking water contaminants in California. A PHG is the concentration of a contaminant in drinking water that is estimated to pose no significant health risk to individuals consuming the water on a daily basis over a lifetime. In 2011, OEHHA established a PHG of 0.02 ppb for Cr(VI) based on tumors of the small intestine in male mice and a noncancer HPC of 2 ppb based on liver toxicity in female rats (OEHHA, 2011). This document presents an update of the noncancer HPC and incorporates a thorough review of the current scientific literature and the most current risk assessment practices and methods, such as use of physiologically based pharmacokinetic (PBPK) modeling and benchmark dose modeling.

Chromium (Chemical Abstracts Service Registry Number 18540-29-9) is a heavy metal that occurs naturally throughout the environment. Hexavalent chromium has been detected in over 2,000 California public drinking water supply wells within the last three years, and the highest level detected was 240 ppb.[1]

Cr(VI) is reduced to the less soluble trivalent form, Cr(III), in the stomach, which is less toxic than Cr(VI). Cr(VI) that escapes reduction is rapidly absorbed in the small intestine, leading to toxicity. Species differences in the reduction of Cr(VI) in the stomach have been studied and toxicokinetic models that describe this process have been developed for multiple species. This update of the noncancer HPC for Cr(VI) incorporates the use of these models to reduce the uncertainty of deriving the HPC from animal studies.

[1] Data accessed with GeoTracker GAMA, July 11, 2023: https://gamagroundwater.waterboards.ca.gov/gama/gamamap/public/

LITERATURE SEARCH

Human Studies

The primary goal of the epidemiology review of non-cancer endpoints was to identify published human epidemiologic studies that could potentially be used to improve the dose-response analyses for noncancer endpoints that were conducted for OEHHA's 2011 Cr(VI) PHG (OEHHA, 2011). To accomplish this, an extensive literature search was performed to identify all human epidemiologic studies on the toxic effects of Cr(VI) published since OEHHA's last PHG (i.e., since January 1, 2011). Sources for this literature search included PubMed, the Web of Science, bibliographies of all included research articles, reference lists and publications provided during the 2016 and 2023 Cr(VI) data call-ins, and relevant reviews and risk assessments. All articles published from January 1, 2011 to April 4, 2023 were included in the search. Searches were also performed after April 23, 2023 but only those studies identified in these searches that materially affected the conclusions of this review will be discussed here. Detailed descriptions of the search strategy and inclusion criteria for screening studies can be found in Appendix 1.

Animal Studies

OEHHA evaluated studies published from the 2011 finalization of the Cr(VI) PHG to the present. OEHHA utilized references identified by US Environmental Protection Agency's (EPA's) systematic review protocol for Cr(VI) (US EPA, 2022) as a starting point to identify relevant animal toxicity studies for this update. The systematic review protocol by US EPA (2022) was a comprehensive search that was approved by the Science Advisory Board in 2019 and updated in 2022. US EPA's references were collected from database searches conducted yearly from 2013 up to August 2022. OEHHA also conducted two data call-in periods in 2016 and 2023 to solicit from the public any data that may be of relevance to the PHG update. Two independent reviewers conducted full-text screening and evaluation of studies identified as relevant to the assessment of the noncancer effects of Cr(VI).

METHODOLOGY

Development of an updated PHG for a chemical in drinking water entails a two-part process:

1. Toxicological evaluation of human and animal studies

The toxicological evaluation of a chemical starts with a thorough review of the PHG being updated and its toxicological basis, as well as a review of the relevant scientific literature published subsequent to its issuance. Relevant studies and toxicity endpoints are identified. The data and study findings are critically evaluated, and the quality of each study is assessed. In evaluating toxicity studies, consideration is given to the potential molecular and cellular mechanisms by which toxicity is induced (modes of action), corroborating data from different studies, and the relevance of toxicity endpoints in animal studies to humans.

2. PHG derivation

After a review of the toxicity studies of sufficient quality, the most sensitive endpoints from studies determined to be relevant to human health are selected, and analyses of the dose-response relationships are performed. The adverse effect or a physiological change that leads to an adverse effect that occurs at the lowest dose is selected as the critical effect from which the PHG is derived.

If a chemical has been identified as a human or animal carcinogen, HPCs are determined for both cancer and noncancer endpoints and the lowest value is selected as the PHG.

This draft document presents a proposed updated HPC for noncancer effects only; an updated HPC for cancer effects and the PHG for Cr(VI) will be addressed in a future draft document that will be subject to the notice and comment process.

Deriving Health-Protective Concentrations for Noncancer Effects

Calculation of an HPC for noncancer effects involves a four-step approach: determination of the point of departure (POD), estimation of an acceptable daily dose (ADD), determination of the relative source contribution (RSC) and calculation of an HPC.

Point of Departure (POD)

The POD is the dose of a chemical (in units of milligrams per kilogram of body weight per day, mg/kg-day) from a study in animals or humans that is used as a starting point for calculation of the ADD. The POD is typically determined by fitting a mathematical model to the dose-response data. OEHHA generally uses the publicly available Benchmark Dose Software version 3.3 (BMDS) program developed and maintained by the US EPA (US EPA; https://www.epa.gov/bmds). BMDS fits mathematical models to the data and determines the dose (benchmark dose or BMD) that corresponds to a pre-determined level of response (benchmark response or BMR). The BMR is typically set at a response level of 5% extra risk for dichotomous data (OEHHA, 2008). For continuous data, a BMR of one standard deviation from the control mean is typically used when there are no data to indicate what level of response is biologically significant (US EPA, 2012). To account for the uncertainty in a BMD estimate, the 95% lower confidence limit of the BMD, called the BMDL (L stands for the lower confidence limit) is calculated. For PHG development, OEHHA uses the BMDL as the POD for the calculation of a health-protective drinking water concentration when the data are amenable to BMD modeling.

When data are not amenable to BMD modeling (BMDS output is “questionable model fit”), OEHHA uses the no-observed-adverse-effect level or concentration (NOAEL or NOAEC), or lowest-observed-adverse-effect level or concentration (LOAEL or LOAEC)

as the POD.

Model selection criteria when comparing outputs of different models for the same endpoint/dataset in BMDS are: the lowest Akaike's information criterion (AIC), goodness of fit p-value ≥0.05, scaled residual at the dose closest to the BMD estimate ≤ the absolute value of 2, and visual inspection of the dose-response curve. When using BMD modeling, the BMDL of the selected model is the POD.

Application of BMD modeling for noncancer effects mitigates some of the limitations of the NOAEL/LOAEL approach, including:

- dependence on dose spacing and sample size;
- inability to account for uncertainty and variability in the experimental results;
- the need to use an additional uncertainty factor when a NOAEL cannot be determined in a study;
- inability to account for the shape of the dose-response curve; and difficulty in quantitatively comparing studies with distinct dosing designs.

Additional consideration supporting the BMD approach as the preferred method for identifying a POD is that BMD modeling incorporates and conveys more information than the NOAEL/LOAEL approach. For instance, a BMD (or BMDL) can be estimated even when all doses in a study are associated with a significant adverse response (i.e., when there is no NOAEL). Furthermore, the BMD and BMDL are less influenced by study design, as they are not constrained to be one of the experimental doses, unlike NOAELs and LOAELs (US EPA, 2012).

Acceptable Daily Dose (ADD)

The ADD is the estimated maximum average daily dose of a chemical (in milligrams per kilogram of body weight per day, mg/kg-day) that can be consumed by a human for a lifetime (assumed to be 70 years) without adverse effects. This is similar to the term "reference dose" used by US EPA. To determine the ADD, the POD is adjusted by factors that account for uncertainty and variability in the risk assessment, such as differences between animals and humans, and differences among humans in response to a chemical exposure. Additionally, factors may be applied to extrapolate from subchronic to chronic exposure duration, from LOAEL to NOAEL when a NOAEL or BMDL is not available, and also when the toxicity database is incomplete. These factors combined are referred to as the composite uncertainty factor (UFc).

Uncertainty and Variability Factors (UF)

UFs are applied to a dataset when there is insufficient data to support the use of chemical-specific and species-specific extrapolation factors. Default uncertainty factors for ADD derivation are shown in Appendix 4. These default factors are applied unless there is an alternative method to quantitatively address uncertainties in the standard

approach.

When developing health-protective levels for noncancer effects based on animal toxicity studies, OEHHA generally applies a composite UF of 300 (OEHHA, 2008).

The composite UF is comprised of the following UFs:

- 10 for interspecies extrapolation, accounting for possible differences in the way laboratory animals and humans respond to the chemical, consisting of:
  - √10 for pharmacodynamics
  - √10 for pharmacokinetics
- 30 for intraspecies variability, which accounts for some human subpopulations, such as children and the elderly, possibly being more sensitive to the chemical than the general population, consisting of:
  - √10 for pharmacodynamics
  - 10 for pharmacokinetics.

There are instances when OEHHA deviates from the use of the default composite uncertainty factor, for example, if a PBPK model is available for interspecies scaling. In this case, the interspecies extrapolation uncertainty factor for pharmacokinetics would be reduced from √10 to 1 (Appendix 4). OEHHA used PBPK modeling for Cr(VI) and a detailed description of why and how OEHHA used a PBPK model is provided in the Toxicokinetics section of this document.

The ADD is calculated using the following equation:

$$ADD = POD \div \text{composite UF}.$$

Daily Water Intake

To calculate a health-protective concentration for a chemical, the ADD is converted to a concentration in drinking water that accounts for the total exposure to the chemical that people receive from using tap water. It includes intake from ingestion as well as inhalation and dermal contact with the chemical in tap water from household uses (e.g., drinking, cooking, bathing, and showering). Inhalation exposure can take place when the chemical volatilizes out of the water during showering. Dermal absorption of the chemical can occur during bathing and other household uses of tap water.

For oral intake rates, the PHG program uses age-specific water ingestion estimates (OEHHA, 2012) derived from a nationwide survey of food and beverage intake from approximately 20,000 people (US Department of Agriculture's Continuing Survey of Food Intake of Individuals 1994-1996, 1998 dataset). These age-specific intake rates are normalized to body weight and expressed as liters per kilogram body weight per day (L/kg-day). Updated water ingestion rates indicate that drinking water ingestion per unit body weight is higher in infants than in adults. These refined estimates replace previous ingestion rates of 2 liters per day (L/day) for adults and 1 L/day for a 10 kg child used in

older PHGs. For noncancer endpoints, the time-weighted average daily water ingestion rate for a 70-year lifetime is typically used for the general population. However, if there is a particularly sensitive age group or other subgroup that comprises a meaningful portion of the general population, the high-end estimates of the age-specific water ingestion rate for this subgroup will be used in the PHG calculations in place of a life-time average value (OEHHA, 2012). OEHHA is mandated by Health and Safety Code Section 116365.2 to give special consideration to sensitive subgroups, such as children and infants, who may be at greater risk of adverse health effects due to their disproportionately high exposure to contaminants in comparison to the general population and greater susceptibility to contaminants.

Relative Source Contribution

The relative source contribution (RSC) is the proportion of exposures to a chemical attributed to tap water, as part of the total exposure from all sources (including food and air). The RSC values typically range from 20% to 80% (expressed as 0.20 to 0.80) and are determined based on available exposure data. For certain PHGs, the RSC can be as high as 1.0 (tap water is the only source of the chemical) when it is deemed appropriate. OEHHA uses this approach to ensure that the PHG identifies a concentration of a contaminant in tap water that is health-protective while considering exposures from all other sources.

Derivation of the Health-Protective Concentration (HPC)

Following the determination of the ADD, the health-protective concentration (HPC, in milligrams per liter, mg/L or in micrograms per liter, µg/L) in drinking water is derived by incorporating the drinking water intake (DWI) and RSC of the chemical:

$$HPC = (ADD \times RSC) \div DWI.$$

BASIS FOR THE 2011 HPC FOR NONCANCER EFFECTS

In 2011, OEHHA developed a PHG of 0.02 ppb for Cr(VI) in drinking water, based on cancer endpoints from drinking water studies in rats and mice conducted by the National Toxicity Program (NTP, 2008a). The noncancer HPC of 2 ppb was developed for noncancer effects based on chronic inflammation and fatty changes in the liver of female rats in the same study (NTP, 2008a). Toxicokinetic adjustments were not made in the derivation of the PHG or HPC. The PBPK models used for toxicokinetic adjustments in the present document were not available when the original PHG was being developed in 2011.

In the NTP (2008a) studies, male and female F344 rats and B6C3F1 mice (50/dose/sex) were given sodium dichromate dihydrate in drinking water at concentrations ranging from 0 to 516 mg/L for male rats, female rats, and female mice, and 0 to 257.4 mg/L for male mice for 2 years. The most sensitive noncancer endpoints from these studies included chronic inflammation and fatty changes in the liver of female rats.

The health-protective concentration of 2 ppb for noncancer effects was derived using a LOAEL of 0.2 mg/kg-day based on the liver effects in female rats. The derivation utilized: a composite UF of 1,000 (10 for extrapolation from rats to humans, 10 for intraspecies variability, and 10 for LOAEL-to-NOAEL extrapolation); an RSC of 0.8; and a daily drinking water intake of 0.067 L/kg-day (the upper 95th percentile water intake for children ages 0 to 11 years).

TOXICOKINETICS

The reduction of Cr(VI) to its less toxic form Cr(III) occurs primarily in the stomach in humans and animals. The extent to which Cr(VI) is reduced in the stomach determines the amount of Cr(VI) that is then absorbed in the small intestine. The small intestine, which has a higher pH than the stomach, has a lower capacity to reduce Cr(VI). Species differences in the reduction rate in the stomach therefore affect the absorption of Cr(VI) in the small intestine and how animal data are extrapolated to humans. In the previous PHG, OEHHA used uncertainty factors to account for interspecies differences. Since then, several physiologically-based pharmacokinetic (PBPK) models have been developed to estimate Cr(VI) reduction in the stomach (Kirman et al., 2013; Kirman et al., 2012; Kirman et al., 2016; Kirman et al., 2017; Proctor et al., 2012; Sasso and Schlosser, 2015; Schlosser and Sasso, 2014).

Toxicokinetic studies and PBPK models

Proctor et al. (2012) conducted ex vivo studies to determine the rate of reduction of Cr(VI) in rodent stomach contents. Stomach contents from fed F344/N Fischer rats and B6C3F1 mice were collected and were spiked with sodium dichromate dihydrate. The amount of Cr(VI) and Cr(III) was measured at several timepoints within one (1) hour after spiking, using speciated isotope dilution mass spectroscopy (SIDS), which allows for the identification of the different forms of chromium. Proctor et al. (2012) determined that Cr(VI) reduction followed mixed second-order kinetics. The rate of reduction of Cr(VI) is dependent on the concentration of Cr(VI) and the concentration of the reducing agent. Modeling Cr(VI) concentrations over time yielded second-order rate constants of 0.2 L/mg-h in mice and 0.3 L/mg-h in rats.

Kirman et al. (2012) developed a multi-compartment rodent PBPK model in rats and mice based on reduction data from Proctor et al. (2012), as well as time-course data investigating total chromium concentration in tissues of rodents exposed to Cr(VI) in drinking water for 90 days. The model included multiple compartments for bone, kidney, gastrointestinal (GI) tract, liver, plasma, red blood cells and other (for the remaining tissues). The GI compartment included oral mucosa, stomach, duodenum, jejunum, ilium, and large intestine. The model was optimized using tissue total chromium concentration data from chronic oral studies with Cr(VI) and Cr(III) by NTP (2008a); (2008b) (rats and mice) and Mackenzie et al. (1985) (rats), subchronic oral studies with Cr(VI) by Thomann et al. (1994) (rats) and Kargacin et al. (1993) (rats and mice) and ex vivo data from Proctor et al. (2012).

A limitation of the toxicokinetic data from these studies is the inability to speciate

between Cr(III) and Cr(VI) in tissues because only total chromium was measured. Therefore, fitting and validation of the model was performed with total chromium concentration data. Model fit to tissue data from NTP (2008a) showed that the model prediction of concentrations of total chromium in erythrocytes and urine of mice matched well. In rats, the model predicted concentrations of total chromium in the liver, urine, and kidney reasonably. However, the model overpredicted total chromium concentrations in the kidney and plasma of mice and in the plasma of rats by close to an order of magnitude. The model predictions for tissue total chromium concentrations were validated using data from a 21-day oral study by NTP (2007). Results showed that the model overpredicted total chromium concentrations in the kidney of mice, but predicted total chromium concentrations in blood were similar to measured values in rats and mice. Model predictions for other tissues such as liver, urine, and erythrocytes were not presented. Model predictions of total chromium in the GI tract were not presented in model development and validation. Using the model, the flux of Cr(VI) leaving the stomach lumen was extrapolated and used as an internal dose metric for dose-response analysis. Sensitivity analysis showed that stomach pH, small intestine section volume and stomach lumen transit rate were sensitive parameters that affected model predictions of the flux of Cr(VI) leaving the stomach in rodents.

Kirman et al. (2013) described a multi-compartment PBPK model for oral exposure to Cr(VI) in humans. The model structure is similar to the rodent model by Kirman et al. (2012) with slight modifications, such as grouping the compartments for duodenum, jejunum and ileum into a single small intestine compartment. Absorption in the model was treated as a first order process, unlike in rodents, where absorption was considered a saturable process. This is because human studies were conducted at lower doses than rodent studies. Serum and urine data from several human studies (Anderson and Kozlovsky, 1985; Anderson et al., 1983; Anderson et al., 1982; Gargas et al., 1994; Kerger et al., 1996; Lukaski et al., 2007; Mohamedshah et al., 1998; Paustenbach et al., 1996; Rubin et al., 1998; Volpe et al., 2001) were used for model optimization.

Ex vivo studies were conducted using fasted human stomach fluids to determine the reduction of Cr(VI) in humans and were used in model development (Kirman et al., 2013). Samples from patients (n = 2 or 3) not on proton pump inhibitors were pooled according to various stomach pHs (pH ~1, 2, or 4) and patients on proton pump inhibitors were grouped in a pool with a pH of ~7. Reduction of Cr(VI) in the fasted stomach was found to be dependent on pH, with higher reduction rates associated with lower pH. Similar to ex vivo studies in rodents by Proctor et al. (2012), reduction in fasted human gastric fluid showed mixed second order reaction kinetics. For use in the model, the reducing agents in gastric fluid were grouped together as a single pool of reducing equivalents.

The PBPK model was validated using data from Finley et al. (1997). Model predictions, compared with data from Finley et al. (1997), showed that predicted plasma total chromium concentrations were lower than observed data. Performance of the model in predicting urine chromium concentrations was not presented. Similar to the rodent model, the flux of Cr(VI) leaving the stomach lumen can be extrapolated using the model. Sensitivity analysis determined that stomach pH, small intestine section volume

and stomach lumen transit rate were sensitive parameters that affected model predictions of the flux of Cr(VI) leaving the stomach in humans.

After evaluating the rodent (Kirman et al, 2012) and human (Kirman et al., 2013) models, OEHHA noted some weaknesses that would preclude the use of these models for interspecies extrapolation. Firstly, the human model was optimized using serum and urine levels of total chromium in various human studies. The model includes several estimated parameters contributing to high uncertainty in the model for predicting levels of Cr(VI) in humans. Also, the accuracy of the model to predict flux in the small intestine is questionable because the model assumes the small intestine has a uniform pocket of fluid after water ingestion; however, the small intestine contains multiple fluid pockets that vary with time and gastric emptying (Mudie et al., 2014). Thus, this model (Kirman et al., 2013) may not accurately represent Cr(VI) kinetics in humans. Furthermore, although the authors optimized their model using data for various stomach pHs in the fasted state, they did not include stomach pH as a variable in the fed state, a source of uncertainty the authors acknowledge because the presence of food can affect the reduction capacity in the stomach (De Flora et al., 2016).

Sasso and Schlosser (Schlosser and Sasso, 2014; Sasso and Schlosser, 2015) revised a component of the models by Kirman et al. (2012; 2013) to improve the model fit of ex vivo data from Proctor et al. (2012). While the models by Kirman et al. (2012; 2013) are whole-body models that included multiple compartments, the models by Sasso and Schlosser only included the gastric compartment and are structurally similar to the GI compartment in the Kirman et al. (2012; 2013) models. A gastric compartment only model was developed because it is where the majority of Cr(VI) reduction occurs in humans, and differences in reduction kinetics between rodents and humans can contribute to interspecies pharmacokinetic differences (Schlosser and Sasso, 2014).The model was developed using ex vivo reduction data from Proctor et al. (2012) and Kirman et al. (2013) and model predictions were compared against model predictions by Kirman et al. (2013). The model (Schlosser and Sasso, 2014; Sasso and Schlosser, 2015)) assumes multiple reduction pathways (i.e., multiple reducing agent pools) in rats and mice compared to a single pathway in the models by Kirman et al. (2012; 2013).

The assumption of multiple reduction pools is more biologically accurate because there are multiple reducing agents, such as ascorbate, NADH (nicotinamide adenine dinucleotide + hydrogen) and glutathione present in gastric fluid that have different rates of reduction (Proctor et al., 2012). In comparing the use of a single reduction pool versus multiple reduction pools in rodents, the Kirman et al. (2012; 2013) models overestimated internal doses of Cr(VI) because with the single reduction pool assumption, model predictions showed that reduction of Cr(VI) did not occur beyond 60 minutes post-Cr(VI) exposure, contrary to ex vivo data used for model development (Schlosser and Sasso, 2014). The model by Sasso and Schlosser showed continued reduction after 60 minutes, consistent with the ex vivo data, and is relevant when using the model to predict doses from long-term exposure. Insufficient data from human ex vivo experiments by (Proctor et al., 2012) precluded the identification of distinct reduction pools, so human model simulations were run with a single pool. Additionally,

the model by Sasso and Schlosser (Schlosser and Sasso, 2014; Sasso and Schlosser, 2015) took the pH dependence of Cr(VI) reduction in the stomach into account. The updated assumptions provide better fits to the ex vivo reduction data. Model predictions showed that mice were less efficient at reducing Cr(VI) compared to rats and humans. This is consistent with data from Kirman et al. (2012) and the NTP studies (NTP, 2008a, 2008b; Collins et al., 2010).

