# Responses to Peer Review and Public Comments and List of Updates to Final Draft

## Technical Support Document: Public Health Goals for Chromium (VI) in Drinking Water

February 2026

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

# Responses to Peer Review and Public Comments and List of Updates

# Technical Support Document: Noncancer Health Protective Concentration For Chromium (VI) in Drinking Water

**Prepared by**

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

**February 2026**

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# INTRODUCTION

This document contains responses to public comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the noncancer Health Protective Concentration (HPC) technical support document for Chromium (VI) (Cr(VI)) during the first and second public comment periods, and responses to comments from the external scientific peer reviewers.

OEHHA released the first draft of this HPC document and held a public comment period from November 21, 2023, to January 8, 2024, and held a hybrid public workshop on January 8, 2024. OEHHA received no comments from stakeholders at the public workshop and two comments from stakeholders during the public comment period.

Pursuant to Health and Safety Code section 116365(c)(3)(D), OEHHA submitted the noncancer Cr (VI) HPC document for scientific peer review following the closure of the first comment period. Comments were received from the peer reviewers in March 2024.

The external scientific peer reviewers were:

1. Gary L. Ginsberg, Ph.D.
Yale University, Clinical Professor
New York State Department of Health
Director, Center for Environmental Health
NYS DOH, Empire State Plaza, Corning Tower, Room 1619
Albany, NY 12237

2. Carly Hyland, MS, Ph.D.
Assistant Professor of Cooperative Extension
UC Berkeley School of Public Health
UC Cooperative Extension
2121 Berkeley Way
Berkeley, CA 94704

3. Haizhou Liu, Ph.D., P.E.
Professor of Chemical and Environmental Engineering
Dept. of Mechanical Engineering
Bourns Hall A239
University of California Riverside
Riverside, CA 92521

4. Emanuela Taioli MD, Ph.D.
Oregon State University
41 West 82nd Street, 4C
New York, NY 10024

OEHHA made changes in response to the public and peer review comments as appropriate, and incorporated them into the HPC technical support document, which was released for a second public comment period from March 28, 2025, to April 28, 2025. OEHHA received comments from three stakeholders during the second public comment period. Minor revisions were made, as appropriate, to the technical support document in response to these comments.

The public comments and peer review comment letters are posted on the OEHHA website along with this response document, and the final version of the PHG technical support document.

In this document, comments appear in quotation marks where they are directly quoted from the submission. Note that for the public comments where the commenter included a footnote, OEHHA did not copy the footnote into the response document. Footnotes can be seen in the original public comment letters posted on the OEHHA website. Editorial comments resulting in non-substantive changes have been addressed and are not included in this document.

For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA web site at www.oehha.ca.gov.

OEHHA may also be contacted at:

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P.O. Box 4010, MS-12B
Sacramento, California 95812-4010
Attention: PHG Program

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**ABBREVIATIONS:**

ATSDR, Agency for Toxic Substances and Disease Registry

AUC, Area Under curve

BMD. Benchmark Dose

BMDS, Benchmark Dose Software

BMDL. Benchmark Dose Limit

Cr, Chromium

Cr(III), Trivalent Chromium

Cr(VI), Hexavalent Chromium

$CrO_4^{-2}$, Chromate

GI, Gastro-Intestinal

HED, Human Equivalent Dose

HPC, Health-Protective Concentration

ID, Identification

MCL, Maximum Concentration Level

LOAEL, Lowest Adverse Effect Level

$Na_2Cr_2O_7 \cdot 2H_2O$, Sodium Dichromate Dihydrate

NOAEL, No Adverse Effect Level

NTP, National Toxicology Program

OEHHA, Office of Environmental Health Hazard Assessment

PBPK, Physiologically Base Pharmacokinetic Modelling

PC, Public Commenter

PHG, Public Health Goal

PPM, Parts Per Million

POD, Point of Departure

PR, Peer Reviewer

RBC, Red Blood Cells

SDWA, Safe Drinking Water Act

SWRCB, State Water Resource Control Board

UF, Uncertainty Factor

$UF_A$, Interspecies Uncertainty Factor

$UF_H$, Intraspecies Uncertainty Factor

US EPA, United States Environmental Protection Agency

## IDENTIFICATION (ID) AND DRAFT ALIGNMENT OF RESPONSES TO PEER REVIEW AND PUBLIC COMMENTS

Peer Reviewers and Public Commenters.