To test the model for use in risk assessment, Sasso and Schlosser calculated human equivalent doses (HEDs) and compared them with HEDs calculated using the Kirman et al. (2012; 2013) models (Thompson et al., 2012; Thompson et al., 2013). The internal dose metric used to calculate the HED was pyloric flux, which is the mass of unreduced Cr(VI) transferred from the stomach to the small intestine, normalized to the volume of the small intestine. When using the Sasso and Schlosser gastric component only model, results were comparable to the whole-body Kirman models. The authors state that despite neglecting the kinetics in the small intestine and the rest of the body, the gastric compartment only model was able to show that the Cr(VI) dose in the small intestine is a "function of how effectively the stomach will reduce Cr(VI) to Cr(III)." The gastric only model has fewer parameters compared to the whole-body PBPK model and these parameters are well characterized in rodents and humans. Despite obtaining comparable results, there are still uncertainties in the Sasso and Schlosser model because it only describes species differences in gastric reduction. The model does not take into account differences in clearance or excretion of Cr(VI) and further adjustments would be required to more fully account for species differences between rodents and humans. Furthermore, susceptibility differences, such as stomach pH and life stages (e.g., infants and children), are not captured by the model.

The rodent and human models by Sasso and Schlosser assume that any Cr(VI) not reduced in the stomach will be completely (100%) absorbed in the small intestine. Due to the limited scope that the Sasso and Schlosser model covers, the question remains whether kinetics of Cr(VI) absorption in the small intestine at low, environmentally relevant doses is adequately captured. However, there is no evidence that absorption of chromium becomes less efficient at low doses, thus causing a sub-linear relationship between applied and absorbed dose. Chromate is rapidly absorbed into cells by non-specific anion sulfate transporters independent of concentration (Alexander and Aaseth, 1995). Sulfate, which can compete for binding to these non-specific transporters, is not an efficient inhibitor of chromate uptake. This is illustrated by the lower Km of 1.8 mM for chromate binding by transporters versus the Km of 93 mM for sulfate uptake (Bergeron et al., 2013). Additionally, Collins et al. (2010) analyzed the NTP (2008a) data and showed that the relationship between applied dose and absorbed dose is linear.

Kirman et al. (2016) conducted ex vivo experiments to fill in data gaps from their previous ex vivo studies. New data included reduction kinetics from fed human gastric fluid and from fasted individuals taking proton pump inhibitors. Results from this study showed that in humans, there are three reducing agent pools, similar to the findings of Schlosser and Sasso (2014) in rodents.

Kirman et al. (2017) updated their previous models Kirman et al. (2012; 2013) to better describe gastric reduction and incorporate new ex vivo reduction data by Kirman et al. (2016). Considering the changes Schlosser and Sasso (2014) made to the gastric model, Kirman et al. (2017) incorporated three reducing pools, in which the rate constants are pH dependent. The authors modified the drinking water exposure simulations in rodents from continuous infusion in Kirman et al. (2012) to distinct periods of water ingestion with varying gastric lumen volumes during water intake periods and gastric emptying. The human model was modified to address differences in pH during and between meals (fed versus fasted state). The rodent model was validated using tissue data from NTP (2008a). Predicted total chromium concentrations in erythrocytes, liver, stomach, and kidney were similar to observed concentrations. However, the model overpredicted plasma concentrations of total chromium by an order of magnitude in rats and mice, similar to Kirman et al. (2012). Validation of the human model was not presented. Compared to the Sasso and Schlosser models, the updated Kirman models have approximately 100 parameters, which adds to the uncertainty in the model because of the limited availability of in vivo data to inform the parameters.

A summary of available PBPK models is presented in Table 1.

Table 1. Summary of available PBPK models

Model, Reference	Notes
Rodent model, Kirman et al. (2012)	Describes whole body kinetics of chromium *Strengths* Model takes into account clearance and excretion of chromium, not just reduction Model performance was adequate for describing total chromium concentration in blood of mice and rats in validation studies *Weaknesses* Overpredicts total chromium concentration in kidney of mice Performance in predicting concentrations in liver, erythrocytes and urine is unknown. Concentration in these tissues included in fitting the model, but not used in validation. Performance in predicting concentrations in GI unknown
Human model, Kirman et al. (2013)	Describes whole body kinetics of chromium *Strengths* Model takes into account clearance and excretion of chromium, not just reduction *Weaknesses* Underpredicts total chromium concentrations in plasma Inaccurate representation of Cr(VI) kinetics in the small intestine
Rodent model, Schlosser and Sasso (2014); Sasso and Schlosser (2015)	Describes Cr(VI) gastric reduction *Strengths* Provides better fit to ex vivo Cr(VI) reduction data Reduced uncertainty because less parameters are fitted and parameters are well characterized in rodents *Weaknesses* Only describes reduction kinetics in the stomach

Model, Reference	Notes
Human model, Schlosser and Sasso (2014); Sasso and Schlosser (2015)	Describes Cr(VI) gastric reduction *Strengths* Provides better fit to ex vivo Cr(VI) reduction data Reduced uncertainty because less parameters are fitted and parameters are well characterized in humans *Weaknesses* Only describes reduction kinetics in the stomach
Rodent model, Kirman et al. (2017)	Describes whole body kinetics of chromium *Strengths* Provides better fit to ex vivo Cr(VI) reduction data by including multiple reduction pools and pH dependence Model performance was adequate for describing total chromium concentration in erythrocytes, liver, stomach, and kidney. *Weaknesses* Overpredicts plasma concentrations of total chromium High uncertainty due to large number of parameters
Human model, Kirman et al. (2017)	Describes whole body kinetics of chromium *Strengths* Provides better fit to ex vivo Cr(VI) reduction data *Weaknesses* Unknown how model validation was performed High uncertainty due to large number of parameters

Use of PBPK models in risk assessment

Overall, there are two main methods to address toxicokinetic differences in chromium reduction that are available for use in risk assessment: the whole-body PBPK rodent and human models by Kirman et al. (2013; 2012; 2017); and the gastric compartment only rodent and human models by Sasso and Schlosser (Schlosser and Sasso, 2014; Sasso and Schlosser, 2015). The models have advantages and disadvantages summarized in Table 1 above. Taking this into consideration, OEHHA used the following step-wise toxicokinetic adjustments for dose-response analysis:

1. Using a rodent model by Sasso and Schlosser that is similar to their previously published models (Schlosser and Sasso, 2014; Sasso and Schlosser, 2015; model code in R Statistical Software v4.2.2 was provided by study authors), an internal dose of Cr(VI) was calculated based on the average dose escaping stomach reduction in rodents.

2. The rodent internal dose calculated in the first step was allometrically scaled to derive a human equivalent internal dose. Allometric scaling was done to account for toxicokinetic differences not considered in the models by Sasso and Schlosser.

3. An estimated daily Cr(VI) dose to achieve the human equivalent internal dose calculated in step 2 was derived using the human model by Sasso and Schlosser (Schlosser and Sasso, 2014; Sasso and Schlosser, 2015). Monte Carlo analysis was used in this step to account for interindividual variability. Parameters of this PBPK model include gastric emptying rates for both the fed state (30 minutes; ICRP, 2002; 2006) and the fasted state (15.8 minutes; Mudie et al., 2014). Because the rate of gastric emptying of the different states is included in the model, variability in gastric emptying time is included in the model. Additionally, Monte Carlo analysis takes gastric emptying time into account as all MC simulations assumed lognormal distributions for the fed and fasted parameters with a coefficient of variance of 20% for gastric emptying.

Rationale for use of this approach is listed below:

- The advantage of using this simpler gastric compartment only model is there are fewer parameters than a whole-body model, with comparable accuracy (Sasso and Schlosser, 2015).
- The modified model by Sasso and Schlosser (US EPA, 2022) takes into account fed and fasted states for humans and different physiological parameters obtained from the literature.
- The gastric reduction component of Cr(VI) toxicokinetics is well characterized. Proctor et al. (2012) and Kirman et al. (2013; 2017) specifically conducted experiments to study the reduction of Cr(VI) in the stomach of rodents and humans. Other toxicokinetic studies that investigated the distribution of chromium in tissues cannot differentiate between the hexavalent and trivalent forms of chromium, therefore there is uncertainty in predicting species differences in accumulation of Cr(VI) in target issues.
- Because the modified Sasso and Schlosser model only addresses species differences in gastric reduction, other interspecies differences such as clearance and excretion of Cr(VI) are not taken into account. When there is uncertainty in toxicokinetic differences between species that are not addressed by PBPK models, the use of allometric scaling can be used to account for these differences (US EPA, 2011).

- Sensitivity analyses indicated that variability in stomach pH (mouse gastric model) and increases in pH during feeding (human model) had the greatest impact on the model output (Tables C-12, C-13 in US EPA, 2024). OEHHA used Monte Carlo simulations run at a median pH of 4 and the default pH of 1.3 (with a coefficient of variance of 20%) to evaluate how the variability in these parameters impacted model output. This approach enabled OEHHA to evaluate model outputs for subpopulations with a variety of stomach pH values, although attempts at modeling pH values above approximately 5.25 were unsuccessful.

UPDATED TOXICOLOGICAL REVIEW

Toxicological effects in humans

Study descriptions: The information from each study identified in the detailed reviews of study quality and causal inference are shown in Tables A2.1-6 in Appendix 2. Overall, the numbers of studies meeting the inclusion and exclusion criteria described in Appendix 2 are as follows: 15 studies of noncancer hematologic outcomes, 15 studies of noncancer immunologic outcomes, 3 studies of noncancer GI outcomes, 8 studies of noncancer liver outcomes, 2 studies of reproductive or developmental outcomes, and 30 studies of noncancer respiratory or nasal outcomes. These studies were performed in a variety of different countries and areas, including the US, China, Europe, India, Iran, and elsewhere. A variety of different study designs were used, including retrospective and prospective cohort, case-control, cross-sectional, ecologic, and a controlled exposure chamber study (of stainless steel welding fumes). Sample sizes ranged from 15 to over 300,000 participants. Most studies included both sexes, but many of the occupational studies were confined to males, and only a few studies were done in children. Exposure assessment methods included classifying exposure based on work activities, measurements of ambient or workplace Cr(VI) air concentrations, residence near an industrial facility using Cr(VI) or in an area with known Cr(VI) environmental contamination, and national or regional industrial toxic emissions data (e.g., US EPA National Emission Inventory). A number of studies measured chromium in blood, urine, hair, or another biological matrix, although this always involved total Cr (Cr(III) plus Cr(VI)). The large majority of studies were adjusted or otherwise controlled for age and sex. Many studies also adjusted or otherwise controlled for one or more other potential confounder(s) including race/ethnicity, socioeconomic status, smoking, or other exposures (e.g., nickel, asbestos). Several studies did not report any statistical adjustments, or any other procedures commonly used to control for confounding (e.g., matching or restriction).

Cr(VI) and noncancer outcomes: Multiple studies identified possible associations between Cr(VI) and a variety of noncancer health outcomes. Descriptions and the results of these studies are presented in Tables A2.1-6. None of these studies presented findings that were suitable for dose-response analysis. The most common reason for this was that exposure in many of these studies was based solely on whether a worker performed a specific type or set of work activities (e.g., stainless steel

welding), and specific levels of Cr(VI) in water or any other environmental or biological media were not reported. For example, of the 14 studies of pulmonary function presented in Table A2.3, every study identified a statistically significant decline in at least one aspect of pulmonary function. Importantly though, the large majority of these studies simply compared pulmonary function in exposed workers to that in unexposed workers, with exposure categorization based only on job titles or activities, not on actual Cr(VI) levels. The remaining studies of pulmonary function were also not appropriate for dose-response analysis either because they only assessed Cr(VI) levels in air (Ba et al., 2012), only assessed total Cr levels (Cr(III) plus Cr(VI)) in blood (Zhang et al., 2022), assessed welding fumes without specific data on Cr(VI) (Kauppi et al., 2015), presented results as correlation coefficients (Liu et al., 2019), or based exposure only on residence in an area with known Cr(VI) drinking water contamination (Sharma et al., 2012). Other common weaknesses of these studies, and of the studies of other respiratory or nasal outcomes, included a lack of information on potentially important confounders like smoking, unclear exposure data, or little or no information on participant selection and the potential for selection bias.

A number of studies of GI, reproductive, developmental, immunologic, hematologic, or hepatic outcomes also found at least some evidence of associations with Cr(VI) (Tables A2.2-6). The hematologic outcomes for which some evidence of an association was reported include higher white blood cell counts (or higher counts or percentages of white blood cell subtypes) (Kauppi et al., 2015; Wang et al., 2012; Xu et al., 2020), lower red blood cell counts (Kauppi et al., 2015; Lacerda et al., 2019; Ramzan et al., 2011; Sazakli et al., 2014), lower hemoglobin concentrations (Kauppi et al., 2015; Khan et al., 2013; Lacerda et al., 2019; Sazakli et al., 2014), and lower platelet counts (Khan et al., 2013; Sharma et al., 2012; Xu et al., 2020). The GI outcome for which some evidence of an association was seen was “all diseases of the digestive system” combined (results for more specific diseases were not provided) (Sharma et al., 2012). For immune outcomes, some evidence of association was seen for increased infections, flu-like illness, or fever (Islam et al., 2019; Kashyap et al., 2021; Remy and Clay, 2014); decreased serum immunoglobulin (Islam et al., 2019; Qian et al., 2013); increased serum c-reactive protein (CRP) concentrations (Khan et al., 2013; Wang et al., 2012); or increased serum interleukin or tumor necrosis factor-alpha (TNF-α) concentrations (Li et al., 2015; Liu et al., 2019; Sazakli et al., 2014; Wang et al., 2019). For liver outcomes, evidence of associations was primarily seen for increases in alanine transaminase (ALT) or aspartate aminotransferase (AST) (Khan et al., 2013; Lacerda et al., 2019; Richard et al., 2016; Xu et al., 2022). For reproductive or developmental outcomes, evidence of associations were seen for smaller head circumference or lower ponderal index in neonates (Kim et al., 2020), lower birth rate (Remy et al., 2017), or broad categories of other childhood diseases (Remy et al., 2017).

Importantly, many of the studies reporting statistically significant associations between Cr(VI) and the noncancer outcomes evaluated here had at least one potentially major

study quality weakness that made it difficult to interpret the validity of their results. These potential weaknesses included minimal information on participant selection and potential selection bias; little to no data on potentially important confounders such as smoking or other relevant co-exposures; a lack of specific information on Cr(VI) levels; incomplete reporting of results; or a lack of internal consistency, external consistency, or replication. Overall, because of these issues, none of the noncancer studies identified in this review were selected for dose-response analysis.

Summary: Overall, many of the studies reviewed for noncancer effects provide at least some additional evidence that Cr(VI) could cause, respiratory and nasal, GI, immune, liver, hematologic, reproductive/developmental, and other adverse effects in humans. However, OEHHA was unable to find any epidemiologic study that could be used to accurately evaluate the dose-response relationship between Cr(VI) in drinking water and these effects. This conclusion does not necessarily apply to dose-response analyses of other routes of exposure, which is beyond the scope of this particular review. The primary weakness of the studies reviewed here is that many did not present specific information on Cr(VI) levels. Rather, most relied solely on job titles, work activities, or residential location to define exposure. Another common weakness was that many studies assessed exposure using only metrics of total Cr exposure, without a clear way of distinguishing the effects of Cr(VI) and Cr(III). Several studies presented dose-response information on Cr(VI) levels in air, but because of the complexities and unknowns of converting Cr(VI) levels in air to equivalent levels in water or oral intake, these studies were not selected for dose-response analysis.

Toxicological effects in animals

OEHHA identified 29 published animal noncancer toxicity studies conducted with oral administration of Cr(VI) since the original PHG was published in 2011. These studies are summarized in alphabetical order of first author in Table 2. The critical study by NTP (2008a) used in the 2011 PHG is also included.

Table 2. Summary of noncancer studies in animals

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Female (pregnant) Swiss Webster albino mice (10/dose) Arshad et al. (2017)	0, 11, 22, or 44 mg/kg potassium dichromate (0, 3.88, 7.77, or 15.53 mg/kg Cr(VI)) by gavage on GD 6	fetal abnormalities (exencephaly, omphalocele, hygroma, and limb abnormalities); ↓ body weights	LOAEL: 3.88 mg/kg Cr(VI) for fetal abnormalities

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Female (pregnant) Sprague-Dawley rats (25/dose) Banu et al. (2015)	0 or 25 ppm (3.3 mg/kg-day[c]) potassium dichromate (1.2 mg/kg-day Cr(VI)) in drinking water from GD 9.5-14.5	premature ovarian failure: ↑ germ cell/oocyte apoptosis; ↑ germ cell nest breakdown; ↑ X-prolyl aminopeptidase; ↓ Xpnpep2 during postnatal follicle development; ↑ colocalization of Xpnpep2 with Col3 and Col4; ↑ follicle atresia	LOAEL[b]: 1.2 mg/kg-day Cr(VI)
Female Sprague-Dawley rats (10/dose) Banu et al. (2016)	0 or 50 ppm (6.6 mg/kg-day[c]) potassium dichromate (2.4 mg/kg-day Cr(VI)) in drinking water from PND 1-21	alterations in the ovary: ↑ cytochrome C; ↑ cleaved caspase-3; ↓ antiapoptotic proteins; ↓ E2 biosynthesis; ↑ metabolic clearance of E2; ↑ oxidative stress; ↓ endogenous antioxidants; ↑ atresia of follicles	LOAEL[b]: 2.4 mg/kg-day Cr(VI)
Female (pregnant) Sprague-Dawley rats (5/dose) Banu et al. (2017)	0 or 50 ppm (6.6 mg/kg-day[c]) potassium dichromate (2.4 mg/kg-day Cr(VI)) in drinking water from GD 9.5-14.5	disruption of trophoblast proliferation of placenta: ↓ trophoblast cell population; ↑ ROS; ↓ expression of AOX proteins	LOAEL[b]: 2.4 mg/kg-day Cr(VI)
Male Wistar rats (8/dose) Bashandy et al. (2021)	0 or 10 mg/kg-day potassium dichromate (0 or 3.53 mg/kg-day Cr(VI)) in drinking water for 8 weeks	↓ plasma sex hormones; ↓GSH, SOD, and CAT; ↓ carnitine; ↓ sperm motility; ↓ sperm count; ↑ testicular malondialdehyde levels, nitric oxide concentrations; ↑ testicular abnormalities	LOAEL[b]: 3.52 mg/kg-day Cr(VI)
Male Sprague-Dawley rats (11/dose) Elshazly et al. (2016)	0 or 520 ppm (72 mg/kg-day[c]) sodium dichromate dihydrate (25 mg/kg-day Cr(VI)) in drinking water for 6 months	↑ oxidative stress; ↑ hepatic histopathological alterations; ↑ serum ALT and ALP; hepatic DNA damage	LOAEL[b]: 25 mg/kg-day Cr(VI)

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Male Wistar rats (68-70/dose) Karaulov et al. (2019)	0 or 20 mg/kg- day potassium dichromate (0 or 7.06 mg/kg-day Cr(VI)) in drinking water for 45, 90 or 135 days	↓ thymus and spleen absolute weights; ↓ in populations of thymocytes and splenic karyocytes after 135 days; ↓ lymphoid and plasma cells and ↑ erythroid cells after 90 and 135 days; ↓ myeloid cells and neutrophils and ↑ lymphoid and erythroid cells in bone marrow after 135 days; ↓ CD3+ and CD4+ lymphocytes after 90 and 135 days; structural and functional changes in thymus morphology; ↑ oxidative stress in liver and spleen after 90 and 135 days	LOAEL[b]: 7.06 mg/kg-day Cr(VI)
Male Wistar rats (50/dose) Krim et al. (2013)	0 or 15 mg/kg- day potassium dichromate (0 or 5.30 mg/kg-day Cr(VI)) in drinking water for 30 days	↓ red blood cells, hemoglobin, hematocrit, and mean corpuscular volume; ↑ urea, creatinine and uric acid; ↑ total lipids, total triglyceride, cholesterol, ALT, AST, ALP, LDH and bilirubin; ↑ GSH in liver, kidney, heart, intestines, testes and spleen	LOAEL[b]: 5.30 mg/kg-day Cr(VI)
Female (pregnant) Wistar rats (10/dose) Kumar et al. (2017)	0, 50, 100, or 200 ppm (0, 7, 14, or 28 mg/kg- day[c]) potassium dichromate (0, 2.47, 4.94 or 9.88 mg/kg-day Cr(VI)) in drinking water from embryonic days 9-14	F1 males: ↓ body weight and relative testis weight; ↓ anogenital distance; ↓ sperm forward motility and viability; ↓ sperm count; ↓ seminiferous tubule diameter; ↓ seminiferous tubule lumen diameter; ↓ Sertoli cells, sperm count, elongated spermatids and rounded spermatids; ↓ FSH, LH, testosterone; ↓ testicular interstitial fluid testosterone	LOAEL: 2.5 mg/kg-day Cr(VI) for majority of observed endpoints
Male and female New Zealand white rabbits (4/sex/dose) Mo et al. (2018)	0, 0.35, 2.09 mg/kg-day potassium dichromate (0, 0.12, or 0.74 mg/kg-day Cr(VI)) by oral gavage for 3 months	liver histopathological changes: ↑ necrosis of the hepatocytes; ↑ ductular reaction at portal area and canal of Herings	LOAEL: 0.12 mg/kg-day Cr(VI)

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Female (pregnant) Wistar rats (N not specified) Navin et al. (2021)	0, 50, 100, or 200 ppm (0, 7, 14, 28 mg/kg- day[c]) potassium dichromate (0, 2.47, 4.94 or 9.88 mg/kg-day Cr(VI)) in drinking water from GD 9-14	F1 males: ↓ body weight; ↓ relative and absolute testes weight; ↑ LH, FSH, PRL, E2; ↓ testosterone; ↓ expression of LHR, PRLR, AR, ERα; ↑ expression of ERβ; ↓ expression of STAR, CYP11a1, 3β HSD, CYP17A1 and 17βHSD5a, 5α reductase, P450 aromatase in Leydig cells	LOAEL: 2.47 mg/kg-day Cr(VI) for ↓ body weight and changes in hormone levels
Male and female F-344/N rats (50/sex/dose) NTP (2008a)	0, 14.3, 57.3, 172, or 516 mg/L (0, 0.6, 2.2, 6, or 17 mg/kg-day in males and 0, 0.7, 2.7, 7, or 20 mg/kg-day in females) sodium dichromate dihydrate (0, 0.21, 0.77, 2.1, or 5.9 mg/kg-day Cr(VI) in males and 0, 0.24, 0.94, 2.4, or 7.0 mg/kg-day Cr(VI) in females) in drinking water for 2 years	<u>Males</u>: liver lesions: histiocytic infiltration, chronic inflammation, basophilic focus; histiocytic infiltration of the duodenum and mesenteric lymph node; ↑ ALT and ALP at 12 months; ↑ creatine kinase and urea nitrogen at 12 months; ↓ erythrocytes at 12 months; ↓ mean red blood cell volume and mean cell hemoglobin concentration, mean cell hemoglobin and segmented neutrophils, leukocytes at 12 months <u>Females</u>: liver lesions: histiocytic infiltration, chronic inflammation, fatty change, clear cell focus; histiocytic infiltration of the duodenum and mesenteric lymph node; histiocytic infiltration of the pancreatic lymph node; atrophy of the salivary gland; ↑ erythrocytes at 12 months; ↓ mean red blood cell volume, mean cell hemoglobin and platelets, segmented neutrophils at 12 months	LOAEL: 0.24 mg/kg-day Cr(VI) for chronic inflammation of the liver in females

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Male and female B6C3F1 mice (50/sex/dose) NTP (2008a)	0, 14.3, 28.6, 85.7, or 257.4 mg/L (0, 1.1, 2.6, 7, or 17 mg/kg-day) sodium dichromate dihydrate in males and 0, 14.3, 57.3, 172, or 516 mg/L (0,1.1, 3.9, 9, or 25 mg/kg-day) sodium dichromate dihydrate in females (0, 0.38, 0.91, 2.4, or 5.9 mg/kg-day Cr(VI) in males and 0, 0.38, 1.4, 3.1, or 8.7 mg/kg-day Cr(VI)in females) in drinking water for 2 years	Males: histiocytic cellular infiltration in the mesenteric and pancreatic lymph node; diffuse epithelial hyperplasia in the small intestine; hyperplasia in duodenum; histiocytic infiltration in the duodenum; cytoplasmic alteration in the pancreas Females: histiocytic infiltration in the mesenteric, and pancreatic lymph node and liver; diffuse epithelial hyperplasia in the small intestine; hyperplasia in duodenum; histiocytic infiltration in the duodenum; cytoplasmic alteration in the pancreas	LOAEL: 0.38 mg/kg-day Cr(VI) for hyperplasia in the duodenum, diffuse epithelial hyperplasia in the small intestine, and histiocytic infiltration in the liver in females
Female Wistar rats (12/dose) Samuel et al. (2011)	0, 50, or 200 ppm (0, 7, 29 mg/kg-day[c]) potassium dichromate (0, 2.47, or 10.24 mg/kg-day Cr(VI)) in drinking water from PND 1-21, animals sacrificed on PND 45 and 65	↓ body weight and uterus weight; ↓ antioxidant enzyme activities (SOD, CAT, GPx, GR, GST) in uterus; delayed puberty; extended estrous cycle; ↓ testosterone, estradiol, progesterone, LH and FSH; ↑ LPO and H_2O_2 in uterus	LOAEL: 2.47 mg/kg-day Cr(VI) for all observed endpoints except ↓ uterus weight
Unspecified sex Wistar rats (8/dose) Sánchez et al. (2015)	0 or 12.5 mg/kg- day potassium dichromate (0 or 4.41 mg/kg-day Cr(VI)) by gavage (PND 4-15)	delayed tooth eruption: ↓ periodontal width and bone volume; ↓ percentage of bone formation surfaces; ↑ percentage of quiescent surfaces	LOAEL[b]: 4.41 mg/kg-day Cr(VI)
Wistar rat (sex and sample size not specified) Sánchez and Ubios Á (2020)	0 or 12.5 mg/kg-day potassium dichromate (0 or 4.41 mg/kg-day Cr(VI)) by oral gavage from PND 4-8, PND 4-14, or PND 4-22	delayed tooth eruption	LOAEL[b]: 4.41 mg/kg-day Cr(VI)

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Unspecified sex Wistar rats (8/dose) Sánchez and Ubios Á (2021)	0 or 12.5 mg/kg- day potassium dichromate (0 or 4.41 mg/kg-day Cr(VI)) by gavage (PND 4-9 or PND 4-15)	delayed tooth eruption: ↓ percentage of bone formation surfaces; ↓ percentage of bone resorption surfaces on PND9; ↑ percentage of bone resorption surfaces on PND15	LOAEL[b]: 4.41 mg/kg-day Cr(VI)
Male and female C57BL/6J mice (4/sex/dose) Sánchez-Martín et al. (2015)	0 or 5.5 ppm (1.47 mg/kg-day[c]) sodium dichromate dihydrate (0.51 mg/kg-day Cr(VI)) in drinking water for 60 days	histopathological changes in GI tract: ↑ enterocyte hypertrophy; ↑ cell proliferation DNA damage in GI tract	LOAEL[b]: 0.51 mg/kg-day Cr(VI)
Female (pregnant) Wistar rats (6/dose) Shobana et al. (2017)	0, 50, 100, or 200 ppm (0, 18, 36, or 72 mg/kg- day[d]) potassium dichromate (0, 6.4, 12.7, or 25 mg/kg-day Cr(VI)) in drinking water from GD 9-14, F1 males sacrificed on PND 60	F1 males: ↑ serum insulin levels; ↓ IRS-1 expression in liver; ↓ p-IRS-1^{Tyr632}; ↑ AKT^{Ser473} in liver; ↑ GLUT2 in the liver; ↑ ^{14}C-2-deoxyglucose uptake in the liver; ↑ ^{14}C-glucose oxidation in liver at low dose and ↓ at mid and high dose	LOAEL: 6.4 mg/kg-day Cr(VI) for ↑ serum insulin levels

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Female (pregnant) Wistar rats (12/dose) Shobana et al. (2020)	0, 50, 100, or 200 ppm (0, 7, 13, 27 mg/kg- day[c]) potassium dichromate (0, 2.5, 4.6, or 9.5 mg/kg-day Cr(VI)) in drinking water from GD 9-14, or GD 15-21	Sertoli cells of F1 males: ↓ antioxidant enzyme activities (SOD, CAT, GPx); ↑ LPO, H_2O_2 and or OH^-; ↓ GR, GST and GSH; ↓ mRNA and protein expression of secretory proteins (inhibin B, ABP, and transferrin); ↓ secretory products (lactate, pyruvate and retinoic acid); ↓ TJ proteins (claudin-11 and occludin-11) altered expression of androgen and follicle stimulating hormone receptors; ↑ serum FSH, LH, PRL, E2; ↓ serum testosterone; ↓ AR, FSHR expression; ↓ transcriptional regulators of FSHR (USF-1, USF-2, SF-1, GATA-1, c-jun, c-fos); ↓ transcriptional regulators of FSHR and AR (USF-1-FSHR, USF-2-FSHR, and sp-1-AR)	LOAEL: 2.5 mg/kg-day Cr(VI) for all observed endpoints
Female Rats (strain unknown) 5/dose Sivakumar et al. (2014)	0 or 25 ppm (2.5 mg/kg-day[c]) potassium dichromate (0.88 mg/kg-day Cr(VI)) in drinking water from GD 9.5-14.5	early reproductive senescence in F1 offspring: ↑ germ cell apoptosis; ↑ germ cell cyst (GCC) breakdown; ↑ primordial follicle assembly and primary follicle transition; ↓ p-AKT, p-ERK, and XIAP	LOAEL[b]: 0.88 mg/kg-day Cr(VI)
Female (pregnant) SD rats (10/dose) Sivakumar et al. (2022)	0 or 10 ppm (0, or 1 mg/kg-day[c]) potassium dichromate (0, or 0.35 mg/kg-day Cr(VI)) in drinking water from GD 9.5-14.5	↑ germ cell apoptosis; ↑ expression of acetyl-p53 in ovaries; ↑ expression of cleaved caspase-3; ↑ expression of BAX and PUMA; ↓ expression of Bcl2, BCL-XL, pAKT; ↑ expression of acetyl p53-SIRT1 ratio; ↓ p53-SIRT-1 co-localization; ↓ SIRT1 expression in ovary; ↓ interaction between p53-SIRT1	LOAEL[b]: 0.35 mg/kg-day Cr(VI)

Sex/Species/ (N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Female (pregnant) Wistar rats (6/dose) Soudani et al. (2011a)	0 or 700 ppm (0 or 26.46 mg/kg- day) potassium dichromate (0, or 9.34 mg/kg-day Cr(VI)) in drinking water from GD 14 to PND 14	F0 females and F1 males and females: ↓ body weight; ↑ urinary volume; ↓ creatinine clearance; ↑ creatinine in plasma, urea in plasma, uric acid in urine; ↓ creatinine in urine, urea in urine, uric acid in plasma; ↑ MDA, NO, GSH; ↓ NPSH; ↑ plasma LDH; ↓ kidney LDH; histopathological changes in the kidney. F0 females only: ↑ CAT, SOD, GPx. F1 males and females only: ↑ relative kidney weight; ↓ CAT, SOD, GPx	LOAEL[b]: 9.34 mg/kg-day Cr(VI)
Female (pregnant) Wistar rats (6/dose) Soudani et al. (2011b)	0 or 700 ppm (0 or 26.46 mg/kg- day) potassium dichromate (0, or 9.34 mg/kg-day Cr(VI)) in drinking water from GD 14 to PND 14	F1 males and females: ↓ final body weight, femur weight and femur length; ↓ bone and urinary calcium levels; ↓ bone and plasma phosphorus levels; ↑ plasma calcium and urinary phosphorus levels; ↑ MDA; ↓ GSH, NPSH and vitamin C levels in femur; ↓ CAT, SOD and GPx in femur, ↓ plasma ALP; ↓ plasma ACP	LOAEL[b]: 9.34 mg/kg-day Cr(VI)

Sex/Species/(N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Female (pregnant) Wistar rats (6/dose) Soudani et al. (2013)	0 or 700 ppm (0 or 26.46 mg/kg-day) potassium dichromate (0, or 9.34 mg/kg-day Cr(VI)) in drinking water from GD 14 to PND 14	F0 females and F1 males and females: ↓ final body weight; ↓ liver CAT activity; ↓ liver GPx activity; ↑ ALT, AST and bilirubin; ↑ plasma LDH activity; ↓ plasma LDH activity; leukocyte inflammatory cells F0 females: ↑ liver SOD activity; extensive necrosis F1 males and females: ↓ rel liver weight; ↓ liver SOD activity	LOAEL[b]: 9.34 mg/kg-day Cr(VI)
Female Sprague-Dawley rats (5/dose) Stanley et al. (2014)	0, 5, 10, 25, 50, 100, or 200 ppm (0, 0.7, 1, 3, 47, 13 or 26 mg/kg-day[c]) potassium dichromate (0, 0.2, 0.5, 1.2, 2.3, 4.6 or 9.3 mg/kg-day Cr(VI)) in drinking water from parturition to PND 21	ovarian toxicity: ↑ oxidative stress; ↓ antioxidant enzyme levels; ↑ follicular atresia; ↓ steroidogenesis; delayed puberty	LOAEL: 0.2 mg/kg-day Cr(VI)
Female B6C3F1 mice (5-20/dose) Thompson et al. (2011)	0, 0.3, 4, 14, 60, 170, or 520 ppm (0, 0.07, 0.9, 3.1, 13.2, 33.0, 88.7 mg/kg-day) sodium dichromate dihydrate (0, 0.02, 0.31, 1.08, 4.61, 11.52, or 30.96 mg/kg-day Cr(VI)) in drinking water for 7 or 90 days	↓ reduced-to-oxidized glutathione ratio (GSH/GSSG) at 90 days; intestinal lesions (villous cytoplasmic vacuolization, atrophy, apoptosis, crypt hyperplasia) at 90 days	NOAEL: 1.08 mg/kg-day Cr(VI) for intestinal lesions

Sex/Species/(N)/Reference	Exposure[a]	Endpoints	NOAEL/ LOAEL
Female Fischer 344/N rats (5-15/dose) Thompson et al. (2012)	0, 0.3, 4, 60, 170, or 520 ppm (0, 0.05, 0.6, 8.3, 20.4, or 58.6 mg/kg-day) sodium dichromate dihydrate 0, 0.02, 0.21, 2.90, 7.12, or 20.45 mg/kg-day Cr(VI)) in drinking water for 7 or 90 days	↓ reduced-to-oxidized glutathione ratio (GSH/GSSG) at 90 days; intestinal lesions (villous atrophy, apoptosis, crypt cell hyperplasia, histiocytic infiltration) at 90 days	NOAEL: 0.21 mg/kg-day Cr(VI) for intestinal lesions
Female CRL:B6C3F1 mice (10/dose) Thompson et al. (2020)	0, 0.3, 4, 14, 170, or 516 ppm sodium dichromate dihydrate (0, 0.016, 0.23, 0.73, 7.3, or 17.7 mg/kg-day Cr(VI)) in drinking water for 90 days	ovarian toxicity (ovarian follicular counts, differentiation, rate of atresia)	NOAEL: 17.7 mg/kg-day Cr(VI)
Male Wistar rats (12/dose) Younan et al. (2019)	0, 120, 240, or 360 mg/kg-day potassium dichromate (0, 42.36 or 84.72 mg/kg-day Cr(VI)) in the diet for 90 days	↓ final body weight; ↑ rel liver weight and rel kidney weight; ↑ ALT, AST, ALP, GGT, creatinine, urea, glucose, triglycerides, total cholesterol, LDL; ↓ serum proteins, albumin, globulins, HDL; inflammation of hepatocytes; renal tubular necrosis	LOAEL: 42.36 mg/kg-day Cr(VI) for ↓ body weight, liver effects, and renal tubular necrosis
Female (pregnant) SD rats (6/dose) Zheng et al. (2018)	0, 3, 6, or 12 mg/kg-day potassium dichromate (0, 1.06, 2.12, or 4.24 mg/kg-day Cr(VI)) by oral gavage from GD12-21	biphasic effects on fetal Leydig cell steroidogenesis; changes in fetal Leydig cell distribution; biphasic effects on fetal Leydig cell size; changes in Leydig cell protein expression; changes in Sertoli cell protein expression	LOAEL: 1.06 mg/kg-day Cr(VI) for fetal Leydig cell steroido-genesis

[a] The administered dose of potassium dichromate ($K_2Cr_2O_7$) in drinking water was converted to Cr(VI) by multiplying the administered dose by 0.353 (the molecular weight of two Cr atoms divided by the molecular weight of $K_2Cr_2O_7$). For sodium dichromate dihydrate ($Na_2Cr_2O_7$ $2H_2O$) the administered dose

was by multiplied by 0.349 (the molecular weight of two Cr atoms divided by the molecular weight of $Na_2Cr_2O_7$ $2H_2O$).
[b] This LOAEL was identified from a single dose study.
[c] Administered dose was calculated by OEHHA using reference drinking water consumption rates and body weights from US EPA (1988).
[d] Administered dose was calculated by OEHHA using reference drinking water consumption rates from US EPA (1988) and body weight from Shobana et al. (2017).
Abbreviations: ABP, androgen binding protein; ACP, acid phosphatase; AKT, protein kinase B; ALT, alanine transaminase; ALP, alkaline phosphatase; AOX, antioxidant; AR, androgen receptor; AST, aspartate transaminase; BAX, B-cell lymphoma-2 associated apoptosis regulator; BCL, B-cell lymphoma; CAT, catalase; CD, cluster of differentiation; Col, collagen; CYP, cytochrome P450; E2, 17β-Estradiol; ER, estrogen receptor; FSH, follicle stimulating hormone; FSHR, follicle stimulating hormone receptor; GATA, transcription factor that kinds to DNA sequence GATA; GD, gestation day; GGT, γ-glutamyltransferase; GI, gastrointestinal; GLUT, glucose transporter; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; GST, glutathione-S-transferase; H_2O_2, hydrogen peroxide; HDL, high-density lipoproteins; HSD, hydroxysteroid dehydrogenase; IR, insulin receptor; IRS, insulin receptor substrate; LDH, lactate dehydrogenase; LDL, low-density lipoproteins; LH, luteinizing hormone; LHR, luteinizing hormone receptor; LPO, lipid peroxidation; MDA, malondialdehyde; NO, nitro oxide; NPSH, kidney non-protein thiols; OH^-, hydroxyl radical; p-AKT, phosphorylated protein kinase B; p-ERK, phosphorylated extracellular signal-regulated kinase; PND, postnatal day; PPAR, peroxisome proliferator-activated receptor; ppm, parts per million; PRL: prolactin hormone; PRLR, prolactin hormone receptor; PUMA, p-53 upregulated modulator of apoptosis; rel, relative; ROS, reactive oxygen species; SC, Sertoli cells; SF-1, steroidogenic factor-1; SIRT-1, sirtuin 1; SOD, superoxide dismutase; sp-1, specificity protein 1; STAR, steroid acute regulatory protein; TJ, tight junction, USF, upstream stimulatory factor; XIAP, X-linked inhibitor of apoptosis protein; Xpnpep2, X-propyl aminopeptidase

Several noncancer effects from oral exposure to Cr(VI) were identified in the literature published since the 2011 PHG. These include:

- Hepatotoxic effects, such as changes in relative weight, lesions, necrosis, and changes in enzyme activity (Elshazly et al., 2016; Krim et al., 2013; Mo et al., 2018; Shobana et al., 2017; Soudani et al., 2013).
- Female reproductive effects such as premature ovarian failure, oxidative stress, changes in hormone production and estrous cycle (Banu et al., 2015; Banu et al., 2016; Banu et al., 2017; Samuel et al., 2011; Sivakumar et al., 2022; Stanley et al., 2014; Thompson et al., 2020).
- Effects on male reproduction, such as changes in testis weight, altered expression of proteins in Leydig cells, testicular damage, oxidative stress and changes in fetal Leydig cell distribution (Bashandy et al., 2021; Kumar et al., 2017; Navin et al., 2021; Shobana et al., 2020; Zheng et al., 2018).
- Reduced renal function and damage (Krim et al., 2013; Soudani et al., 2011a; Younan et al., 2019).
- Hypertrophy and lesions in the gastrointestinal tract, (Sánchez-Martín et al., 2015; Thompson et al., 2012).
- Developmental effects such as fetal abnormalities, delayed tooth eruption, delayed puberty, and changes in bone development (Arshad et al., 2017; Sánchez and Ubios Á, 2020, 2021; Soudani et al., 2011b; Stanley et al., 2014).

In 2008, California's Developmental and Reproductive Toxicant Identification Committee (DARTIC) determined that Cr(VI) was shown to cause developmental toxicity, and male and female reproductive toxicity, and Cr(VI) was added to California's Proposition 65 list of chemicals known to cause reproductive toxicity (OEHHA, 2009, 2010).

- Immunotoxicity (Karaulov et al., 2019).

With the exception of Karaulov et al. (2019), all studies identified were either subchronic or shorter in study duration. However, many studies investigating developmental effects and exposures occurred during critical windows of development.

Of the recent studies identified, none were more sensitive than the critical study (NTP, 2008a) used in the development of the noncancer HPC in the 2011 PHG and several were not suitable for dose-response analysis due to having only one exposure group. Some studies with multiple dose groups had quality issues, such as small sample size, and most were not chronic in duration. The NTP (2008a) study was chronic in duration, with a large sample size and multiple doses and exposure via drinking water. Therefore, the NTP (2008a) study is retained as the critical study for this assessment. A thorough review of the NTP (2008a) study was done in the previous PHG (OEHHA, 2011). A brief summary of the study results is presented below.

NTP (2008a) exposed male and female F-344/N rats to 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate in drinking water (equivalent to 0, 0.21, 0.77, 2.1, or 5.9 mg/kg-day Cr(VI) in males; 0, 0.24, 0.94, 2.4, or 7.0 mg/kg-day Cr(VI) in females) for 2 years. There were significantly increased incidences of chronic liver inflammation in all dosed female groups and doses ≥0.77 mg/kg-day Cr(VI) in males. There was also a significantly increased incidence in fatty change in the liver at doses ≥0.94 mg/kg-day Cr(VI) in female rats. There was a significantly increased incidence of histiocytic cellular infiltration of the small intestine and mesenteric lymph node in males at doses ≥0.77 mg/kg-day Cr(VI) and in females at doses ≥2.4 mg/kg-day Cr(VI). Hemorrhage of the mesenteric lymph node was also increased in males at doses ≥0.77 mg/kg-day Cr(VI).

NTP (2008a) exposed B6C3F1 male mice to 0, 14.3, 28.6, 85.7 or 257.4 mg/L sodium dichromate dihydrate (0, 0.38, 0.91, 2.4 or 5.9 mg/kg-day Cr(VI)) and female mice to 0, 14.3, 57.3, 172, or 516 mg/L sodium dichromate dihydrate (0, 0.38, 1.4, 3.1, or 8.7 mg/kg-day Cr(VI)) in drinking water for 2 years. Both males and females had increased incidences of diffuse epithelial hyperplasia in the duodenum at all doses, and histiocytic cellular infiltration of the duodenum at doses ≥2.4 mg/kg-day Cr(VI) and ≥3.1 mg/kg-day Cr(VI), respectively. Histiocytic cellular infiltration was also observed in the liver (females only) and mesenteric lymph node (males and females) at all doses. Histiocytic cellular infiltration was observed in the duodenum (two highest doses), pancreatic lymph node (two highest doses), and mesenteric lymph node (all doses) in both males and females. Cytoplasmic alteration in the pancreatic acini was observed in all dosed groups

for females and at doses ≥2.4 mg/kg-day Cr(VI) for males.

DOSE-RESPONSE ASSESSMENT

OEHHA develops HPCs that are expected to result in no adverse effects from daily exposure over a lifetime. For noncancer effects, HPC derivation starts with the PODs derived from the most sensitive animal or human studies, i.e., those studies that observed adverse health effects at the lowest doses.

The most sensitive endpoints were selected for BMD modeling (BMDS, version 3.3) to determine the POD. OEHHA identified three candidate critical effects in the liver: chronic inflammation, fatty change and histiocytic infiltration (NTP, 2008a). A fourth candidate critical effect, epithelial hyperplasia in the small intestine, was significantly increased at all doses in male and female mice (NTP, 2008a). Quantitative data and BMD modeling results are presented in Table 3. For all four endpoints, OEHHA used the default BMR of 5% extra risk for dichotomous data. The LOAEL in male and female mice for epithelial hyperplasia in the small intestine was 0.38 mg/kg-day Cr(VI), which was slightly higher than the LOAEL for liver inflammation and fatty change in female rats (0.24 mg/kg-day Cr(VI)). Because the noncancer effects observed in the liver are more sensitive than the noncancer effects in the GI, health-protective concentrations derived from liver endpoints will be protective of effects in the GI.