Several commenters submitted comments together, those commenters are grouped together under one ID.

| ID | Peer Reviewer (PR) or Public Commenter (PC) | Name | Affiliation |
|---|---|---|---|
| Commenters on First Public Review Draft | | | |
| 1 | PR | Gary L. Ginsberg, Ph.D | NY State Dept. of Health, Yale University |
| 2 | PR | Carly Hyland, MS, Ph.D. | U.C. Berkeley |
| 3 | PR | Haizhou Liu, Ph.D., P.E. | U.C. Riverside |
| 4 | PR | Emanuela Taioli MD, Ph.D. | Icahn School of Medicine at Mount Sinai |
| 5 | PC | Tim Shestek | American Chemistry Council |
| | | Michael Miller | California Association of Winegrape Growers |
| | | Brenda Bass | California Chamber of Commerce |
| | | Trudi Hughes | California League of Food Producers |
| | | Robert Spiegel | California Manufacturers & Technology Association |
| | | Craig Johns | Partnership for Sound Science in Environmental Policy |
| | | Kerry Stackpole | Plumbing Manufacturers International |
| | | Gail Delihant | Western Growers Association |
| | | Ryan Pessah | Western Wood Preservers Institute |
| | | NA | Tox Strategies |
| 6 | PC | Karina Cervantez | CalMutuals |
| | | Timothy Worley, PhD | Community Water Systems Alliance |
| | | Sue Mosburg | CA NV American Water Works Association |
| Commenters on Second Public Review Draft | | | |
| 7 | PC | Tim Shestek | American Chemistry Council |
| | | Nick Cammarota | California Building Industry Association |
| | | Jonathan Kendrick | California Chamber of Commerce |
| | | Adam Harper | California Construction & Industrial Materials Association |

| ID | Peer Reviewer (PR) or Public Commenter (PC) | Name | Affiliation |
|---|---|---|---|
| | | Trudi Hughes | California League of Food Producers |
| | | Lance Hastings | California Manufacturing & Technology Association |
| | | Craig Johns | Partnership for Sound Science in Environmental Policy |
| | | Mathew Allen | Western Grocers |
| 8 | PC | NA | Tox Strategies |
| 9 | PC | Isabella Escutia | Student, University of San Francisco |

# RESPONSES TO EXTERNAL SCIENTIFIC PEER REVIEW COMMENTS

Reviewers were charged with determining whether the scientific work product is “based upon sound scientific knowledge, methods, and practices.” Specifically, reviewers were requested to address the: 1) critical study selection, 2) critical endpoint, 3) dose-response assessment, 4) toxicokinetics and uncertainty factors and 5) any additional concerns that would impact the overall reviewers’ charge.

**1. CRITICAL STUDY SELECTION -** The two-year drinking water studies in rats and mice performed by the National Toxicology Program (NTP, 2008) are retained as the critical studies to develop the noncancer health-protective concentration (HPC).

**Comment (PR.1.1):** Reviewers 1, 2, and 3 agreed that the NTP (2008) study is appropriate as the critical study.

**Response (PR 1.1):** No response needed.

**Comment (PR 1.2):** Reviewer 4 suggested moving the literature search start date back to September 2010, to make sure that there are no missing articles.

**Response (PR.1.2):** The 2011 PHG included literature through the end of 2010. The noncancer Cr(VI) HPC document includes literature beginning in January 2011, and therefore the combined literature searches include the dates suggested by the reviewer.

**Comment (PR.1.3):** Reviewer 1 suggested further use of human plasma studies would improve the assessment.

Reviewer 4 suggested focusing on the molecular epidemiology papers reporting blood Cr(VI) measurements and biomarkers of chromium exposure in healthy subjects and using the results to extrapolate levels and doses to then apply to studies that include health outcomes.

**Response (PR.1.3):** OEHHA agrees that, in general, the strategy proposed by the reviewers could potentially be useful for certain exposures. For Cr(VI), however, adequate data to perform such a strategy are not available. One of the major issues is that most human studies that have assessed chromium levels in blood reported measurements of total chromium, that is trivalent chromium (Cr(III)) plus Cr(VI). Total chromium in blood can provide an inaccurate picture of Cr(VI) exposure since many people who are highly exposed to Cr(VI) are also highly exposed to Cr(III) (Santonen et al., 2022). Measurements of total chromium will generally be unable to distinguish between these two chromium species, and using this metric would likely add considerable uncertainty to the Cr(VI) dose-response assessment.

Measuring chromium levels in red blood cells (RBCs) could provide a more accurate indicator of Cr(VI) exposure (ATSDR, 2012; Lewalter et al., 1985). However, relatively few human studies have used this metric. A few studies have examined chromium

levels in RBCs after giving participants known doses of Cr(VI) in drinking water. However, these studies are limited by small sample sizes, limited number of dose levels, their acute nature and lack of information on long-term exposures, and the large variability in responses seen from one participant to the next (Finley et al., 1997; Kerger et al., 1997; Kerger et al., 1996; Paustenbach et al., 1996).

**2. CRITICAL ENDPOINT -** After reviewing the literature on Cr(VI) since the publication of the PHG in 2011, OEHHA concludes that liver toxicity remains the most sensitive noncancer adverse health effect associated with exposure to this chemical. OEHHA is retaining this critical endpoint and its supporting studies for HPC derivation.

**Comment (PR.2.1):** All 4 reviewers agreed that liver toxicity is an appropriate critical endpoint.

**Response (PR 2.1):** No response needed.

**Comment (PR.2.2)**: Reviewer 4 suggested that pre-neoplastic effects should be considered in the noncancer HPC document.

**Response (PR.2.2):** In response to this comment, the evaluation of diffuse epithelial hyperplasia is now included in the noncancer Cr(VI) HPC document (presented in the following sections: *Toxicological Effects in Animals* (Table 2, page 22) *Dose-Response Assessment* (Table 3, pages 30-32), *Human Point of Departure* (Table 4, page 33), *Acceptable Daily Dose* (page 34), *Health-Protective Concentration* (Table 5, page 35), *Other Regulatory Standards and Guidance Values* (page 37), Appendix 3 (Figure A3.4, pages 90-91).

**Comment (PR.2.3)**: Reviewer 4 also proposed that OEHHA: 1) “ask Sazakli et al. to conduct some additional analyses/send the de-identified data set to the EPA for further analyses” and 2) “look for papers reporting blood CrVI measurements and biomarkers of Cr exposure in healthy subjects and use the results to extrapolate levels and doses to be then applied to studies that include health outcomes.”

**Response (PR.2.3):** In Sazakli et al. (2014), a correlation was observed for consumption of Cr (chromium) vs. blood and hair Cr concentrations. No adverse effects were noted in the study population, and therefore these data would not be suitable for dose-response analysis. Reanalysis of the study data would not impact critical study and endpoint conclusions in OEHHA’s Cr(VI) assessment. Suggestion 2 is addressed in the Critical Study Selection response above (PR 1.3).

**3. DOSE-RESPONSE ASSESSMENT –** OEHHA is applying benchmark dose modeling to derive the point of departure from the two-year drinking water studies.