Table 3. Dose-response modeling results for Cr(VI) noncancer candidate critical endpoints

Study/ Sex/Species/ (N)/Duration	Dose (mg/kg-day Cr(VI)[a])	Critical Effect	Critical Effect Value	NOAEL or LOAEL (mg/kg-day Cr(VI))	BMD/BMDL (mg/kg-day) p-value model
NTP (2008a) Female F-344/N rats (50/dose) 2 years	0 0.24 0.94 2.44 7.00	Chronic liver inflammation	12/50 21/50* 28/50*≠ 35/50*≠ 39/50*≠	LOAEL: 0.24	0.1060/0.065 0.37 Log-logistic
NTP (2008a) Female F-344/N rats (50/dose) 2 years	0 0.24 0.94 2.44 7.00	Fatty change in the liver	3/50 7/50 10/50* 13/50*≠ 16/50*≠	LOAEL: 0.24	0.1641/0.027 0.91 Dichotomous Hill
NTP (2008a) Female B6C3F1 mice (50/dose) 2 years	0 0.38 1.36 3.14 8.73	Histiocytic infiltration of the liver	2/49 15/50*≠ 23/50*≠ 32/50*≠ 45/50*≠	LOAEL: 0.38	0.07890/0.058 0.45 Log-logistic
NTP (2008a) Male B6C3F1 mice (50/dose) 2 years	0 0.38 0.91 2.44 5.93[b]	Diffuse epithelial hyperplasia in the small intestine	0/41 11/45*≠ 18/46*≠ 42/48*≠ 32/41*≠	LOAEL: 0.39	0.07214/0.059 0.53 Multistage degree 1

≠ Significantly different (p≤0.05) from the control group using the Fisher Exact test performed by OEHHA.
* Significantly different (p≤0.05) from the control group using the Poly-3 test performed by study authors (NTP, 2008a).
[a] The administered dose of sodium dichromate dihydrate in drinking water ($Na_2Cr_2O_7$ $2H_2O$) was converted to Cr(VI) dose by multiplying the administered dose by 0.349 (the molecular weight of two Cr atoms divided by the molecular weight of $Na_2Cr_2O_7$ $2H_2O$).
[b] High dose (5.93 mg/kg-day) omitted from BMD modeling to achieve acceptable model fit.

BMDLs of 0.065 mg/kg-day for chronic liver inflammation in female rats, 0.058 mg/kg-day for histiocytic infiltration of the liver in female mice, and 0.059 for diffuse epithelial hyperplasia in the small intestine of male mice were considered for HPC derivation. While fatty change in female rat liver had the lowest BMDL value of 0.027 mg/kg-day, it was not considered for HPC derivation because its BMD/BMDL ratio indicated greater uncertainty in the BMD estimate for this endpoint than for the other endpoints modeled. Also, BMD modeling of diffuse epithelial hyperplasia in the small intestine of female mice did not produce an acceptable model fit. BMD modeling of diffuse epithelial hyperplasia in the small intestine of male mice required omission of the highest dose group to achieve an acceptable model fit. All dose groups were used for BMD modeling

of the other candidate noncancer critical endpoints (Table 3). Details of the BMD modeling are shown in Appendix 3.

Human Point of Departure (POD)

To derive a human POD from the animal POD, OEHHA used the PBPK model published by Sasso and Schlosser (Sasso and Schlosser, 2015; Schlosser and Sasso, 2014). The BMDL values from the previous section were converted to an internal dose, which was based on the average amount of Cr(VI) escaping stomach reduction in rodents. To calculate the corresponding human internal dose, a body weight (BW) scaling adjustment was applied to the rodent internal dose to account for interspecies differences in toxicokinetics and dose to the intestine of Cr(VI) following gastric reduction. BW scaling is calculated using the following formula:

$$BW\ scaling = \left(\frac{BW_{animal}}{BW_{human}}\right)^{1/4}$$ US EPA (2011).

Subsequently, 20,000 Monte Carlo pharmacokinetic simulations were run from the adjusted internal dose and the lower 1% value of all the simulation runs was calculated. This value is the point of departure represented as a human equivalent dose (POD_{HED}).

Table 4. POD_{HED} for Cr(VI) noncancer endpoints from the candidate critical study

Study Sex/Species/(N)/ Duration	Critical Effect	Rodent POD (mg/kg-day)	Internal Rodent POD (mg/kg-day)	Internal Human POD[a] (mg/kg-day)	POD_{HED} (mg/kg-day)
NTP (2008a) Female F-344/N rats (50/dose) 2 years	Chronic liver inflammation	0.065	0.0049	0.00123	0.020
NTP (2008a) Female B6C3F1 mice (50/dose) 2 years	Histiocytic infiltration of the liver	0.058	0.0088	0.00146	0.024
NTP (2008a) Male B6C3F1 mice (50/dose) 2 years	Diffuse epithelial hyperplasia in the small intestine	0.059	0.0088	0.00146	0.024

[a]BW_A is the time-weighted body weight average (0.274 kg for rats and 0.0525 kg for mice) from NTP

(2008a) and BW_H is 70 kg.

Acceptable Daily Dose (ADD)

A detailed description of uncertainty factors is presented in Appendix 4.

To calculate the human POD, a toxicokinetic model and allometric scaling of internal dose were used to quantitatively account for interspecies differences in toxicokinetics. Because of this, an interspecies UF of √10 was applied to account for differences in toxicodynamics when extrapolating data from animal studies to humans.

For the intraspecies UF, OEHHA applied √10 for the toxicodynamic component and 6 for the toxicokinetic component. OEHHA typically applies an intraspecies toxicokinetic UF of √10 when there are some toxicokinetic data (e.g., PBPK models for adults only). To account for toxicokinetic diversity within susceptible populations, including infants and children, an intraspecies toxicokinetic UF of 10 is applied when human toxicokinetic data are not available. OEHHA modeled gastric reduction of Cr(VI) using a toxicokinetic model with Monte Carlo simulation, which simulated stomach pH variability up to approximately 5.25. This pH range encompasses typical adults, plus those with hypochlorhydria (high stomach pH, typically in the range of pH 3-5). However, adults medicated with proton pump inhibitors (stomach pH ≈ 6) and infants and children up to about 2.5 years of age (stomach pH ≈7) fall outside of the pH range included in this model (Laine et al., 2008; Neal-Kluever et al., 2019; Rahman et al., 2016). Thus, OEHHA incorporated an additional uncertainty factor of 2 to account for residual uncertainty related to pH that was not adequately captured by the gastric reduction model, resulting in an overall intraspecies toxicokinetic UF of 6 (√10 × 2). The combined intraspecies UF is 20 (rounded). Therefore, the composite UF is 60.

To calculate the ADD, the POD_{HED} is divided by the composite UF.

For chronic liver inflammation in female rats:

$$ADD = {0.020 \times \frac{mg}{kg-day}}\Big/{60} \text{ x } 1{,}000 \text{ µg/mg} = 0.34 \text{ µg/kg-day}$$

For histiocytic infiltration of the liver in female mice:

$$ADD = {0.024 \times \frac{mg}{kg-day}}\Big/{60} \text{ x } 1{,}000 \text{ µg/mg} = 0.40 \text{ µg/kg-day}$$

For diffuse epithelial hyperplasia in small intestine of male mice:

$$ADD = {0.024 \times \frac{mg}{kg-day}}\Big/{60} \text{ x } 1{,}000 \text{ µg/mg} = 0.40 \text{ µg/kg-day.}$$

HEALTH-PROTECTIVE DRINKING WATER CONCENTRATION

To calculate a noncancer health-protective concentration for a chemical, the ADD is converted to a concentration in drinking water that accounts for the total exposure to the chemical that people receive from using tap water. This includes intake from multiple routes of exposure (oral, inhalation, and dermal) to contaminants in tap water from household uses (e.g., drinking, cooking, bathing, and showering). For Cr(VI), exposures via inhalation and dermal routes are negligible (OEHHA, 2011).

Drinking Water Intake (DWI)

The endpoints of liver toxicity reflect lifetime exposure, therefore the oral DWI is weight-averaged over life stages for a 70-year lifetime for the general population and equals 0.053 L/kg-day. This DWI differs from the 2011 PHG, which used a value of 0.067 L/kg-day, the upper 95th percentile water intake for children ages 0-11 years. OEHHA was unable to identify evidence that children are more susceptible to liver inflammation, and thus OEHHA considered the upper 95th percentile lifetime average drinking rate of 0.053 L/kg-day to be more appropriate. This drinking rate is a time-weighted lifetime average incorporates the increased drinking water rates, relative to body weight, of infants and children.

Relative Source Contribution (RSC)

The RSC is the proportion of exposures to a chemical attributed to tap water (including inhalation and dermal exposures, e.g., during showering), as part of total exposure from all sources (including food and air pollution). For Cr(VI), the RSC is 0.8 as the major source of exposure is drinking water (OEHHA, 2011).

Health-Protective Concentration (HPC)

The HPC is calculated as follows:

HPC = ADD × RSC ÷ DWI, where:

ADD = acceptable daily dose,

RSC = relative source contribution of 0.8, and

DWI = 0.053 L/kg-day.

For chronic liver inflammation in female rats:

HPC = 0.34 µg/kg-day × 0.8 ÷ 0.053 L/kg-day = 5.1 µg/L or 5 ppb (rounded).

For histiocytic infiltration of the liver in female mice:

HPC = 0.04 µg/kg-day × 0.8 ÷ 0.053 L/kg-day = 6.0 µg/L or 6 ppb (rounded).

For diffuse epithelial hyperplasia in the small intestine of male mice:

HPC = 0.04 µg/kg-day × 0.8 ÷ 0.053 L/kg-day = 6.0 µg/L or 6 ppb (rounded).

The lowest HPC of 5 ppb, based on chronic liver inflammation in female rats from the NTP (2008) study is selected as the noncancer health-protective drinking water concentration. As chronic liver inflammation is associated with adverse human health outcomes including nonalcoholic steatohepatitis and cholestasis (reduction or blockage of bile), this is a relevant endpoint on which to base the HPC (Tilg and Moschen, (2010); Chen and Zhang, (2023)).

HPC calculations are summarized in Table 5.

Table 5. Calculation of Health-Protective Concentrations (HPCs) for candidate critical endpoints

Endpoint	POD_{HED} (mg/kg-day)	UFc	ADD (µg/kg-day)	RSC	DWI (L/kg-day)	HPC (µg/L) (rounded)
Chronic liver inflammation female rats NTP (2008a)	0.020	60	0.34	0.8	0.053	5
Histiocytic infiltration of the liver female mice NTP (2008a)	0.024	60	0.40	0.8	0.053	6
Diffuse epithelial hyperplasia in the small intestine male mice NTP (2008a)	0.024	60	0.40	0.8	0.053	6

RISK CHARACTERIZATION

The proposed HPC of 5 ppb for Cr(VI) is based on chronic inflammation of the liver observed in female rats exposed for 2 years (NTP, 2008a). Comparisons between the 2011 HPC and the proposed HPC are summarized in Table 6 below. The differences include the use of benchmark dose modeling for POD determination, toxicokinetic adjustments using a PBPK model and OEHHA's current drinking water ingestion rate. The updated methodologies reduce the overall uncertainty of the health- protective

value derived from the same animal study and endpoints used in the 2011 PHG.

Table 6. OEHHA (2011) noncancer HPC vs. the proposed updated noncancer HPC

	2011 noncancer HPC	Proposed noncancer HPC
Critical study	NTP (2008a)	NTP (2008a)
Endpoint	Chronic inflammation and fatty changes in the liver	Chronic liver inflammation
Point of departure (mg/kg-day)	LOAEL: 0.2	BMDL: 0.065
LOAEL to NOAEL factor	UF of 10	UF of 1
Toxicokinetic adjustment for interspecies differences	UF of √10	UF of 1[c]
Toxicodynamic adjustment for interspecies differences	UF of √10	UF of √10
Toxicokinetic adjustment for intraspecies differences	UF of √10[b]	UF of 6
Toxicodynamic adjustment for intraspecies differences	UF of √10[b]	UF of √10
Total Uncertainty factor	1000	60
Lifetime daily water intake (L/kg-day)	0.067[a]	0.053
HPC (ppb)	2	5

[a] DWI for child 0-11 years
[b] The default intraspecies uncertainty factor was 10 (√10 for toxicodynamics, √10 for toxicokinetics) in 2011. Since then, the default has been changed to 30 (√10 for toxicodynamics, 10 for toxicokinetics).
[c] Toxicokinetic adjustment was made using rat and human PBPK models along with allometric scaling of internal dose.

OTHER REGULATORY STANDARDS AND GUIDANCE VALUES

The Agency for Toxic Substances and Disease Registry (ATSDR) developed an oral minimal risk level (MRL) of 0.0009 mg/kg-day (0.9 µg/kg-day) for chronic exposure to Cr(VI) based on the observed diffuse epithelial hyperplasia in the duodenum of female mice in the NTP (2008a) study (ATSDR, 2012). This value was based on a $BMDL_{10}$ (0.09 mg/kg-day) and a combined uncertainty factor (UFc) of 100 (UF_A:10 for interspecies differences and $UF_{H:}$10 for intraspecies variability).

The US EPA's oral reference dose (RfD) is 0.0009 mg/kg-day for Cr(VI) (0.9 µg/kg-day)

based on diffuse epithelial hyperplasia in the small intestine of female mice observed in the 2008 National Toxicology Program study (US EPA, 2024). This value was based on a LOAEL (0.09 mg/kg-day) and UFc of 100 (UF_A: $\sqrt{10}$, UF_H: $\sqrt{10}$, UF_L:10 for LOAEL to NOAEL extrapolation). US EPA's MCL for total chromium in drinking water is 0.1 mg/L or 100 ppb based on potential adverse dermatological effects such as allergic dermatitis (US EPA, 2005).

The California State Water Resources Control Board adopted an MCL of 10 ppb for Cr(VI) in drinking water (SWRCB, 2024). The MCL for total chromium in California drinking water is 50 ppb. These values are based on the 2011 Cr(VI) PHG which is derived from a LOAEL (0.2 mg/kg-day), UFc of 1,000 (UF_A:10, UF_H:10,UF_L:10), and a drinking water intake of 0.067 L/kg-day (Table 6).

Health Canada has a maximum acceptable concentration (MAC) of 0.05 mg/L or 50 ppb for total chromium in drinking water based on diffuse hyperplasia in the small intestine observed in male and female mice. This value is based on a $BMDL_{05}$ (0.11 mg/kg-day), UFc of 25 (UF_A:2.5, UF_H:10) and a drinking water of intake 0.02 L/kg-day (Health Canada, 2015). The World Health Organization (WHO) guideline value for total chromium in drinking water is also 50 ppb based on hyperplasia in the small intestine and the detection limit for chromium (WHO, 2020; WHO, 2022). The NTP (2008) study is the critical study for both Health Canada and WHO in developing their respective guideline values.

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APPENDIX 1. LITERATURE SEARCH STRATEGY

Initial inclusion criteria for screening human studies: The inclusion criteria for the literature searches included research involving any epidemiologic study design (e.g., cohort, case-control, cross-sectional, case cross-over, ecologic, case reports), any exposure route (e.g., inhalation, drinking water, diet), any exposure setting (e.g., occupational exposure, general population exposure, areas with known Cr(VI) environmental contamination), or any exposure metric (e.g., blood, urine, air, water, food, workplace activities). Research involving several different forms of Cr(VI) was included (e.g., chromate, hydrochromate, and dichromate). Studies involving any adverse health effect were included, although as described below, only studies involving a more refined set of outcomes were evaluated in the detailed reviews of causal inference and study quality. Research that did not involve direct measurements of Cr(VI), but took place in occupational settings known to involve high Cr(VI) exposures, was included. These occupations were stainless steel welding and grinding, chromium electroplating, Portland cement production or use, ferrochromium production, leather tanning, and chromium pigment production (NIOSH, 2013; OSHA, 2006; Shaw Environmental Inc, 2006). No age or language restrictions were used. Conference abstracts were included if they provided essential information on study population, study design, and results, although this was rarely the case.

Search terms: The terms used in the PubMed and Web of Science searches are shown in Tables 1 and 2. These terms included several different chemical forms or identifiers for Cr(VI), several different occupations associated with high Cr(VI) exposure, and terms or subject areas intended to help limit the search to human epidemiologic studies.

Table A1. PubMed search terms for human epidemiologic studies of hexavalent chromium toxicity

((chromium[tiab] AND electroplating[tiab]) OR (chrome[tiab] AND plating[tiab]) OR (stainless steel[tiab] AND weld*[tiab]) OR (stainless steel[tiab] AND grind*[tiab]) OR (portland cement[tiab]) OR (ferrochrome production[tiab]) OR ("chrome pigment*"[tiab]) OR ("chromium pigment*"[tiab]) OR (chrom*[tiab] AND "leather tann*"[tiab])) OR ((chromium OR chromate* OR CRVI OR CR VI OR "Chromic acid" OR "Calcium chromate" OR "Potassium dichromate" OR "Potassium chromate" OR "Sodium chromate" OR "lead chromate" OR "zinc chromate" OR "strontium chromate" OR "ammonium dichromate" OR 13765-19-0[RN] OR 1333-82-0[RN] OR 7789-00-6[RN] OR 7778-50-9[RN] OR 7775-11-3[RN] OR 7789-12-0[RN] OR 13530-65-9[RN] OR 7738-94-5[rn] OR 18540-29-9[rn] OR 7758-97-6[RN] OR 11119-70-3[rn] OR 11103-86-9[rn] OR 13530-65-9[rn] OR 7788-98-9[rn] OR 77898-09-5[rn] OR 7789-06-2[rn]) AND ((("Epidemiologic Studies"[mh] OR "epidemiology"[sh] OR "Meta-Analysis"[pt] OR "Case Reports"[pt] OR workmen*[tiab] OR Worker*[tiab] OR "occupational exposure"[mh] OR Seroepidemiologic-Stud*[tiab] OR retrospective-stud*[tiab] OR prospective-stud*[tiab] OR Mortality[tiab] OR longitudinal-stud*[tiab]

OR follow-up stud*[tiab] OR ecological-study[tiab] OR ecological-studies[tiab] OR Cross-Sectional Stud*[tiab] OR Correlation-stud*[tiab] OR cohort*[tiab] OR case-control*[tiab] OR cancer-registr*[tiab] OR case-series[tiab] OR case-referent[tiab] OR record-link*[tiab])) OR ((metaanalysis[tiab] OR case-report[tiab] OR metaanalyses[tiab] OR meta-analys*[tiab]) OR ("randomized controlled trial"[tiab]) OR ("case-crossover"[tiab]) OR ("case-cross over"[tiab]) OR ("systematic review"[pt]) OR community[tiab]))))

Table A2. Web of Science search terms for human epidemiologic studies of hexavalent chromium toxicity

(TS=(chromate* OR chromium OR (chrom* AND electroplat*) OR (“stainless steel” AND weld*) OR (“stainless steel” AND grind*) OR (“portland cement”) OR (“ferrochrome production”) OR (“chrome pigment*”) OR (“chromium pigment*”) OR (chrom* AND “leather tann*”) OR (hexavalent chromium) OR (hexavalent AND chromium) OR CRVI OR CR VI OR "Chromic acid" OR "Calcium chromate" OR "Potassium dichromate" OR "Potassium chromate" OR "Sodium chromate" OR "lead chromate" OR "zinc chromate" OR "strontium chromate" OR "ammonium dichromate")) AND (TS=(workmen* OR Worker* OR "occupational exposure” OR "Case Report*” OR case-series OR Seroepidemiologic-Stud* OR retrospective-stud* OR prospective-stud* OR Mortality OR incidence OR longitudinal-stud* OR follow-up stud* OR ecological-stud* OR Cross-Sectional Stud* OR Correlation-stud* OR cohort* OR case-control* OR case-referent OR cancer-registr* OR record-link*OR "randomized controlled trial" OR "case-crossover" OR "case-cross over")) AND (SU = (Toxicology or Biochemistry molecular biology or Public environmental occupational health or Dermatology or Cell biology or Oncology or Life sciences biomedicine other topics or Allergy or Veterinary sciences or Developmental biology or Immunology or Reproductive biology or Pathology or Physiology or Urology nephrology or Hematology or Neurosciences neurology or Respiratory system or Cardiovascular system cardiology or Obstetrics gynecology or Infectious diseases or Gastroenterology hepatology or Microscopy or Endocrinology metabolism or general internal medicine or Otorhinolaryngology or Pediatrics or psychiatry or environmental sciences ecology or nursing))

Title and abstract review: The numbers of publications identified or excluded at each stage of the literature search and study review process are shown in Figure 1. All publications identified in the PubMed and Web of Science searches described above were placed into a single database and duplicate publications were removed. The titles and abstracts of all remaining publications were then reviewed in order to identify all studies of Cr(VI)-related human health effects. The following types of publications were excluded in this step (“Exclusion 1” in Figure 1): studies in laboratory animals, studies of concrete materials sciences, ecology studies (e.g., Cr(VI) soil remediation or waste water treatment), studies of human exposure but not health effects, studies in human or

laboratory animal cell lines or similar types of mechanistic studies (e.g., DNA methylation, metabolome, micronuclei), review articles, risk assessments, or other unrelated studies. Most of the excluded studies classified as “other unrelated” were of orthopedic or dental issues, materials sciences, or articles that did not involve chromium. In a few instances, it was unclear from the abstract and title whether an article met one of these exclusion criteria. In these instances, the full article was examined and excluded from further review if one of the exclusion criteria listed above was met.