**Comment (PR.3.1):** Reviewers 1, 2, and 3 agreed with the dose-response approach (BMD modeling).

**Response (PR 3.1):** No response needed.

**Comment (PR.3.2)**: Reviewer 4 had the following comments/suggestions: a) need additional support why the current method (BMD modeling) is better than the previous method (NOAEL), b) would like to see calculations using a NOAEL for comparison (as in the 2011 PHG), c) the NOAEL is much lower than the BMDL and d) provide rationale for why the POD was calculated from the BMDL derived from rodent data when there were corresponding human data, referring to the Sasso and Schlosser, and Kirman publications.

**Response (PR.3.2):** a) There are multiple advantages in using BMDL vs. a traditional NOAEL/LOAEL approach, which were noted in page 4 of the *Methodology* section. Application of BMD modeling for noncancer effects mitigates some of the limitations of the NOAEL/LOAEL approach, including: 1) dependence on dose spacing and sample size, 2) inability to account for uncertainty and variability in the experimental results, 3) the need to use an additional uncertainty factor when a NOAEL cannot be determined in a study, 4) inability to account for the shape of the dose-response curve, and 5) difficulty in quantitatively comparing studies with distinct dosing designs. OEHHA's current practice is to use BMD modeling over the NOAEL/LOAEL approach when possible.

b) For reference, Table 6 provides a comparison of the differences between the NOAEL approach used for the 2011 PHG and the current BMD modeling approach.

c) The NOAEL from the 2011 PHG listed in Table 6 is the LOAEL divided by a UF of 10 to account for extrapolating from LOAEL to NOAEL. Table 6 (*Risk Characterization*) has been updated to reflect this. Although the BMDL is higher than the NOAEL, it has the advantages outlined above, namely less uncertainty (no UF to extrapolate from LOAEL to NOAEL), and the ability of the model to account for the shape of the dose-response curve and not rely on the experimental dose spacing.

d) As highlighted in the epidemiology section of the document, no suitable human data are available for dose-response analyses. For this reason, animal data were used for POD derivation. Specifically, with respect to the reviewer's comment, the POD could not be calculated from the Sasso and Schlosser, and the Kirman publications because these publications focus on kinetics based on animal data and do not contain any human or animal toxicity data. As such, it is not possible to conduct a human dose-response analysis to generate a POD based on these publications.

**4. TOXICOKINETICS AND UNCERTAINTY FACTORS –** A critical issue for the determination of an HPC for Cr(VI) in drinking water is the extent to which this form of

chromium is absorbed through the gastrointestinal tract in order to cause an adverse effect. A body weight scaling adjustment (to account for interspecies differences in toxicokinetics) and physiologically-based pharmacokinetic (PBPK) modeling (to quantify the internal dose of Cr(VI)) were used to derive a human point of departure (POD) from a chronic study in laboratory animals. These adjustments also influence the uncertainty factors used to derive the acceptable daily dose and reflect the best available science to determine the HPC of Cr(VI).

**Comment (PR.4.1):** Reviewer 3 agreed with the modeling approach; Reviewers 2 and 4 abstained.

Reviewer 1 indicated the application of toxicokinetic modeling and uncertainty factors needed further consideration, with the following comments and suggestions:

“Another consideration is that an advantage to conducting systemic PBPK modeling rather than allometric scaling of dose is that the systemic modeling could produce estimates of liver dose (AUC [area under the curve] concentration) comparisons across species. Given that the most sensitive outcome is pathologic changes in liver, the ideal internal dose metric for cross-species extrapolation would be AUC liver dose. According to Kirman et al. 2013 there are limited human liver Cr data that might be useful in calibrating a human PBPK model. That data suggests greater liver:kidney Cr concentration ratio in humans as compared to rats. The simplification of allometric scaling loses the potential for utilization of whatever limited human liver data exist. Further the scaling approach doesn’t allow for the establishment of liver AUC as a key dose metric for cross-species TK [toxicokinetic] extrapolation.”