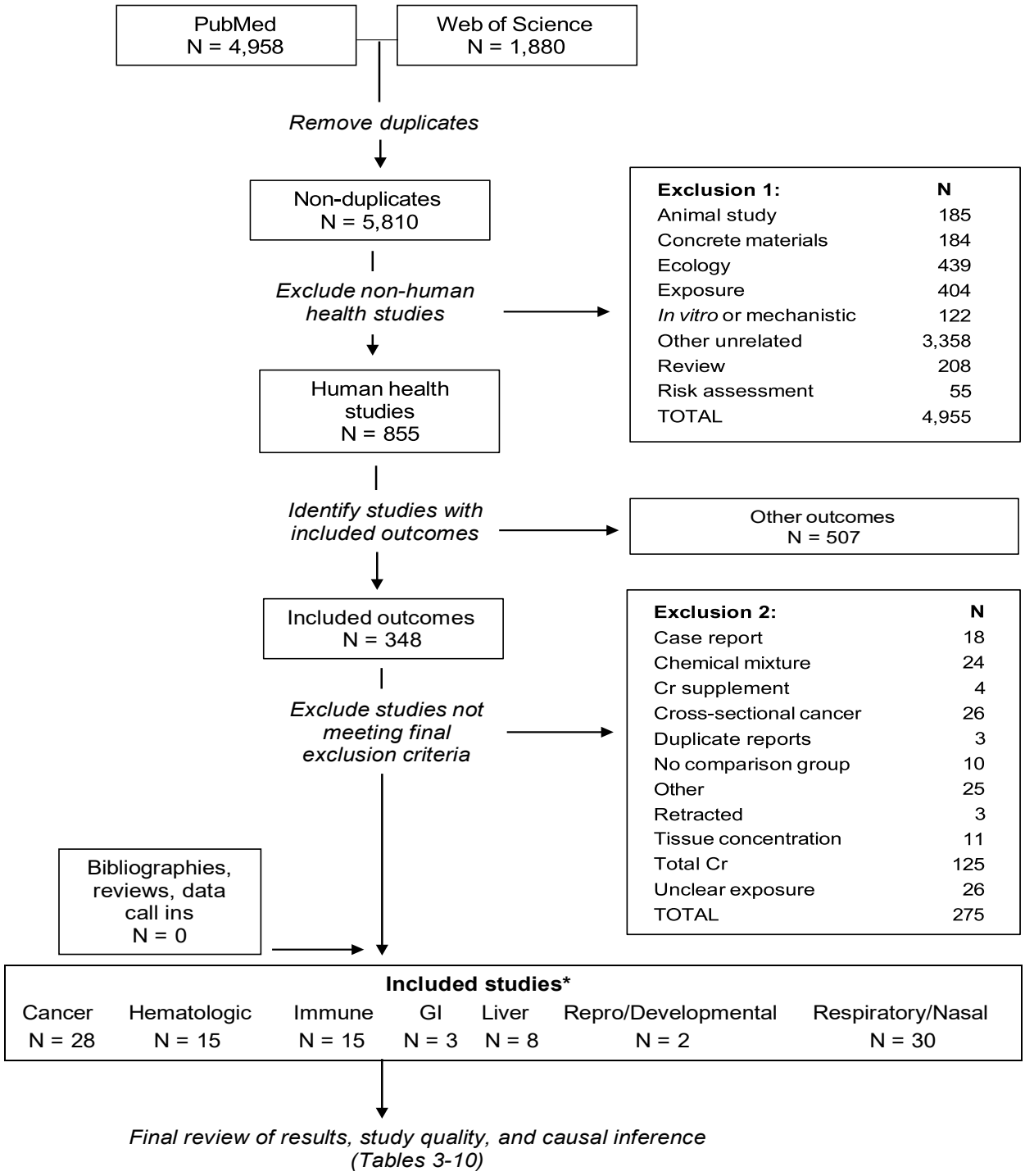
Outcome selection: The purpose of the literature search and the title and abstract review described above was to identify human research on any Cr(VI)-related adverse health effect. However, because the ultimate goal of this process was to find data that could be used for dose-response assessment, the focus of the subsequent more detailed evaluations of study quality and causal inference was limited to research involving outcomes already known or most likely to be related to Cr(VI). These outcomes were chosen based on the conclusions of previous reviews and hazard identification documents from multiple agencies and authors including OEHHA (OEHHA, 2011, 2010), the US Environmental Protection Agency (US EPA) (US EPA, 1998, 2022), the Agency for Toxic Substances and Disease Registry (ATSDR) (ATSDR, 2012), the International Agency for Research on Cancer (IARC) (IARC, 2018), and others (Health Canada, 2015; OSHA, 2006; Alvarez et al., 2021; Batyrova et al., 2022; Binazzi et al., 2015; Deng et al., 2019; Dutta et al., 2022; Georgaki and Charalambous, 2023; Hessel et al., 2021; Hossini et al., 2022; Pereira et al., 2021; Yatera et al., 2018). The selected outcomes included cancer, as well as noncancer respiratory (including nasal), gastrointestinal (GI), hepatic, hematologic, immunologic, reproductive, and developmental health effects.

It is acknowledged that other health outcomes could be caused by Cr(VI), including neurologic disease, cardiovascular disease, diabetes, or renal disease. However, a preliminary assessment of the studies of these outcomes found that they commonly involved only total chromium exposure (that is, Cr(VI) plus chromium-3 (Cr(III))), reported findings that were not consistent across different studies, involved non-oral routes of exposure, did not include relevant or suitable dose-response data, or had some other significant weakness that might limit their validity or would likely preclude their use for assessing dose-response.

Identifying relevant studies of included outcomes: Following the title and abstract review described above, the remaining publications were screened and those with at least one of the included health outcomes (respiratory, GI, hepatic, hematologic, immunologic, reproductive, developmental, or cancer) were identified. All of these studies then underwent a second review where an additional set of exclusion criteria were applied (“Exclusion 2” in Figure 1). In some instances, this involved only a review of the publication abstract, but in many instances, it required a review of the full publication. Here, the following types of studies were excluded: case reports; studies

involving only chemical mixtures (e.g., results only presented for multiple chemical agents combined); Cr(III) supplement clinical trials; cross-sectional studies of cancer; studies without an appropriate comparison group (e.g., no unexposed or lower exposure comparison group); retracted articles; studies only involving concentrations of chromium in tissues (other than blood); studies in which the effects of Cr(III) and Cr(VI) could not be reasonably distinguished; and studies with unclear exposure information. Cross-sectional studies of cancer (Proctor et al., 2016; Gibb et al., 2015), i.e., those in which exposure was assessed only at the time of cancer diagnosis were excluded. Because of the potentially long latency of Cr(VI)-induced cancer, exposure information at the time of diagnosis may not present the relevant exposure period, which is likely to be many years prior to cancer diagnosis. Cross-sectional studies of noncancer outcomes were included, although the possibility of reverse causation was assessed. Ecologic studies were included, but the possibility of ecologic fallacy or confounding was assessed. Studies were excluded if they only involved participants from the general population (i.e., people or groups without a known high Cr(VI) exposure source) and the exposure assessment only examined total Cr (Cr(III) plus Cr(VI)). However, studies in populations with known high exposures to Cr(VI), either occupationally or environmentally, were included, even if the primary exposure metric was total Cr. The rationale for this is that a large fraction of the total Cr intake in the exposed participants of these studies could have been Cr(VI). If two publications presented findings on the same study population ("duplicate reports") only one was selected for further review using the following criteria in the following order: adjustments for important confounders, more specific and accurate exposure information, larger sample size, or most recently published. For duplicate reports involving cancer outcomes, publications presenting information on cancer incidence were selected over those reporting on cancer mortality.

Figure A1.1 Literature search and the review process for human epidemiologic studies of hexavalent chromium toxicity published since January 1, 2011



*Some publications provided results for more than one included outcome

Detailed study review: The included studies underwent a more detailed review for study quality and causal inference. The factors assessed in these detailed reviews included study design, participant selection, exposure and outcome assessment, the potential for exposure or outcome misclassification, reporting completeness, statistical analyses, internal and external consistency, confounding, dose-response, temporality, generalizability, and dose-response. The selection of these factors was based on the principles and practices presented by Hill and the National Toxicology Program (Hill, 1965; NTP, 2019). Tables were developed for this document that include at least some information on most if not all of these study quality or causal inference factors (Tables 3-10). Importantly though, since the primary goal of this review was to identify data that could be used for dose-response calculations, the information in these tables is sometimes limited to those factors most relevant to achieving this goal.

APPENDIX 2. HUMAN EPIDEMIOLOGIC STUDIES OF CR(VI)

Table A2.1 Human epidemiologic studies of hexavalent chromium and respiratory and nasal effects published since January 1, 2011[1]

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Ba et al., 2012	Cross-sectional	China: Henan Province	Work activities	Spirometry	Spirometry measured and questionnaire information collected from 95 chromate exposed workers and 42 workers not exposed to chromate (logistics and administrative) all from a chromate manufacturing facility	Approximately 5-10% decreases in FVC, FEV1, PEF and other spirometry metrics in chromate exposed workers vs. controls (all $p<0.05$)	Adjusted for age, sex, height, and weight. Few details on selection methods and participation rates.	No: exposure based only on work activities
Chandrase-karan et al., 2014	Cross-sectional	India: Ambur	Work activities and duration	Spirometry	Spirometry measured and questionnaire information collected from 130 male leather tannery workers and 130 male unexposed office workers	Indices of pulmonary function lower in exposed participants than controls; FVC: 2.92±0.80 vs. 3.35±0.67 liters, $p<0.001$; FEV1: 2.52±0.68 vs. 3.01±0.59, $p<0.001$; FEV1/FVC: 0.86±0.62 vs. 0.9±0.03, $p<0.001$, in exposed and control groups, respectively	Subjects worked at least two years at the facility. Subjects with tuberculosis or with recent eye or abdominal surgeries excluded. Exposed and unexposed groups were of similar ages and BMIs. No other demographic comparisons provided. No other details on selection methods or participation rates. No statistical adjustments mentioned. Unusually small standard deviation for FEV1/FVC ratio in the control group.	No: results based only on work activities and duration
Elhosary et al., 2014	Cross-sectional	Egypt: multiple sites	Work history; blood and urine total Cr	Nasal injury and respiratory symptoms	Physical exams and symptom reports collected from 20 tannery workers and 23 unexposed controls; all participants were male and ages 14-56 years	The correlation between duration of tannery work and nasal symptoms was 0.546, $p=0.01$; the correlation between duration of tannery work and respiratory symptoms was 0.529, $p=0.01$; weaker correlations seen with blood total Cr; comparisons with the unexposed control group unclear	Cement workers also included in the study, but exposure to Portland cement is not mentioned. People with severe medical illnesses were excluded. Tannery workers and controls were similar in terms of age, education levels, and smoking. Few details on selection methods or participation rates. Nasal symptoms included sneezing, rhinorrhea, allergic rhinitis, septal perforation, and bleeding. Respiratory symptoms included cough, wheeze, asthma, hemoptysis, and chest infections. No statistical adjustments mentioned.	No: only unadjusted correlation coefficients presented

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Gibb et al., 2015	Retro-spective cohort	US: Baltimore	Job titles and workplace Cr(VI) air measure-ments	Respiratory disease	Job history and mortality information collected on all 2,354 male workers at a chromium production facility who worked at sometime between 1950-1974	All noncancer respiratory system disease SMR = 0.90 (0.75-1.08, n=120 deaths); similar SMRs for COPD and pneumonia; elevated ORs seen for perforated nasal septum (OR = 2.656 (1.148-6.145)) and other nasal irritation outcomes	Includes all male workers at the included facility. Includes long and short-term workers (i.e., worked <90 days). Deaths ascertained from the National Death Index. Adjustments or stratification for age, race, and calendar year. State rates used for comparison. Follow-up through 2011. Average follow-up of 38.9 years. ICD9 codes not provided.	No: SMR or ORs for whole cohort, no Cr(VI) specific data
Giordano et al., 2012	Retro-spective cohort	Italy: Rome	Employ-ment at cement factory	Respiratory disease	Mortality assessed in all 748 male Portland cement production workers employed sometime between 1956-2006 at a single cement plant; vital status assessed for 1969-2006 from local health units or municipal death records; includes a total of 280 deaths; regional and city death rates used for comparison	Diseases of the respiratory system SMR = 1.41 (0.95-2.03, n=29 deaths); SMRs similar in the higher and medium exposure groups, and higher in those with prior asbestos cement exposure (SMR = 2.29 (0.74-5.34, n=5 cases))	Some workers had prior asbestos cement exposure. No clear dose-response relationship based on years worked (i.e., greater vs. less than 10 years worked). No information on smoking or other potential confounders. Results for specific respiratory conditions not provided. Includes ICD9 codes 460-519.	No: exposure based only on employment at the included facility
Hamzah et al., 2014, 2016	Cross-sectional	Malaysia: Tereng-ganu	Workplace personal air measures of Cr(VI); air sampling data and years worked used to calculate cumulative exposure	Spirometry and respiratory symptoms	Spirometry (n=184) measured and respiratory symptom information (n=402) collected in male steel plant workers ages 18-56 years employed at least one year at a steel factory	Approximately 5-10% decline in FEV1 and FVC comparing participants with cumulative Cr(VI) exposures ≥2.0 mg/m^3-years to those with cumulative exposures <0.50 mg/m^3-years ($p<0.001$ and $p<0.05$, respectively); effect sizes diminish after adjustments; little change in FEV1/FVC with increasing cumulative exposure; shortness of breath OR for each mg/m^3-year cumulative Cr(VI) exposure = 1.86 (1.19-2.90); ORs for chronic cough, chronic phlegm, or chest tightness near 1.0	Few details on selection methods or participation rates for spirometry portion. 436 of 1,000 workers were randomly selected and 94% completed the symptom questionnaire. Average duration of employment was 12.2 years. ATS criteria used for spirometry. British Medical Respiratory Council questionnaire used to collect symptom information. Results adjusted for age, height, smoking, past dusty occupations, past respiratory illnesses, and frequency of wearing mask. All participants were the same ethnicity.	Occupational Cr(VI) levels in air

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Huvinen and Pukkala, 2016	Retro-spective cohort	Finland: Kemi Mine and Tornio Works	Job histories	Respiratory disease	Mortality assessed in 8,088 ferrochromium and stainless steel production workers employed sometime between 1967-2004; causes of death obtained from Statistics Finland; regional death rates used for comparison	Diseases of the respiratory system SMR = 0.71 (0.43-1.09, n=20 deaths). SMRs for pneumonia, bronchitis, and emphysema are below 1.0.	Includes all workers at the included facilities. Standardized for age and sex. Follow-up through 2012.	No: results based only on work area
Islam et al., 2019	Cross-sectional	Bangla-desh: Hazari-bagh	Work activities; serum total Cr measured but not used to test associa-tions with respiratory conditions	Respiratory symptoms	Questionnaire information and serum collected from 195 male leather tannery workers who worked at least 2 years and 125 controls who worked in the same region in other jobs (i.e., offices, shops, banks, and student dormitories)	Respiratory problems including rhinitis, cough, and chest sounds combined were greater in tannery workers than controls (12.3% vs. 4.0%, $p<0.05$)	Participants with chronic illnesses excluded. Exposed and controls similar in terms of age, blood pressure, and BMI. No statistical adjustments mentioned. Few details on control selection and participation rates. Multiple respiratory conditions combined, results not given for specific conditions.	No: exposure based only on work activities
Jeyamala et al., 2012	Cross-sectional	India: Madurai District	Work activities and durations	Respiratory symptoms	Symptom reports, hair and blood samples collected from 23 workers in the thread cutting and punch press operations areas randomly selected from several electroplating facilities in the study area and 7 unexposed controls from "outside this environment and not related to any industry"	Percentage reporting cough (29% vs. 1%), nasal irritation (35% vs.11%), congestion (41% vs. 0%), and phlegm discharge (29% vs. 0%) higher in exposed than unexposed participants	No other details on control selection or participation rates provided. No demographic comparisons of exposed and controls, and no statistical adjustments mentioned. P-values or confidence intervals not provided.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Kakooei et al., 2012	Cross-sectional	Iran: Ghaen	Work activities and personal respiratory dust measure-ments	Spirometry and respiratory symptoms	Respiratory symptoms (ATS Questionnaire on Respiratory Symptoms), and spirometry assessed in 94 workers exposed to cement dust and 54 lesser exposed administrative workers from a Portland cement factory	Prevalence of cough, wheezing, sputum production, and dyspnea approximately 20-30% higher in the exposed group compared to the lesser exposed group (all p-values >0.05); pulmonary function parameters lower in the exposed group; FEV1: 3.1 vs. 3.42 liters (p<0.001); FVC: 3.86 vs 4.17 liters (p=0.006); FEV1/FVC: 0.79 vs. 0.82 (p=0.006) in the exposed group vs. controls, respectively	Few details on selection methods or participation rates. ATS guidelines used for spirometry. Exposed and lesser exposed groups similar in terms of age, BMI, work duration at facility, and smoking. No statistical adjustments mentioned.	No: exposure based only on work activities
Kargar Shouroki et al., 2018	Cross-sectional	Iran: Yazd City	Work activities; urine total Cr collected but not used to test associa-tions with health effects	Spirometry	Spirometry measured in 49 male ceramic glazers ages 22-50 years who worked with Cr(VI) pigments and 55 similarly aged male office workers from the same facility	FEV1 and FVC approximately 10-20% lower in glazers than in controls (p=0.001 for both); FEV1/FVC ratio approximately 10% lower in glazers (p=0.001)	People with chronic respiratory diseases, asthma, and lung infections were excluded. No subjects were smokers. No statistical adjustments mentioned. Few details on selection methods or participation rates.	No: exposure based only on work activities
Kashyap et al., 2021	Cross-sectional	India: Kanpur City	Work in leather tannery and years worked	Respiratory symptoms	Respiratory symptom information collected from 284 leather tannery workers and 289 non-tannery workers ages 18-70 years, from multiple facilities	For tannery work >10 years: chronic bronchitis OR = 2.90 (0.97-8.64); asthma symptoms OR = 2.51 (0.87-7.27)	Participants randomly selected from a household survey in the study area. Participation rate of approximately 95%. Unexposed comparison group were mostly manual laborers, and business and shop owners. Average duration of tannery work in tannery workers was 18 years. Statistical adjustments are unclear.	No: exposure based only on work activities and years worked

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Kauppi et al., 2015	Controlled trial	Finland: Helsinki	Controlled single exposure to stainless steel welding fumes	Spirometry	15 participants with suspected occupational asthma referred to the Finnish Institute of Occupational Health underwent stainless steel challenge test in an exposure chamber; spirometry assessed 22 hours after challenge	4% decline in FEV1 (p=0.26) and 7% decline in PEF (p=0.022) following challenge test. 5 participants met occupational asthma criteria following challenge.	Generalizability and relevance to chronic toxicity are unclear. Average inhalable stainless steel welding particle mass concentration of 40.2 mg/m^3.	No: single challenge test, relevance unclear
Kristiansen et al., 2015	Retrospective cohort	Denmark: multiple areas	Work history, air measurements for total dust, and an exposure matrix used to assess total cumulative dust exposure	Medication use for asthma	Danish Medicinal Product Registry searched for asthma medication use in 5,303 male workers from 79 companies reporting welding work any time between 1995 to 2011; 1,729 and 15 welders had medium (15-100 mg/m^3-year) and high cumulative exposure (>100 mg/m^3-year) to total dust from stainless steel welding, respectively	HR for medication use in non-smokers for high dust exposure from stainless steel welding = 1.46 (1.06-2.02) compared to low exposure group (<15 mg/m^3 year). HRs for medium exposure group and for smokers near 1.0.	Small number of participants in the high exposure group. Outcome based only on medication registry. Adjustments or stratification made for age, education, reported lung disease, grinding, and lubricant or quartz sand exposure.	No: exposure based only on work activities
Li et al., 2015	Cross-sectional	China: Henan Province	Work activities; blood total Cr also measured but not used to test health effects associations	Spirometry and Clara cell protein	Spirometry and serum Clara cell protein levels measured in 91 chromium-exposed workers and 38 unexposed controls (from administrative offices in the same factory) in a factory using water soluble hexavalent chromium compounds (potassium dichromate); all worked at the factory at least 1 year and were ages 25-50 years	FVC and FEV1 approximately 10-15% lower in the exposed group vs. controls (p=0.196 and 0.011, respectively). No major difference in FEV1/FVC. Clara cell protein levels approximately 10% lower in the exposed group vs. controls (p=0.027).	Participants with major medical conditions were excluded. Few other details on selection methods or participation rates. ATS spirometry guidelines used. No other statistical adjustments mentioned. Exposed and control group mostly similar in terms of age, gender distribution, smoking, alcohol use, and BMI.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Li et al., 2016	Cross-sectional	China: Shandong and Henan Provinces	Work activities; air, blood, and urine total Cr	Nasal injury	"Nasal injury" assessed via self-reported questionnaire in 262 participants who worked in Cr(VI) producing factories for at least one year sometime in 2006, 2008, or 2011, and 135 control participants "without chromium exposure" from administrative offices or "a place approximately 20 km away from the factory;" all were ages 25-50 years	No clear increase in nasal injury in the group with blood total Cr >20 µg/L (2 cases in 13 exposed participants vs. 1 case in 21 controls, p=0.621). Nasal injury results only given for participants in 2011.	All participants free of major medical illnesses. Somewhat more smokers in the Cr(VI) exposed group but ages, gender distribution, and percentage of alcohol consumers was similar between exposure groups. Few other details on selection methods or participation rates. Nasal injury not defined. Sample sizes are unclear.	No: exposure based only on work activities
Lipworth et al., 2011	Retro-spective cohort	US: Burbank	Job histories and classifica-tions by experts; job activity with chromate exposure	Nonmalig-nant respiratory disease	Mortality assessed in 77,943 workers employed at an aircraft manufacturing facility exposed to chromates; includes workers employed at least one year from 1960; cases ascertained from state and national death records; state and national death rates used for comparison	Nonmalignant respiratory disease SMR = 0.95 (0.85-1.05, n=361 deaths). Bronchitis, emphysema, and asthma combined SMR = 1.23 (1.04-1.45, n=143 deaths).	Adjusted for race, age, sex, and year. Follow-up through 2008. Average follow-up of 31.8 years. Includes ICD9 codes 460-519.	No: exposure based only on work activities
Liu et al., 2019	Cross-sectional	Mongolia: Baotou City	Work history and blood total Cr	Spirometry	Spirometry measured in 22 chromate exposed workers and 44 unexposed controls from the same electroplating facility	Correlations between whole blood total Cr and PEF, MVV and FEF25-75% were -0.53, -0.52, and -0.44 (all p-values <0.05).	Average exposure duration of 31 years. Workers with serious illnesses excluded. Few other details on selection methods or participation rates. Adjusted for age, sex, BMI, smoking, and alcohol consumption.	No: results provided only as correlation coefficients or based on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Mbelambela et al., 2018	Cross-sectional	Democra-tic Republic of Congo: Kongo Central Province	Work activities	Spirometry and respiratory symptoms	Spirometry measured and questionnaire information collected from 123 Portland cement production workers and 82 less exposed (administration, laboratory, and other) workers from the same cement facility; workers from another facility were also investigated but did not work with Portland cement at the time of the study; all participants worked >5 years at the facility, and were ages 30-65 years	FEV1, FVC, and FEV1/FVC ratio approximately 10-30% lower in the exposed group vs. controls ($p<0.05$ for all). ORs for chronic cough, chronic phlegm, and COPD were 2.25 (1.08-4.67), 1.10 (0.49-2.45), and 4.93 (1.75-13.84), respectively. ORs for wheezing, shortness of breath, and chest pain near or below 1.0.	ATS guidelines used for spirometry. No major differences in demographic characteristics, including smoking, between exposed and unexposed groups. Few other details provided on selection methods or participation rates. Adjusted for age, BMI, duration of employment, education, medical history, and smoking.	No: exposure based only on work activities
Rabbani et al., 2021	Cross-sectional	Bangladesh: Hazaribagh	Work activities and years worked	Respiratory symptoms	Respiratory questionnaire in 167 workers randomly selected from 10 leather tanneries age >15 years and working in tanneries at least 2 years	ORs per each 1 year worked at tannery for "breathing difficulty" (includes self-reported asthma, shortness of breath and wheezing, tightness of chest, or any other lung disease) was 1.32 (1.07-1.64). Higher ORs in those in wet and dry finishing.	Adjusted for age, smoking, education, and income. Exposure based primarily on years worked. Workers were randomly selected from all full-time workers at the tannery. Response rates of 72%.	No: exposure based only on work activities and years worked
Rafeemanesh et al., 2015	Cross-sectional	Iran: Mashhad	Work activities	Spirometry and respiratory symptoms	Spirometry measured and respiratory questionnaire information collected from 100 exposed and 120 unexposed workers at a Portland cement facility who worked at least 2 years	Self-reported dyspnea (8% vs. 4.1%, $p=0.23$), sputum production (7% vs. <1%, $p=0.02$), and cough (6% vs. <1%, $p=0.04$) greater in the exposed group than in controls. Rates of chest pain and wheezing were similar between the exposed and control group. FEV1 and FVC about 2-3% lower in the exposed group ($p>0.05$). FEF approximately 6% lower in the exposed group vs. controls ($p=0.04$).	People with chronic lung disease were excluded. Participants were randomly selected from all workers at the factory. ATS criteria used for spirometry. No other statistical adjustments mentioned. Exposed and unexposed groups were similar in age, years worked, BMI, and smoking history.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Remy and Clay, 2014	Ecologic	US: Willits	Residence in area with Cr(VI) water contami-nation	Respiratory disease	Hospital discharge data for the years 1991-2012 comparing residents from the exposed area (Willits, California) to residents from the rest of the county; discharge data from California's Office of Statewide Health Planning and Development	Any disease of the respiratory system relative risk = 1.19 (1.11-1.27, n=151 excess cases) in males and 1.43 (1.34-1.52, n=371 excess cases) in females	Area with drinking water contamination with Cr(VI) by a chrome plating facility. County and city population rates used for comparison. Stratified by sex, adjusted by age. All residents in Willits and Mendocino Counties included. Results not given for specific respiratory outcomes. Multiple other outcomes assessed.	No: exposure based only on area of residence
Richard et al., 2016	Cross-sectional	Nigeria: Mfamosing	Work activities and years worked	Peak flow	Questionnaire data collected and peak flow measured in 50 male Portland cement workers exposed to cement dust for at least 2 years, 60 people who lived near the facility for at least 2 years, and 100 people living 45 km away from the exposed facility, all ages 18-60 years	Peak flow lower in workers (mean = 324.96±10.40 L/min) and nearby residents (340.25±10.38 L/min) compared to controls (400.17±9.10 L/min) ($p<0.05$ for both comparisons). Correlation between years worked in cement work and peak flow = -0.416 ($p=0.016$).	Participants were "randomly selected" for the study. Few other details on selection methods or participation rates provided. Nearby residents reportedly had much higher mean serum total Cr levels than workers (1.60±0.125 vs. 0.033±0.013 µg/dL). Demographic characteristics of each group not provided. No statistical adjustments mentioned.	No: exposure based only on work activities and years worked
Roach et al., 2018	Retro-spective cohort	US: Tennessee	Work activities	Spirometry	Medical records reviewed in 39 Cr(VI) welders ages 20-69 years employed at a single company	Years welding was a "statistically significant predictor of PFT" in smokers ($p=0.04$) but not in non-smokers. No other relevant results provided.	Controlled for age and percent time wearing respirator. "Pulmonary function test" is not described. A figure with the individual results is presented but unclear.	No: unclear outcome, and exposure based only on work activities and years worked

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Sharma et al., 2012	Cross-sectional	India: Kanpur	Residence in area with Cr(VI) ground-water contami-nation	Spirometry and respiratory symptoms	Self-reported questionnaires, spirometry, and physical exams collected from or performed in 186 participants from an area with Cr(VI) contamination in ground water, and 230 controls from an area without Cr(VI) contamination; inclusion criteria include age ≥18 years, residence in area >1 year, not consuming bottled water, and no workplace exposure to Cr(VI)	ORs for self-reported respiratory complaints = 1.21 (0.58-2.54) in males and 0.64 (0.27-1.54) in females comparing exposed and unexposed participants. Approximate 6% decline in FEV1 and 12% decline in PEFR in the exposed vs. unexposed groups ($p>0.05$). "Overall spirometric abnormalities" were higher among the exposed group (20% vs. 8.6%, $p<0.05$), but no other details provided for this result.	Few details on selection methods and participation rates. Area with leather tanneries and chrome sulfate manufacturing facilities. ATS criteria used for spirometry. Results adjusted for age, smoking, education, and self-reported allergy and asthma. Cr(VI) levels in water approximately 20 ppm. Few other details on exposure provided.	No: exposure based only on residential location
Singhal et al., 2015	Cross-sectional	India: Haryana	Years worked in exposed activity	Nasal symptoms	Self-reported medical history and examinations in 130 male sodium dichromate manufacturing and chrome plating workers	Severity of abnormalities of the nasal mucous membranes appear to increase (e.g., nasal perforation) with greater duration of exposure (>5 years vs. 0-5 years) but increases don't appear to be statistically significant	Study included "all available workers." Few other details on selection methods or participation rates provided. No truly unexposed comparison group. Details of statistical analyses not provided.	No: exposure based only on years worked
Storaas et al., 2015	Prospec-tive cohort	Northern Europe: multiple sites	Self-reported job history	Respiratory symptoms	Questionnaire information on asthma diagnoses, nasal symptoms, and stainless steel welding was collected from participants of a large prospective cohort (n=16,191); 173 participants reported stainless steel welding >6 months; ages 20-44 at recruitment in 1990-94	HR for rhinitis in stainless steel welders = 1.6 (1.2-2.2, n=38 cases). HR for asthma = 1.8 (0.8-3.7, n=7 cases) in both sexes combined and 2.3 (1.1-4.9, n=7 cases) in males. No incident cases of asthma in females.	The underlying cohort was the Respiratory Health in Northern Europe (RHINE) study. Results adjusted for sex, study center, smoking, and education. Follow-up of approximately 5-10 years. Participation rate at follow-up was 75-84%.	No: exposure based only on work activities
Xu et al., 2022	Retro-spective cohort	China: Shandong Province	Work activities	Multiple	Questionnaire, blood samples, and other data collected in 850 workers exposed to chromate and 598 workers not exposed to chromate (control group) from a steel plant in Shandong Province working in 2016-2017	Incidence of nasal damage (32.4% vs. 7.5%, $p<0.001$) and abnormal chest x-rays (39.2% vs. 30.9%, $p=0.001$) higher in the exposed workers than in controls.	Workers at a steel factory who worked with chrome slag. Workers with major illnesses excluded. Few details on selection methods or participation rates. Average exposure duration of 6.92 years. No statistical adjustments mentioned.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Zhang et al., 2022	Prospec-tive cohort	China: unclear	Whole blood total Cr	Spirometry	Spirometry measured in all 515 workers involved in chromate production from a single plant who worked at least 1 year	Percentage change for each 1 unit increase in lognormal transformed blood Cr: FVC = -1.03 (-2.42-0.30, p=0.115), FEV1 = -1.80 (-3.15 to -0.35, p=0.009), FEV1/FVC = -0.77 (-1.43 to -0.10, p=0.024). Statistically significant declines also seen for PEF and FEF25-75%. Some relatively small differences by age, sex, BMI, and smoking and drinking status. Categorical results by blood total Cr quartiles given in Table S3 of the publication, with mostly linear dose-response relationships.	The cohort was the Occupational Chromate Exposure Dynamic Cohort of China (OCEDCC), which included workers at several chromate production and application plants throughout China. Workers at only one plant were included in this analysis. Participants with major medical illnesses were excluded. Participants were followed from 2010 to 2017. Spirometry appears to have been performed at various times during the follow-up period. ATS guidelines used for spirometry. Follow-up rates not clear. Adjustments made for age, sex, year, smoking, drinking, height and weight.	No: inhalation exposure and exposure assessment based on total blood Cr only
Zheng et al., 2023	Ecologic	China: Guangzhou	Air Cr(VI): 24-hour mean concentra-tions for 265 days from 2017-2019 at a single air monitoring station in the study area	Respiratory disease	Rates of pediatric hospital outpatient visits compared to air levels of Cr(VI) in Guangzhou for the period 2017-2019	Percentage change for each interquartile increase in air Cr(VI) were: all respiratory diseases = 1.56 (1.12-2.01); acute upper respiratory infections = 2.74 (2.13-3.35); acute lower respiratory tract infections = 2.19 (1.17-3.23); and influenza and pneumonia = -6.72 (-8.27 to -5.14). Similar increases seen for other metals including arsenic and nickel.	Includes children ages 18 years and younger. Mean Cr(VI) concentration = 3.22±4.83 ng/m^3. Correlations across different air pollution constituents not provided. Information on outpatient visits obtained from the Guangzhou Yuexiu District Children's Hospital. Statistical adjustments are unclear.	No: clear or relevant dose-response data not provided

Abbreviations: ATS, American Thoracic Society; BMI, body mass index; COPD, chronic obstructive pulmonary disease; Cr, chromium; Cr(VI), hexavalent chromium; FEF25-75%, forced mid expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; ICD, International Classification of Diseases; MVV, maximum voluntary ventilation; OR, odds ratio; PEF, peak expiratory flow; PEFR, peak expiratory flow rate; PFT, pulmonary function test; SMR, standardized mortality ratio

1. Numbers in parentheses following odds ratios or other results are 95% confidence intervals unless otherwise noted; numbers following "±" are standard deviations unless otherwise noted
2. Overall assessment of whether the study can be used to quantitatively estimate the dose-response relationship between hexavalent chromium in drinking water and respiratory outcomes

Table A2.2 Human epidemiologic studies of hexavalent chromium and hematologic effects published since January 1, 2011[1]

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Gibb et al., 2015	Retrospec-tive cohort	US: Baltimore	Job titles and workplace Cr(VI) air measure-ments	Blood and blood forming organ disease	Job history and mortality information collected on all 2,354 male workers at a chromium production facility who worked at some point between 1950-1974	Blood and blood forming organ disease SMR = 1.38 (0.63-2.63, n=9 deaths).	Includes long- and short-term workers (i.e., worked <90 days). Deaths ascertained from the National Death Index. Adjustments or stratification for age, race, and calendar year. State rates used for comparison. Update of several previous reports. Follow-up through 2011. Average follow-up of 38.9 years. ICD9 codes not provided.	No: SMR for whole cohort, no specific data on Cr(VI)
Hu et al., 2017b	Cross-sectional	China	Work activities	Blood erythrocyte levels	Erythrocyte levels in blood measured in 343 chromate exposed workers and 73 unexposed controls	The risk for reduced erythrocyte levels was increased by 0.915 (0.852-0.982) in the chromate-exposed group compared to controls. Greater relative risks in males and in alcohol consumers.	Adjusted for age, gender, smoking, alcohol consumption, and BMI. Only abstract available.	No: exposure based only on work activities
Jeyamala et al., 2012	Cross-sectional	India: Madurai District	Work activities and durations	Hemoglobin concentration and white blood cell percentages	Symptom reports, hair and blood samples collected in 23 workers in the thread cutting and punch press operations areas randomly selected from several electroplating facilities in the study area, and 7 unexposed controls "outside this environment and not related to any industry"	Serum mean hemoglobin concentrations of 11.10±0.58 vs. 10.66±0.52 g/dL, in exposed and unexposed groups, respectively. Percentage of polymorphonuclear leukocytes 9% greater in exposed group than in controls.	No other details on control selection or participation rates provided. No demographic comparisons of exposed and control groups, and no statistical adjustments mentioned. P-values or confidence intervals not provided.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Kauppi et al., 2015	Controlled clinical trial	Finland: Helsinki	Controlled single exposure to stainless steel welding fumes	Multiple blood indices	15 male participants with suspected occupational asthma referred to the Finnish Institute of Occupational Health underwent stainless steel challenge test in an exposure chamber; serum collected before and after the challenge	Eosinophil count lower after challenge (0.25±0.09 before vs. 0.20±0.09 $\times 10^9$/L after, p=0.022). Hemoglobin and erythrocyte counts also lower but difference is <3%, p<0.05 for both). Leukocyte, neutrophil, monocyte, and platelet counts approximately 5-50% higher after challenge (all p-values <0.05). Some differences are smaller when men with occupational asthma are excluded. Statistically significant differences not seen in basophil or lymphocyte counts.	Generalizability and relevance to chronic toxicity are unclear. Timing of blood sampling is unclear. Average inhalable stainless steel welding particle mass concentration of 40.2 mg/m^3.	No: single challenge test, relevance unclear
Khan et al., 2013	Cross-sectional	Pakistan: Sialkot	Job titles; whole blood total Cr measured but not used to test health effect associa-tions.	Hemoglobin, white and red blood cell counts, and platelet count	120 "randomly selected" male leather tannery workers from multiple facilities who worked >5 years, and 120 unexposed controls "recruited from Sialkot city," all ages 23-60 years	Mean hemoglobin (12.52±1.82 vs. 14.55±1.20 g/L, p=0.001) and platelet count (246.50±64.12 vs. 290.26±76.27 $\times 10^9$/L, p=0.001) lower in the exposed group than in controls. Mean white blood cell count higher in the exposed group than in controls (8.79±1.82 vs. 7.56±1.25 $\times 10^9$/L). Mean red blood cell counts similar between exposed group and controls.	Workers with chronic illnesses excluded. Little information on control selection or participation rates. Demographic comparisons of exposed and control groups not provided. No statistical adjustments mentioned.	No: exposure based only on work activities
Lacerda et al., 2019	Cross-sectional	Brazil: Rio Grande do Sul	Work activities and blood and urine total Cr	Multiple blood indices	Blood samples and questionnaire information collected in 50 male chrome plating workers and 50 unexposed controls (administrative occupations)	Hemoglobin, hematocrit, and mean corpuscular hemoglobin all approximately 3-10% lower in the exposed group vs. controls (p<0.05 for all). Red blood cell count about 10% lower in the exposed group vs. controls (p>0.05). None of the blood indices were associated with urinary or blood total Cr (descriptive results only).	Few details on selection methods or participation rates. Blood and urinary total Cr both higher in the exposed group. Exposed group 3 years younger on average, with lower percentage of alcohol consumers (40% vs. 49%), and a greater percentage with sedentary lifestyle (46% vs. 32%) compared to controls.	No: limited results and limited information on exposure

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Qian et al., 2012	Cross-sectional	China: Jinan	Blood total Cr	Mean corpuscular hemoglobin and mean corpuscular volume	Blood samples and other information collected from 115 chromate production workers and 60 unexposed healthy residents from a community away from the factory	Blood total Cr not correlated with mean corpuscular hemoglobin or mean corpuscular volume ($p>0.05$).	Selection methods, participation rates, and adjustments not clear. Only abstract available.	No: no dose-response data provided
Ramzan et al., 2011	Cross-sectional	Pakistan: Shekhupura	Work activities	Multiple blood indices	Blood samples collected from 92 male leather tannery workers ages 20-60 years and 79 similarly aged male controls from a village "far away from tanning industry"	Red blood cell count approximately 10% lower in tannery workers than in controls in all age groups ($p<0.05$) except for ages 50-60 years where the difference was smaller. Mean corpuscular hemoglobin approximately 7% lower in exposed workers but only in workers ages 50-60 years ($p<0.05$). Hemoglobin levels and mean corpuscular volume mostly similar in exposed and unexposed groups ($p>0.05$).	People with major medical illnesses were excluded. Few details on selection methods and participation rates provided. Demographic comparisons of exposed and unexposed groups not provided. No statistical adjustments mentioned.	No: exposure based only on work activities
Remy and Clay, 2014	Ecologic	US: Willits	Residence in area with Cr(VI) drinking water contami-nation	Hospitalization for any disease of "blood/blood-forming organs"	Hospital discharge data for the years 1991-2012 comparing residents from the exposed area (Willits, California) to residents from the rest of the county; discharge data from California's Office of Statewide Health Planning and Development	Any disease of "blood/blood-forming organs" relative risk = 1.09 (1.00-1.19, n=52 excess cases) in males and 1.18 (1.10-1.26, n=150 excess cases) in females.	Area with drinking water contamination with Cr(VI) by a chrome plating facility. County rates used for comparison. Stratified by sex and adjusted by age. All residents in Willits and Mendocino County included.	No: exposure based only on area of residence

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Sazakli et al., 2014	Cross-sectional	Greece: Asopos River Basin	Total Cr in blood and hair, drinking water Cr(VI) levels, drinking water intake rates, and residential history used to calculate lifetime Cr(VI) intake	Multiple blood indices	Questionnaire information and blood collected in 304 men and women from areas with current, past, and no high levels of naturally occurring Cr(VI) in drinking water	Statistically significant regression coefficients seen between cumulative Cr(VI) exposure and hemoglobin concentration (β = -0.093, p=0.041) and hematocrit (β = -0.094, p=0.048). Multiple other blood parameters assessed but associations with cumulative Cr(VI) exposure are not statistically significant. Some inconsistencies between results for cumulative exposure estimates, total Cr in hair, and total Cr in blood.	Selection through age and gender stratified random sampling from telephone directories. 82% response rate. Cr(VI) water levels ranged from <3 to 196 µg/L (median in the current exposure area = 23 µg/L). Gender distribution, median age, education level, smoking rates, marital status, and occupational status similar between the different exposure areas. Results adjusted for age, sex, Cr occupational exposure, smoking, alcohol consumption, physical activity, and consumption of local crops. Over 50 different associations tested (hair, cumulative, and blood Cr with 19 different blood parameters).	No: only regression coefficients given, and some inconsistent results
Sharma et al., 2012	Cross-sectional	India: Kanpur	Residence in area with Cr(VI) ground-water contami-nation	Platelet and red blood cell counts, mean corpuscular volume	Self-reported questionnaires, spirometry, blood draw, and physical exams in 186 participants from an area with Cr(VI) contamination in ground water, and 230 controls from an area without Cr(VI) contamination. Inclusion criteria: age ≥18 years old, residence in area >1 year, not consuming bottled water, and no workplace exposure to Cr(VI)	Mean platelet count lower in the exposed participants than in controls (men: 39% lower; women: 47% lower; p<0.001 for both sexes). Mean red blood cell count higher in the exposed participants than in controls (men: 23% higher; women: 31% higher; p<0.001 for both sexes). Mean corpuscular volume approximately 8% lower in the exposed group but only in men (p<0.001).	Few details of selection methods and participation rates. Exposed area with leather tanneries and chrome sulfate manufacturing. Results adjusted for age and smoking. Cr(VI) levels in water approximately 20 ppm. Few other details on exposure provided.	No: exposure based only on residential location
Song et al., 2012	Cross-sectional	China: Shandong Province	Work activities	Red blood cell count and hemoglobin concentration	Blood samples collected in 100 chromate production workers exposed to Cr(VI) and 50 unexposed controls (farmers, salesmen, and meter checkers living more than 20 km away from the exposed facility)	Mean red blood cell count (4.78±0.75 vs. 4.73±0.43 $\times 10^{12}$/L, p=0.596) and hemoglobin concentrations (148.77±27.16 vs. 144.76±12.55 g/L, p=0.218) are similar in exposed vs. unexposed groups, respectively.	People with significant past medical problems were excluded. Results adjusted for age, sex, smoking, and alcohol consumption. Air total Cr also measured but associations with blood outcomes not reported.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Wang et al., 2012	Cross-sectional	China: Shandong Province	Work activities; urinary total Cr also collected but associa-tions with blood counts or percent-ages not provided	White blood cell count and subtype percentages	86 chromate production workers (sodium dichromate) ages 25-54 years and 45 age matched controls from a housekeeping company living in the same city	Mean white blood cell count higher in exposed group vs. controls (6.96±1.72 vs. 6.17±1.32 $\times 10^9$/L, p=0.025). Percentages of individual cell types mostly similar between exposed participants and controls except the combination of monocytes, eosinophils, and basophils was approximately 25% higher in the exposed group (p<0.001).	People with major illnesses were excluded. Exposed and unexposed participants matched on smoking, alcohol consumption, and SES "as much as possible." Few other details provided on selection methods or participation rates. Average exposure duration of about 12 years. Adjusted for age, gender, and work duration.	No: exposure based only on work activities
Xu et al., 2020	Cross-sectional	China: Jinzhou City	Residence in area with Cr(VI) drinking water contami-nation and blood total Cr	Multiple blood indices	Blood and questionnaire data collected from 282 people from the exposed area and 303 people from an area not known to have Cr(VI) contamination; ages >18 years and all lived in their respective area >10 years	Indices approximately 5-13% lower in people from the exposed area vs. controls include mean corpuscular volume, platelet count, and mean platelet volume (all p<0.001). Indices approximately 2-10% higher in people from the exposed area vs. controls include neutrophil count, red blood cell count, and mean corpuscular hemoglobin concentration (all p<0.01). No major difference in hemoglobin levels. No clear associations with blood total Cr and blood indices except slightly higher hemoglobin levels in the high exposure group (146.7±1.0 vs. 143.0±1.0 g/L, p=0.005). Findings also given by strata of sex, smoking status, and alcohol consumption, as well as mediation analyses by indicators of oxidative stress.	Blood total Cr only slightly higher in people from the exposed area than in those from the unexposed area (means of 0.92 and 0.88 µg/L, respectively). Multiple comparisons performed. Those with workplace Cr exposure were excluded. Little information provided on recruitment methods or participation rates. Only relatively small differences seen in gender distribution, ages, smoking status, and alcohol consumption between participants from exposed and unexposed areas. Educational levels somewhat higher in the exposed area participants. Results adjusted for age, sex, education, income, smoking, and alcohol consumption.	No: dose-response data only given for total Cr, and little difference in blood total Cr between people from Cr(VI) exposed and unexposed areas