Elaborate on the limitations of ex vivo gastric fluid studies and uncertainty with use of these data for in vivo simulations for intraspecies and cross species extrapolations.

Perform a screening cross-check to determine whether the cross species toxicokinetics predicted by gastric modeling is consistent with the underlying systemic data that are available in Table 1.

Table 1: Reality Cross-Check Rat vs Human Internal Dosimetry from Drinking Water Studies (provided by Reviewer 1)

| Species | Dose/Duration | Biomarker | Conc. | Human/Rat[1] | Notes |
|---|---|---|---|---|---|
| Rats | 2.9 mg/kg/d × 90d | Plasma Cr | 0.15 mg/L | --- | N=5 |
| Rats | 7.2 mg/kg/d × 90d | Plasma Cr | 0.20 mg/L | --- | N=5 |
| Rats | 20.5 mg/kg/d × 90d | Plasma Cr | 0.30 mg/L | --- | N=5 |

| Species | Dose/Duration | Biomarker | Conc. | Human/Rat[1] | Notes |
|---|---|---|---|---|---|
| Humans | 0.057 mg/kg/d × 17d | Plasma Cr | 0.01 mg/L | 3.4 – 12 | N=1 |
| Humans | 0.071 mg/kg/d × 1d | Plasma Cr | 0.05 mg/L | 13.6 – 48.1 | N=4 |

[1] Ratios calculated based upon dose ratio of rats to humans per unit of external dose, not accounting for length of exposure period. The range is based upon the range of results in the 3 rat dose groups shown. Plasma concentrations visually estimated from Kirman et al. 2012 (rats) and 2013 (humans, Fig7A and 7C).

"If OEHHA still considers the full PBPK model too uncertain for the current purposes, it may consider restoring the intraspecies uncertainty factor to a full 10 fold rather than reducing it to 6 fold in the current draft document, and for exploring reasons why the available human studies reported in Kirman et al. provide higher plasma Cr results than might be expected based upon the gastric only modeling approach combined with allometric scaling. One direction to consider is that Sasso and Schlosser 2015 report that uptake will be sensitive to not only gastric pH but also to emptying time. However, they select a longer emptying time (35 min, fed state) rather than the shorter emptying time (4-12 min, fasted state); one would expect the longer emptying time (longer retention within the acid pH and reducing environment of the stomach) would result in more reduction and less CrVI absorption."

**Response (PR.4.1):** Several considerations of the whole body PBPK model by Kirman et al. (2012, 2013) were noted in the document. Although these models describe whole body kinetics of chromium, several issues were identified that precluded their use for cross-species extrapolation. The models did not predict total chromium in several compartments (e.g., kidney and plasma in mice, plasma in rats, plasma in humans). In the human model, parameters applied were optimized using serum and urine levels in various human studies. However, the model included several parameters (e.g., uptake and absorption in the gastrointestinal (GI) tract, transit rates between the stomach and GI) that were not validated with experimental data, thus there is high uncertainty in the model in predicting chromium levels in humans. As noted by Reviewer 1, the whole body PBPK model allows for the calculation of the liver AUC, which may be an appropriate dose metric given that the critical study is liver toxicity. However, due to the uncertainties in the model, there is low confidence in using a dose metric derived from this model.

OEHHA selected the gastric-only models by Sasso and Schlosser because the most critical difference in Cr(VI) kinetics between rodents and humans is the difference in gastric reduction. Similar to the whole body PBPK models, the gastric-only model used data from ex vivo gastric fluid studies by Proctor et al. (2012) and Kirman et al. (2013).

As noted by Reviewer 1, there are limitations in the use of these studies (addressed in *Toxicokinetic studies and PBPK models*, pages 8-9). Human variation in dietary patterns, diseases, and ages can affect gastric fluid content. The models by Sasso and Schlosser take into account the fed and fasted states for humans. Allometric body weight scaling was used to account for additional TK differences, such as clearance and excretion of Cr(VI) that the gastric model does not take into account.