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Xu et al., 2022	Retro-spective cohort	China: Shandong Province	Work activities	Multiple blood indices	Questionnaire, blood samples, and other data collected in 850 workers exposed to chromate and 598 workers not exposed to chromate in a steel plant working in 2016-2017	Percentage of "abnormal blood routine" higher in exposed participants than in controls (13.1% vs. 7.7%, p=0.001). Definition of “abnormal” not provided.	Workers at a steel factory who worked with chrome slag. Workers with major illnesses excluded. Few details on selection methods or participation rates. Average exposure duration of 6.92 years. No statistical adjustments mentioned.	No: no information on Cr(VI) levels

Abbreviations: BMI, body mass index; β, regression coefficient; Cr, chromium; Cr(VI), hexavalent chromium; ICD, International Classification of Diseases; SES, socioeconomic status; SMR, standardized mortality ratio

1. Numbers in parentheses following odds ratios or other results are 95% confidence intervals unless otherwise noted; numbers following “±” are standard deviations unless otherwise noted
2. Overall assessment of whether the study can be used to quantitatively estimate the dose-response relationship between hexavalent chromium in drinking water and hematologic outcomes

Table A2.3 Human epidemiologic studies of hexavalent chromium and immunologic effects published since January 1, 2011[1]

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Hu et al., 2017a	Cross-sectional	China: unclear	Work activities; blood total Cr	Serum CRP	Questionnaire information and blood samples collected from 107 male workers at a chromate production facility in northern China: 41 exposed to Cr(VI) who were in the same job for at least 3 months, and 25 controls from the same facility who did not have Cr(VI) exposure	Mean serum log CRP levels are slightly lower in the exposed vs. control group (6.80 ±1.04 vs. 7.05±0.65 log-ng/ml, p=0.247). R^2 value for association between log blood total Cr and log serum CRP = 0.182 (p<0.001) (these data also presented in figure form which shows a negative slope).	Few details on control selection or participation rates. Some differences in smoking and drinking rates between exposure groups, but groups were similar with regards to gender distribution, nationality, BMI, and years working. No statistical adjustments mentioned when comparing exposed and unexposed workers. R^2 value adjusted for age, BMI, smoking, and alcohol consumption.	No: primary result presented as R^2 value
Hu et al., 2022	Cross-sectional	China: unclear	Work activities; blood total Cr	Serum CRP	Questionnaire information and blood samples collected from 1,249 workers at three chromate production facilities in northern China: 639 exposed to Cr(VI), and 610 controls from the same facility who did not have Cr(VI) exposure	Mean serum CRP lower in the exposed vs. control group (0.93±1.51 vs. 1.12±1.55 mg/L, p<0.05). Mean serum CRP decreases by increasing quartiles of blood total Cr(VI) (1.16±1.67 vs. 1.03±0.34 vs. 0.96±1.56 vs. 0.93±1.53 mg/L for quartiles 1-4, respectively, p=0.003).	Few details on control selection or participation rates. Adjusted for age, sex, BMI, education, alcohol drinking status, and smoking.	No: health relevance of outcome (lower CRP) is unclear

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Islam et al., 2019	Cross-sectional	Bangladesh: Hazaribagh	Work activities and serum total Cr	Serum Ig and comple-ment	Questionnaire data and serum collected in 195 male leather tannery workers who worked at least 2 years and 125 male controls who worked in the same region at other jobs (i.e., offices, shops, banks, and student dormitories)	Prevalence of fungal and bacterial infections greater in the tannery workers vs. controls (13.9% vs. 1.6%, p<0.01). Serum IgG, IgA, complement3, and complement4 all approximately 10-30% lower in tannery workers vs. controls (all p-values <0.05). Serum IgE levels >50% higher in tannery workers vs. controls (p<0.01). Correlations between serum total Cr and serum IgG, IgE, IgA, complement3, complement4 were -0.111, 0.051, -0.129, -0.142, and -0.042, respectively (all p>0.05). Correlation between serum IgG and duration of tannery work = -0.330 (p<0.05).	Participants with chronic illnesses excluded. Exposed and control participants similar in terms of age, blood pressure, and BMI. The mean duration of work for the tannery workers was 9.4 years. No statistical adjustments mentioned. Few details on control selection or participation rates.	No: only unadjusted correlation coefficients or exposure based on work activities
Jeyamala et al., 2012	Cross-sectional	India: Madurai District	Work activities and durations	Erythrocyte sediment-ation rate	Symptom reports, hair and blood samples collected from 23 workers in the thread cutting and punch press operations area randomly selected from several electroplating facilities in the study area, and 7 unexposed controls "outside this environment and not related to any industry"	Mean erythrocyte sedimentation rate = 37±2 vs. 29±7 mm/h in exposed and unexposed, respectively	No other details on control selection or participation rates provided. No demographic comparisons of exposed and controls, and no statistical adjustments mentioned. P-values or confidence intervals not provided.	No: exposure based only on work activities
Kashyap et al., 2021	Cross-sectional	India: Kanpur City	Work in leather tannery and years worked	Respiratory symptoms	Respiratory and other symptom information collected from 284 leather tannery workers from multiple facilities and 289 non-tannery workers, mostly manual laborers, and business and shop owners, all ages 18-70 years	Prevalence of flu-like illness higher in the tannery workers than in unexposed controls (50% vs. 26.6%). Prevalence of frequent fever also higher in tannery workers (18.3% vs. 6.6%).	Participants randomly selected from a household survey in the study area. Participation rate of approximately 95%. Average duration of tannery work in tannery workers was 18 years. Statistical adjustments are unclear. P-values not provided.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Kauppi et al., 2015	Controlled clinical trial	Finland: Helsinki	Controlled single exposure to stainless steel welding fumes	Serum IL and TNF-α	15 male participants with suspected occupational asthma underwent stainless steel challenge test in an exposure chamber; serum collected before and after the challenge	Serum IL-1β and IL-6 levels similar, but IL-8 and TNF-α levels 10-15% lower after stainless steel challenge (all p-values >0.05).	Generalizability and relevance to chronic toxicity are unclear. Timing of blood sampling is unclear. Average inhalable stainless steel welding particle mass concentration of 40.2 mg/m^3.	No: single challenge test, relevance unclear
Khan et al., 2013	Cross-sectional	Pakistan: Sialkot	Job titles; whole blood total Cr measured but not used to test health effect associations	Serum CRP	120 "randomly selected" male leather tannery workers from multiple facilities who worked >5 years, and 120 unexposed controls "recruited from Sialkot city," all ages 23-60 years	Mean serum CRP higher in exposed workers than controls (2.95±3.37 vs. 1.07±1.52 mg/L, p=0.01).	Workers with chronic illnesses excluded. Little information on control selection or participation rates. Demographic comparisons of exposed and control groups not provided. No statistical adjustments mentioned.	No: exposure based only on work activities
Li et al., 2015	Cross-sectional	China: Henan Province	Work activities; blood total Cr also measured but not used to test health effects associations	Serum IL-6 and TNF-α	Spirometry and serum IL-6 and TNF-α measured or collected in 91 chromium-exposed workers and 38 controls (from the administrative office in the same factory) in a factory using water soluble hexavalent chromium compounds (potassium dichromate). All participants worked at the factory for at least 1 year and were ages 25-50 years	Mean serum TNF-α higher in the exposed vs. control group (38.25±12.83 vs. 31.90±15.53 ng/L, p=0.022). Mean serum IL-6 also higher in the exposed vs. control group (15.72±2.88 vs. 13.71±4.26 ng/L, p=0.018).	Participants with major medical conditions were excluded. Few details provided on selection methods or participation rates. Exposed and control group similar in terms of age, gender distribution, smoking, alcohol use, and BMI. Average length of employment was 6.74 years. No statistical adjustments mentioned.	No: exposure based only on work activities
Liu et al., 2019	Cross-sectional	Mongolia: Baotou City	Work history and whole blood total Cr	Serum IL and TNF-α	Serum levels of ILs and TNF-α measured in 22 chromate exposed workers and 44 unexposed controls from the same electroplating facility	Mean serum levels of IL-1β, IL-6, IL-8, and TNF-α were all 50% or more higher in the exposed group than in controls (all p-values <0.05).	Average exposure duration of 31 years. Workers with serious illnesses excluded. Few other details on selection methods or participation rates. Adjusted for age, sex, BMI, smoking, and alcohol consumption.	No: results provided only as correlation coefficients or based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Qian et al., 2013	Cross-sectional	China: unclear	Whole blood and urinary total Cr	Serum IL, TNF-α, Igs, and comple-ment	Serum immune or inflammatory markers measured in 106 male potassium dichromate workers who worked at least 3 months at the same location, and 50 unexposed controls who lived about 20 km from the factory; all participants were ages 25-50 years, had no history of allergy, asthma, allergic rhinitis, skin infections, fever, or other clinical diseases	A negative correlation was found between log blood total Cr and serum levels of IL-17A (R = -0.244, p=0.016), IgG (R = -0.325, p=0.002), and IgA (R = -0.231, p=0.031). A positive correlation was found between log blood total Cr and serum levels of complement3 (R = 0.352, p=0.001) and complement4 (R = 0.276, p=0.010). A negative correlation was found between log urinary total Cr and IL-10 (R = −0.250, p=0.040) although minimum slope seen in the figure showing these data (Figure 3 in the publication).	No statistical adjustments mentioned. More smokers and alcohol drinkers in the exposed group vs. controls. Few details on control selection or participation rates.	No: results presented only as correlation coefficients or in figure form
Raulf et al., 2016	Cross-sectional	Germany: WELDOX study	Personal air sampling for total Cr; nasal lavage concentration of total Cr	Nasal lavage fluid IL-8, 8-isopros-tane, tissue inhibitor of metallo-proteinase -1, and immuno-reactive matrix metallo-proteinase -9	Post shift nasal lavage fluid collected in 190 male welders ages 19-61 years, approximately 70% of whom were stainless steel welders	Results appear to be presented as regression coefficients for total air Cr above and below the median. For IL-8, tissue inhibitor of metalloproteinase-1, immunoreactive matrix metalloproteinase-9, and 8-isoprostane, all of the regression coefficients are above 0 but none is statistically significant. Regression coefficients between nasal lavage concentrations of total Cr (ng/ml) and IL-8, tissue inhibitor of metalloproteinase-1, immunoreactive matrix metalloproteinase-9, and 8-isoprostane, were 2.37 pg/ml (p=0.0001), 2.24 ng/ml (0.0235), 1.77 ng/ml (p=0.0130), and 1.66 pg/ml (0.0026), respectively.	Participation rate of 79%. None of the workers reported chronic or acute respiratory disease. Few other details on selection methods. Some statistical methods are unclear. Average duration of welding work was 17 years.	No: results based on total air Cr

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Remy and Clay, 2014	Ecologic	US: Willits	Residence in area with Cr(VI) drinking water contamination	Hospitali-zation for any infectious or parasitic disease	Hospital discharge data for the years 1991-2012 comparing residents from the exposed area (Willits, California) to residents from the rest of the county; discharge data from California's Office of Statewide Health Planning and Development	Any infectious or parasitic disease relative risk = 1.18 (1.09-1.28, n=111 excess cases) in males and 1.32 (1.24-1.40, n=299 excess cases) in females	Area with drinking water contamination with Cr(VI) by a chrome plating facility. County rates used for comparison. Stratified by sex and adjusted by age. All residents in Willits and Mendocino County were included. Results for more specific illnesses not provided.	No: exposure based only on area of residence
Sazakli et al., 2014	Cross-sectional	Greece: Asopos River Basin	Total Cr in blood and hair; drinking water Cr(VI) levels, drinking water intake rates, and residential history used to calculate lifetime Cr(VI) intake	Serum IL and CRP	Questionnaire information and blood collected in 304 men and women from areas with current, past, and no high levels of naturally occurring Cr(VI) in drinking water	Positive association between cumulative exposure and serum IL-12 (β = 0.308, p=0.011). No association between total Cr in blood or hair and serum IL-12. No clear association between any exposure metric and IL-6, IL-8, IL-10, or CRP.	Selection through age and gender stratified random sampling from telephone directories. 82% response rate. Cr(VI) water levels ranged from <3 to 196 µg/L (median in the current exposure area = 23 µg/L). Gender distribution, median age, education level, smoking rates, marital status, and occupational status similar between the different exposure level areas. Results adjusted for age, sex, Cr occupational exposure, smoking, alcohol consumption, physical activity, and consumption of local crops. Over 50 different associations tested (hair, cumulative, and blood Cr with 19 different blood parameters).	No: only regression coefficients given
Wang et al., 2012	Cross-sectional	China: Shandong Province	Work activities; urinary total Cr also collected but associations with serum CRP not reported	Serum CRP	86 chromate production workers ages 25-54 years exposed to sodium dichromate for at least 6 months, and 45 age matched controls from a housekeeping company and who lived in the same city as the exposed group	Mean serum CRP higher in the exposed group than in controls (1.11±1.87 vs. 0.65±0.85 mg/L, p=0.039).	People with major illnesses were excluded. Matched on smoking, drinking and SES "as much as possible." Few other details provided on selection methods or participation rates. Average exposure duration of about 12 years. Adjusted for age, gender, and work duration.	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Wang et al., 2019	Cross-sectional	China: Zhengzhou	Work activities	Serum IL	Questionnaire information and blood samples collected from 40 workers from an electroplating factory with chromium exposure and 20 workers from a machinery factory without chromium exposure	Serum IL-6 levels approximately 2-times higher in chromium exposed workers than controls ($p<0.01$). Results only presented in figure form.	All exposed workers were non-smokers and had at least 3 years of chromium exposure. Unexposed controls were also non-smokers. Few details provided on selection methods or participation rates. No statistical adjustments mentioned. Demographic comparisons of exposed and unexposed participants not provided.	No: exposure based only on work activities

Abbreviations: BMI, body mass index; Cr, chromium; Cr(VI), hexavalent chromium; CRP, C-reactive protein; Ig, immunoglobulin; IL, interleukin; R, correlation coefficient; R^2, coefficient of determination; SES, socioeconomic status; TNF-α, tumor necrosis factor alpha

1. Numbers in parentheses following odds ratios or other results are 95% confidence intervals unless otherwise noted; numbers following "±" are standard deviations unless otherwise noted
2. Overall assessment of whether the study can be used to quantitatively estimate the dose-response relationship between hexavalent chromium in drinking water and immunologic outcomes

Table A2.4 Human epidemiologic studies of hexavalent chromium and hepatic effects published since January 1, 2011[1]

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Khan et al., 2013	Cross-sectional	Pakistan: Sialkot	Job title; whole blood total Cr measured but not used to test health effect associations	Serum ALT, TB, and AP	120 "randomly selected" male leather tannery workers from multiple facilities who worked >5 years, and 120 unexposed controls "recruited from Sialkot city," all ages 23-60 years	Mean serum ALT (33.82±12.23 vs. 27.63±11.26 U/L, p=0.001), TB (12.05±6.603 vs. 9.64±4.26 µmol/L, p=0.001), and AP (197±65 vs. 186±38 U/L, p=0.222) higher in the exposed group than in controls.	Workers with chronic illnesses were excluded. Few details on selection methods for controls or participation rates. Demographic comparisons of exposed and control groups not provided. No statistical adjustments mentioned.	No: exposure based only on work activities
Lacerda et al., 2019	Cross-sectional	Brazil: Rio Grande do Sul	Work activities; blood and urine total Cr measured but not used to test associations with liver enzymes	Serum ALT, AST, and AP	Blood samples and questionnaire information collected in 50 male chrome plating workers and 50 unexposed controls (administrative occupations)	Mean serum ALT (43.28±2.36 vs. 19.40±0.92 U/L, p<0.001), AST (35.54±1.15 vs. 27.30±1.67 U/L, p<0.001), and AP (570.40±24.18 vs. 392.91±27.40 U/L, p<0.001) higher in the exposed group than in controls.	Few details on selection methods or participation rates. Blood and urinary total Cr both higher in the exposed group than in controls. Exposed group 3 years younger on average, with fewer alcohol consumers, and a greater percentage with sedentary lifestyle than controls. No statistical adjustments mentioned.	No: limited results and limited information on exposure
Lipworth et al., 2011	Retro-spective cohort	US: Burbank	Job histories and classifications by experts; job activity with chromate exposure	Mortality due to liver cirrhosis	Mortality assessed in 77,943 workers employed at an aircraft manufacturing facility exposed to chromates; includes workers employed at least one year from 1960; cases ascertained from state and national death records; state and national death rates used for comparison	Cirrhosis SMR = 0.95 (0.77-1.15, n=98 deaths). Deaths due to diseases of the biliary tract and liver SMR = 0.87 (0.56-1.30, n=24 deaths, doesn't include cirrhosis).	Adjusted for race, age, sex, and year. Follow-up through 2008. Average follow-up of 31.8 years.	No: exposure based only on work activities
Rabbani et al., 2021	Cross-sectional	Bangladesh: Hazaribagh	Work activities and years worked	History of jaundice	Self-reported respiratory and health questionnaire information collected in 167 workers randomly selected from 10 leather tanneries ages >15 years and working in tanneries for at least 2 years	History of jaundice OR = 0.93 (0.84-1.03, n=93) for each 1 year of tannery work	Adjusted for age, smoking, education, and income. Exposure based primarily on years of tannery work.	No: exposure based only on work activities and years worked
Richard et al., 2016	Cross-sectional	Nigeria: Mfamosing	Work activities	Serum ALT, AST, TB, and conjugated bilirubin	Serum, questionnaire, and other data collected in 50 male Portland cement workers, 60 nearby residents, and 100 unexposed people living 45 km away, all ages 18-60 years	Mean serum ALT (29.78±2.57 vs. 8.72±0.41 IU, p<0.001), AST (37.00±2.61 vs. 9.46±0.64 IU, p<0.001), TB (18.26±0.91 vs. 13.82±0.62 µmol/L, p<0.001), and conjugated	Participants were "randomly selected" for the study. Few other details on selection methods or participation rates provided. Nearby residents reportedly had much higher mean serum total Cr levels than	No: exposure based only on work activities

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
						bilirubin (7.57±0.58 vs. 5.84±0.27μmol/L, p=0.004) higher in cement workers than in unexposed controls.	workers (1.60±0.125 vs. 0.033±0.013 μg/dL). Demographic characteristics of each group not provided. No statistical adjustments mentioned. Units for ALT and AST only listed as "IU."	
Sazakli et al., 2014	Cross-sectional	Greece: Asopos River Basin	Blood and hair total Cr, drinking water Cr(VI) levels, drinking water intake rates, and residential history used to calculate lifetime Cr(VI) intake	Serum AP, AST, ALT, TB, direct and indirect bilirubin	Questionnaire information and blood and hair collected in 304 men and women from areas with current, past, and no high levels of naturally occurring Cr(VI) in drinking water	Statistically significant regression slopes seen between cumulative Cr(VI) exposure and AP (β = 0.120 U/L per log normal exposure dose, p=0.035). Statistically significant positive associations also seen with total blood and total urine Cr and AP. Clear or consistent associations not seen for other liver parameters.	Selection through age and gender stratified random sampling from telephone directories. 82% response rate. Cr(VI) water levels ranged from <3 to 196 μg/L (median in the current exposure area = 23 μg/L). Gender distribution, median age, education level, smoking rates, marital status, and occupational status similar between the different exposure level areas. Results adjusted for age, sex, occupational exposure to Cr, smoking, alcohol consumption, physical activity, and consumption of local crops. Over 50 different associations tested (hair, cumulative, and blood Cr with 19 different blood parameters).	No: only regression coefficients provided
Xu et al., 2022	Retro-spective cohort	China: Shandong Province	Work activities	Serum ALT	Questionnaire, blood samples, and other data collected in 850 workers exposed to chromate and 598 workers not exposed to chromate from a steel plant, working in 2016-2017	Percentage of abnormal serum ALT levels higher in exposed participants than in controls (8.7 vs. 5.4%, p=0.016). Definition of "abnormal" not provided.	Workers at a steel factory who worked with chrome slag. Workers with major illnesses excluded. Few details on selection methods or participation rates. Average exposure duration of 6.92 years. No statistical adjustments mentioned.	No: no information on Cr(VI) levels

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Zhao et al., 2022	Cross-sectional	China: Jinzhou City	Residential distance from a ferroalloy facility and urinary total Cr	Serum ALT and AST	Serum samples, urinary total Cr, and questionnaire data collected from 1,171 residents living near a site with known Cr(VI) water and soil contamination (364 from a higher exposure area and 807 from an unexposed area)	Mean serum ALT and AST levels were similar in participants from the exposed and unexposed areas. Regression coefficients (change in liver enzyme levels per log normal increase in urinary total Cr divided by urinary creatinine) were 0.24 (-0.22-0.71) for AST and 0.63 (-0.02-1.28) for ALT.	Participants all age ≥18 years, lived in area >10 years, and with no history of liver disease. Few details on recruitment methods and participation rates provided. Exact definitions of exposed and unexposed areas not provided. Greater percentage of males (39% vs. 24%) and fewer with middle or higher education levels (36% vs. 53%) among participants from the unexposed vs. exposed area. Otherwise, demographic characteristics are roughly similar. Results adjusted for age, smoking, alcohol consumption, BMI, education, income, year of investigation, and study area. Median (25th and 75th percentiles) total urinary Cr levels similar in participants from exposed and unexposed areas (4.67 and 4.22 ug/L, p<0.05), respectively. Unclear why results were adjusted for study area.	No: regression coefficients, only given for total urinary Cr

Abbreviations: ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate aminotransferase; β, regression coefficient; BMI, body mass index; Cr, chromium; Cr(VI), hexavalent chromium; SMR, standardized mortality ratio; TB, total bilirubin

1. Numbers in parentheses following odds ratios or other results are 95% confidence intervals unless otherwise noted; numbers following "±" are standard deviations unless otherwise noted
2. Overall assessment of whether the study can be used to quantitatively estimate the dose-response relationship between hexavalent chromium in drinking water and hepatic outcomes

Table A2.5 Human epidemiologic studies of hexavalent chromium and gastrointestinal effects published since January 1, 2011[1]