There are several uncertainties in the systemic data available that hinder a reliable cross-check of the values predicted by the gastric model suggested by Reviewer 1. Levels in the table provided by Reviewer 1 are based on calculations by Kirman et al. (2012) of plasma chromium concentrations which they call “added chromium” in the plasma. Kirman et al. (2012) calculated “added chromium” as the total chromium measured in the plasma of exposed animals minus background (total chromium in non-exposed animals). They did not speciate the different forms of chromium. Thus, there is uncertainty in how much Cr(VI) is in plasma. Additionally, Kirman et al. (2012) compiled total chromium values in exposed and unexposed animals from various studies to calculate the added chromium (Table 1 in Kirman et al., 2012). At times, the study used to obtain the background levels of chromium was different from the study used to obtain the total chromium in exposed animals. Kirman et al. (2012) also acknowledges that at low doses (0.024 - 0.32 mg/kg-day of Cr(VI)), total chromium is similar to background levels of chromium, and therefore the reported measured values of total chromium in the plasma (and other tissues reported) at low doses have higher uncertainty compared to higher dose levels. The uncertainty in measured values precludes the validation of predicted model results.

Furthermore, the plasma concentration of 0.01 mg/L (10 µg/L) in Table 1 above was measured from a single human volunteer exposed to 4 mg/day Cr(VI) (as sodium dichromate) for 17 days and was reported graphically as “added chromium” (which is total chromium in the exposed subject minus mean total chromium in the unexposed group) in Figure 7A in Kirman et al. (2013). Data for the same individual/experiment were obtained from Paustenbach et al. (1996), which reported total plasma concentration at 17 days to be about 4 µg/L. It seems the added chromium (exposed – unexposed) cannot be 10 µg/L (as reported by Kirman et al. (2013), if the total chromium in the exposed group is only 4 µg/L. Due to this incongruency, these data are not considered suitable for an interspecies cross-check.

**Comment (PR.4.2):** Reviewer 1 suggests additional information regarding selection of UF values, especially decreasing the intraspecies toxicokinetic UF from 10 to 6, would be helpful.

**Response (PR.4.2):** OEHHA is providing a more detailed explanation of UFs in the document (including rationale for the selection of 6 for intraspecies toxicokinetic UF). Additional descriptions of UF application have been added to the *Acceptable Daily Dose* section of the revised noncancer HPC document. For the intraspecies UF, OEHHA applied √10 for the toxicodynamic component and 6 for the toxicokinetic component. To account for toxicokinetic diversity within susceptible populations, including infants and children, OEHHA typically applies an intraspecies toxicokinetic uncertainty factor of 10 (as noted by the reviewer) when human toxicokinetic data are not available. OEHHA guidelines (OEHHA, 2008) states that an intraspecies toxicokinetic uncertainty factor of √10 be used when there are some toxicokinetic data (e.g., PBPK models for adults). 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 for up to two hours post feeding (stomach pH ≈ 5.5 - 6.5) fall outside of the pH range included in this model (Laine et al., 2008; Neal-Kluever et al., 2019). Thus, OEHHA incorporated an additional uncertainty factor of 2 (√10 × 2, rendering an overall intraspecies toxicokinetic uncertainty factor of 6) to account for residual uncertainty related to pH that was not adequately captured by the gastric reduction model. The combined intraspecies UF is 20 (rounded). With an interspecies UF of √10 and an intraspecies UF of 20, the composite UF is 60.

**Comment (PR.4.3):** Reviewer 1 was unclear how human variability in gastric reduction was modeled and suggested the following:

It would be particularly of interest to see the ratio of the median to the 1st percentile HED doses.