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Gibb et al., 2015	Retro-spective cohort	US: Baltimore	Job titles and workplace Cr(VI) air measurements	Digestive system diseases mortality	Job history and mortality information collected on all 2,354 male workers at a chromium production facility who worked at sometime between 1950-1974. Deaths ascertained from the National Death Index. State rates used for comparison.	Digestive system disease SMR = 0.90 (0.69-1.16, n=60 deaths).	All male workers at the included facility. Includes long- and short-term workers (i.e., worked <90 days). Adjustments or stratification for age, race, and calendar year. Follow-up through 2011. Average follow-up of 38.9 years. No results given for specific diseases. ICD9 codes not provided.	No: SMR for whole cohort, no Cr(VI) specific data
Giordano et al., 2012	Retro-spective cohort	Italy: Rome	Employment at cement factory	Digestive system diseases mortality	Mortality assessed in all 748 male Portland cement production workers employed at some point between 1956-2006. Vital status assessed for 1969-2006 from local health units or municipal death records. Includes a total of 280 deaths. Regional and city death rates used for comparison.	Diseases of the digestive system SMR = 1.03 (0.58-1.70, n=15 deaths). SMR similar in those with no prior asbestos cement exposure.	Some workers had prior asbestos cement exposure. No clear dose-response relationship based on years worked (i.e., greater vs. less than 10 years worked). No information on smoking or other potential confounders. Results for specific gastrointestinal conditions not provided. Includes ICD9 codes 520-579.	No: exposure based only on employment at the included facility
Sharma et al., 2012	Cross-sectional	India: Kanpur	Residence in area with Cr(VI) groundwater contamination	Gastro-intestinal symptoms	Symptom questionnaires collected from 186 participants from an area with Cr(VI) contamination in ground water, and 230 controls from an area without Cr(VI) contamination. Inclusion criteria include age ≥18 years, residence in area >1 year, not consuming bottled water, and no workplace exposure to Cr(VI).	ORs for self-reported gastrointestinal complaints = 3.1 (1.50–6.39) in males and 2.44 (1.32–4.52) in females comparing exposed and unexposed participants.	Few details on selection methods and participation rates. Area with leather tanneries and chrome sulfate manufacturing facilities. Gastrointestinal complaints include any of the following: poor appetite, stomach upset/indigestion, gaseous discomfort, diarrhea/blood stained diarrhea, vomiting, constipation, or stomach ulcers diagnosed by doctor. No other details on outcomes. Results adjusted for age, smoking, education, and vegetarian diet. Cr(VI) levels in water approximately 20 ppm. Few other details on exposure provided.	No: exposure based only on residential location

Abbreviations: Cr(VI), hexavalent chromium; ICD, International Classification of Diseases; OR, odds ratio; SMR, standardized mortality ratio

1. Numbers in parentheses following odds ratios or other results are 95% confidence intervals unless otherwise noted; numbers following "±" are standard deviations unless otherwise noted

2. Overall assessment of whether the study can be used to quantitatively estimate the dose-response relationship between hexavalent chromium in drinking water and gastrointestinal outcomes

Table A2.6 Human epidemiologic studies of hexavalent chromium and reproductive and developmental effects published since January 1, 2011[1]

Reference	Study design	Location	Exposure	Outcome	Description	Key findings	Notes	Dose-response data[2]
Kim et al., 2020	Cross-sectional	China: Guiyu	Residence in e-waste recycling area and blood total Cr	Birth weight, birth length, head circumference, BMI, and ponderal index	Birth outcomes and blood total Cr assessed in 314 pregnant women from an area where e-waste recycling was performed and with known Cr(VI) contamination. The comparison group was 320 pregnant women from an area with no e-waste recycling.	Neonates from the exposed area had smaller head circumference (mean difference = −1.96 cm (−2.39 to −1.52)), BMI (mean difference = −0.77 kg/m^2 (−1.03 to −0.51)), and ponderal index (mean difference = −2.01 kg/m^3 (−2.54 to −1.47)) compared to those from the unexposed area. Birth weights were lower in neonates from the exposed area compared to those from the unexposed area, but the difference was not statistically significant (mean difference = − 51 gm (−132 to 29)). ORs for small for gestational age and preterm birth = 1.17 (0.57-2.40, n=50 cases) and 1.67 (0.66-4.23, n=33 cases), respectively. Statistically significant associations not seen with blood total Cr although mostly negative regression coefficients.	Detailed selection methods and participation rates not provided. Geometric mean (range) blood total Cr levels in participants from the exposed and unexposed areas were 13.8 (2.4-189) and 8.9 (4.4-175) µg/L, respectively. Adjustments were made for maternal age, education, occupation, BMI, gravidity, environmental tobacco smoke, and neonate sex.	No: no specific data on Cr(VI)
Remy et al., 2017	Ecologic	US: Willits	Residence in area with Cr(VI) drinking water contamination	Multiple	Birth and pregnancy-related hospital records assessed in 5,558 admissions for women from an area with local Cr(VI) contamination and 31,444 admissions for women from the rest of the county for the period 1983-2014.	Birth rate was lower (data provided in figure form); and prevalence of low birthweight, small for gestational age, and preterm births combined (9.43% vs. 8.30%, p=0.0029) was higher in the exposed city compared to the rest of the county. Possible increase in infectious/parasitic diseases in infants in the exposed city (relative risk = 1.09 (1.02-1.16)) but no obvious increase in respiratory or digestive system diseases in infants. No obvious increase in congenital anomalies.	Contamination source was a facility manufacturing heavy-duty steel cylinders hardened with Cr(VI). Dumping of wastes contaminated local water sources. Multiple outcomes assessed.	No: ecologic exposure data, no actual Cr(VI) levels provided

Abbreviations: BMI, body mass index; Cr, chromium; Cr(VI), hexavalent chromium

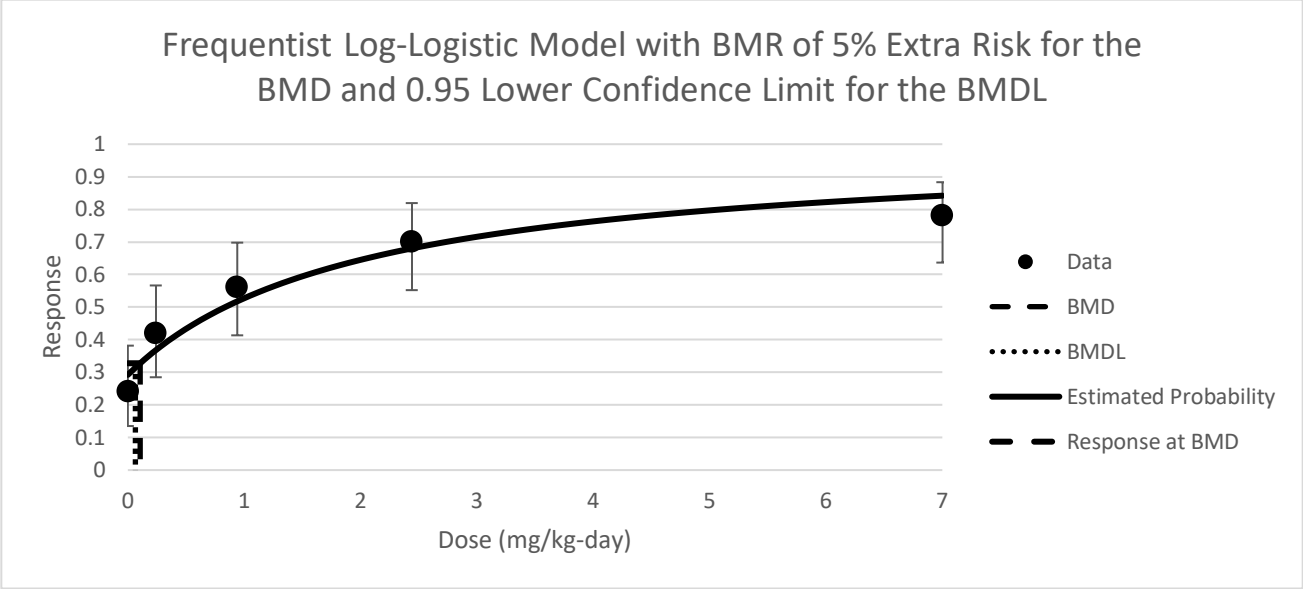
1. Numbers in parentheses following odds ratios or other results are 95% confidence intervals unless otherwise noted; numbers following "±" are standard deviations unless otherwise noted

2. Overall assessment of whether the study can be used to quantitatively estimate the dose-response relationship between hexavalent chromium in drinking water and reproductive/developmental outcomes

APPENDIX 3. BENCHMARK DOSE MODELING

This appendix provides the BMD modeling outputs for Cr(VI) toxicity data that were amenable to dose-response modeling. All models were run with default parameters and a benchmark response of 5% for dichotomous data or one standard deviation from the control mean for continuous data unless otherwise noted.

Figure A3.1 Log-logistic model output for increased chronic liver inflammation in female rats (NTP, 2008a)



Model Run Output for Figure A3.1: Log-logistic Model (Version 3.3.2)

Benchmark Dose	
BMD	0.105953824
BMDL	0.064831609
BMDU	0.236483419
AIC	312.5406985
P-value	0.37015188
D.O.F.	3
Chi^2	3.142637012

Model Parameters
# of Parameters 3

Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.292438	1.64E-02	0.26037419	0.32450182
a	-0.699687075	0.320425156	-1.3277088	-0.0716653
b	Bounded	NA	NA	NA

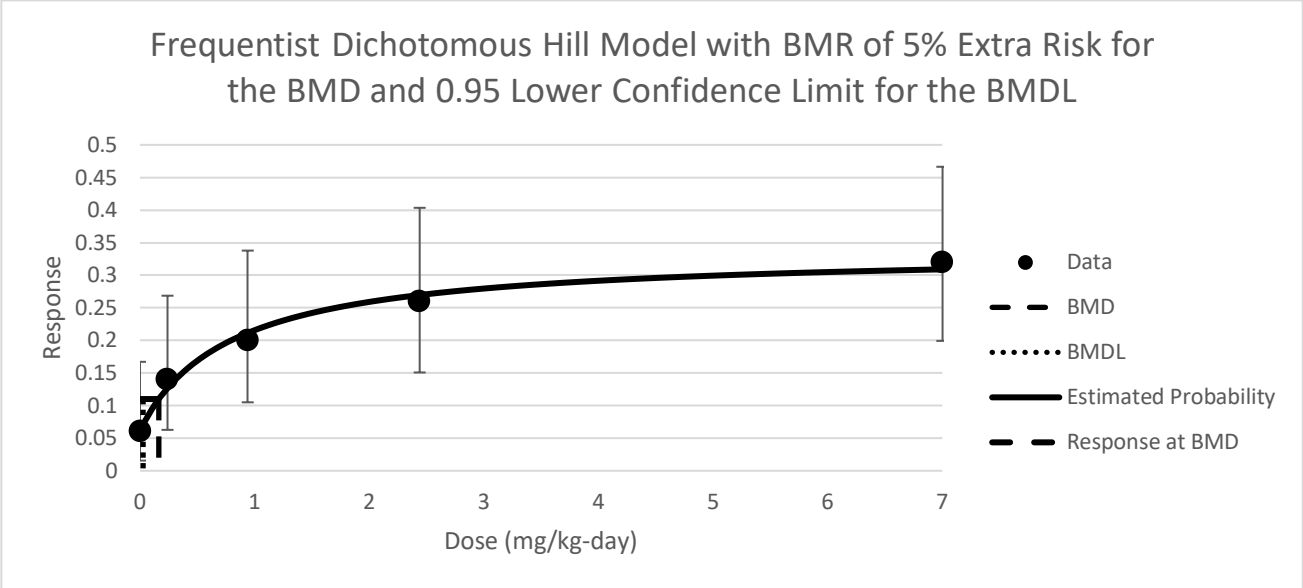
Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.292438	14.62190002	12	50	-0.81514
0.24	0.36780668	18.39033401	21	50	0.765359
0.94	0.517660031	25.88300154	28	50	0.5991514
2.44	0.680132527	34.00662636	35	50	0.3011937
7	0.841962753	42.09813766	39	50	-1.201129

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-152.7536996	5	-	-	NA
Fitted Model	-154.2703493	2	3.03329933	3	0.386519 5
Reduced Model	-172.4859396	1	39.46448	4	<0.0001

Figure A3.2 Dichotomous Hill model output for increased fatty change in the liver in female rats (NTP, 2008a)



Model Run Output for Figure A4.2: Dichotomous Hill (Version 3.3.2)

Benchmark Dose

BMD	0.164146936
BMDL	0.026775455
BMDU	1.05456085
AIC	239.4049309
P-value	0.913678124
D.O.F.	2
Chi2	0.180553863

Model Parameters

# of Parameters 4

Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.06320843	3.71E-02	-0.0094422	0.13585907
v	0.292157377	2.67E-02	0.23979407	0.34452068
a	0.229428476	1.183555401	-2.0902975	2.54915445
b	Bounded	NA	NA	NA

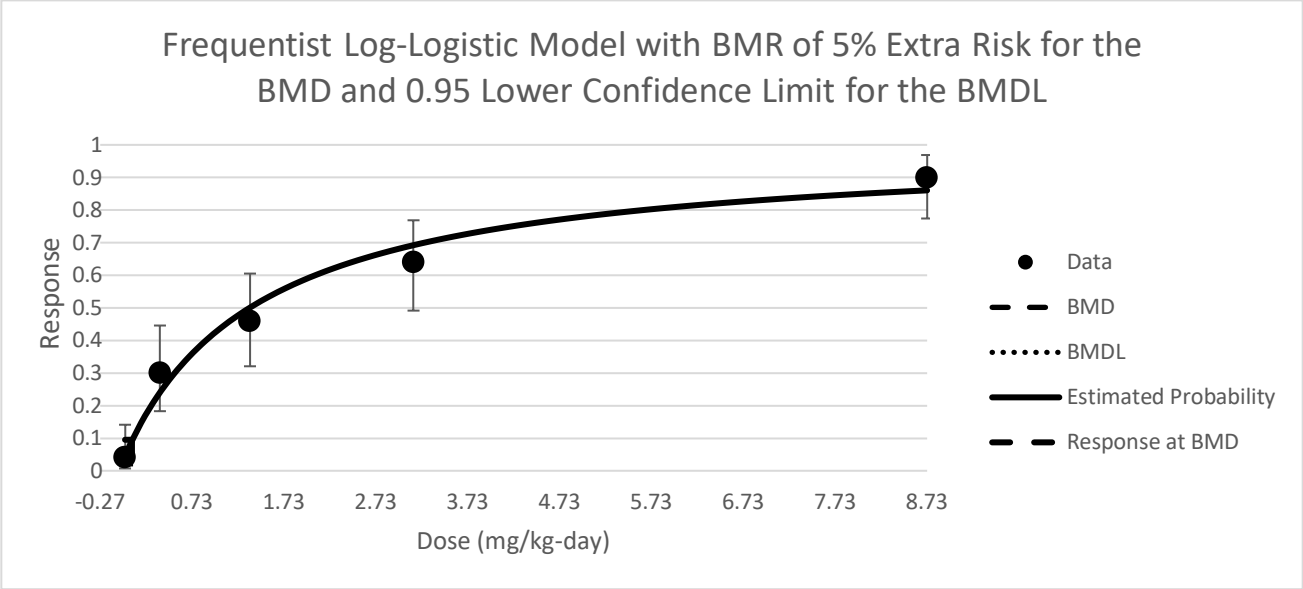
Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.06320843	3.16042148	3	50	-0.093233
0.24	0.126673655	6.333682773	7	50	0.2833118
0.94	0.211491391	10.57456956	10	50	-0.198979
2.44	0.269640423	13.48202114	13	50	-0.15361
7	0.308986103	15.44930515	16	50	0.1685439

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-116.6129903	5	-	-	NA
Fitted Model	-116.7024655	3	0.17895035	2	0.914411
Reduced Model	-123.7017483	1	14.1775161	4	0.0067495

Figure A3.3 Log-logistic model output for increased histiocytic infiltration of the liver in female mice (NTP, 2008a)



Model Run Output for Figure A4.3: Dichotomous Hill (Version 3.3.2)

Benchmark Dose

BMD	0.078897339
BMDL	0.058239072
BMDU	0.180113562
AIC	251.291955
P-value	0.448384379
D.O.F.	3
Chi2	2.652357887

Model Parameters
# of Parameters 3

Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	0.047541043	4.35E-02	-0.0377396	0.13282171
a	-0.404831204	0.190952041	-0.7790903	-0.0305721
b	Bounded	NA	NA	NA

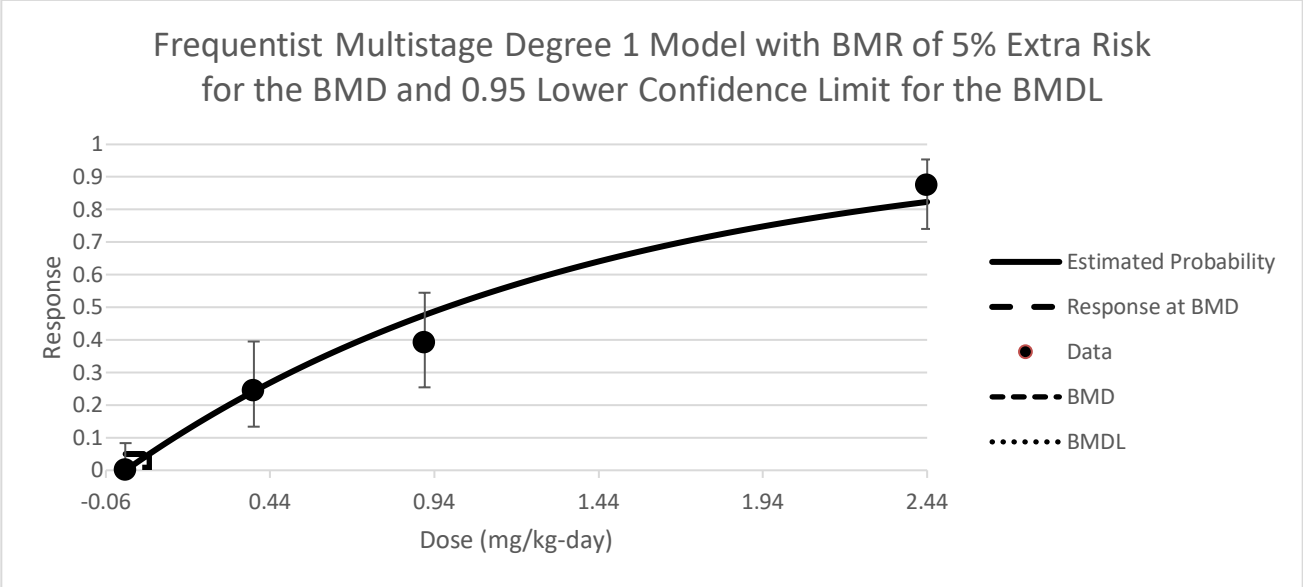
Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.047541043	2.329511084	2	49	-0.221215
0.38	0.240156732	12.00783658	15	50	0.9905831
1.36	0.500609171	25.03045856	23	50	-0.574301
3.14	0.69222508	34.611254	32	50	-0.800062
8.73	0.860418793	43.02093963	45	50	0.8076173

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-122.3214244	5	-	-	NA
Fitted Model	-123.6459775	2	2.64910624	3	0.4489456
Reduced Model	-172.1415671	1	99.6402853	4	<0.0001

Figure A3.4 Multistage degree 1 output for diffuse epithelial hyperplasia of the small intestine in male mice (NTP, 2008a)



Model Run Output for Figure A4.4: Multistage Degree 1 (Version 3.3.2)

Benchmark Dose

BMD	0.072140507
BMDL	0.05875685
BMDU	0.089513172
AIC	152.1047198
P-value	0.529957222
D.O.F.	3
Chi2	2.210122936
Slope Factor	0.850964612

Model Parameters
# of Parameters 2

Variable	Estimate	Std Error	Lower Conf	Upper Conf
g	Bounded	NA	NA	NA
b1	0.711019188	0.221774356	0.27634943	1.14568894

Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	1.523E-08	6.24429E-07	0	41	-0.0007902
0.39	0.242170989	10.89769452	11	45	0.0355997
0.91	0.476400121	21.91440557	18	46	-1.1555832
2.44	0.823579836	39.53183213	42	48	0.9346029

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-73.90076025	4	-	-	NA
Fitted Model	-75.05235991	1	2.30319931	3	0.5119083
Reduced Model	-120.7250427	1	93.6485649	3	<0.0001

APPENDIX 4. DEFAULT UNCERTAINTY FACTORS FOR HEALTH-PROTECTIVE CONCENTRATION (HPC) DERIVATION

This appendix describes the default uncertainty factors OEHHA generally uses to calculate the Acceptable Daily Dose when deriving PHGs. When scientific evidence is compelling, these defaults are supplanted by alternative factors or modeled results. Table A4.1 below is adapted from OEHHA's "Technical Support Document for the Development of Noncancer Reference Exposure Levels" (OEHHA, 2008).

Table A4.1. Default uncertainty factors for PHG derivation, adapted from OEHHA (2008)

Uncertainty Factor	Value
Interspecies uncertainty factor (UF_A)	
Combined interspecies uncertainty factor (UF_A):	1 human observation √10 animal observation in nonhuman primates 10 where no data are available on toxicokinetic or toxicodynamic differences between humans and a non-primate test species
Toxicokinetic component (UF_{A-k}) of UF_A:	1 where animal and human PBPK models are used to describe interspecies differences √10 non-primate studies with no chemical- or species-specific kinetic data
Toxicodynamic component (UF_{A-d}) of UF_A:	1 where animal and human mechanistic data fully describe interspecies differences. (*This is unlikely to be the case.)* 2 for residual susceptibility differences where there are some toxicodynamic data √10 non-primate studies with no data on toxicodynamic interspecies differences

Uncertainty Factor	Value
Intraspecies uncertainty factor (UF_H)	
Toxicokinetic component (UF_{H-k}) of UF_H:	1 human study including sensitive subpopulations (e.g., infants and children), or where a PBPK model is used and accounts for measured inter-individual variability √10 for residual susceptibility differences where there are some toxicokinetic data (e.g., PBPK models for adults only) 10 to allow for diversity, including infants and children, with no human kinetic data
Toxicodynamic component (UF_{H-d}) of UF_H:	1 human study including sensitive subpopulations (e.g., infants and children) √10 studies including human studies with normal adult subjects only, but no reason to suspect additional susceptibility of children 10 suspect additional susceptibility of children (e.g., exacerbation of asthma, neurotoxicity)
LOAEL uncertainty factor (UF_L)	
Values used:	10 LOAEL, any effect 1 NOAEL or BMDL used
Subchronic uncertainty factor (UF_S)[1]	
Values used:	1 study duration >12% of estimated lifetime √10 study duration 8-12% of estimated lifetime 10 study duration <8% of estimated lifetime
Database deficiency factor (UF_D)	
Values used:	1 no substantial data gaps √10 substantial data gaps including, but not limited to, developmental toxicity

[1]Exposure durations of 13 weeks or less are subchronic regardless of species (OEHHA, 2008)