**Response (PR.4.3):**

Table 2: Ratio of median POD to lowest 1% POD

| Species/Sex Endpoint | Rodent POD (mg/kg-day) | Internal Rodent POD (mg/kg-day) | Internal Human POD (mg/kg-day) | Median $POD_{HED}$ (mg/kg-day) | Lowest 1% $POD_{HED}$ (mg/kg-day) | Ratio of median $POD_{HED}$ to the lowest 1% $POD_{HED}$ |
|---|---|---|---|---|---|---|
| F-344/N Rat/F Liver chronic inflammation | 0.065 | 0.0049 | 0.00123 | 0.037 | 0.020 | 1.85 |

| Species/Sex Endpoint | Rodent POD (mg/kg-day) | Internal Rodent POD (mg/kg-day) | Internal Human POD (mg/kg-day) | Median $POD_{HED}$ (mg/kg-day) | Lowest 1% $POD_{HED}$ (mg/kg-day) | Ratio of median $POD_{HED}$ to the lowest 1% $POD_{HED}$ |
|---|---|---|---|---|---|---|
| B6F3F1 Mice/F Histiocytic infiltration of the liver | 0.059 | 0.0088 | 0.00146 | 0.044 | 0.024 | 1.83 |

The median $POD_{HED}$ value for liver chronic inflammation derived from the female rat study is 0.037 mg/kg-day while the lowest 1% $POD_{HED}$ used is 0.02 mg/kg-day. The predicted higher $POD_{HED}$ value using the mean of 20,000 Monte Carlo simulations is less protective than using the lowest 1%.

**Comment (PR.4.4):** Reviewer 1 suggested modeling variability in gastric emptying time if not already done.

**Response (PR.4.4):** Parameters of the PBPK model include both the fed state (30 mins, ICRP, 2006; 2022) and the fasted state (15.8 min, 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. OEHHA updated the Cr(VI) HPC document (*Use of PBPK Models in Risk Assessment* section, page 14) to clarify this point.

**Comment (PR.4.5):** Reviewer 1 suggested evaluating whether other influential parameters have sufficient information to enable their contribution to model variability.

**Response (PR.4.5):** The most influential parameters for model variability include stomach pH (mouse gastric model) and pH spike for the fed state (human model) (as reported in Tables C-12, C-13, US EPA, 2024).

**Comment (PR.4.6):** Reviewer 1 suggests considering whether any adjustments made affect the estimate of 1st percentile HED dose.

**Response (PR.4.6):** As illustrated in Sasso and Schlosser (2015), variation in pH can affect the amount of Cr(VI) escaping stomach reduction. Therefore, OEHHA modeled predicted $POD_{HED}$ values at gastric pH 4 to simulate individuals with higher gastric pH

and compared them to predictions with the default gastric pH of 1.3 for liver chronic inflammation in female rats (Table 3 below).

Table 3: Effect of pH on lowest 1% POD

| Species/Sex Endpoint | Rodent POD (mg/kg-day) | Internal Rodent POD (mg/kg-day) | Internal Human POD[a] (mg/kg-day) | pH | Lowest 1% $POD_{HED}$ (mg/kg-day) |
|---|---|---|---|---|---|
| Rat/F Liver Chronic Inflammation | 0.065 | 0.0049 | 0.00123 | 1.3 | 0.020 |
| Rat/F Liver Chronic Inflammation | 0.065 | 0.0049 | 0.00123 | 4.0 | 0.005 |

Of the 20,000 MC iterations, 22% of the values fell above the 0.020 mg/kg-day $POD_{HED}$ predicted at pH 1.3. This indicates that 22% of the simulated population is not protected at the higher gastric pH. To provide additional protection to individuals in sensitive groups, especially those with higher gastric pH, an additional UF would be warranted. In the updated noncancer Cr(VI) HPC document, instead of reducing the default toxicokinetic component of the intraspecies UF from 10 to √10 because a PBPK model was used, OEHHA reduced the UF to 6 to account for individual differences not captured by the human adult PBPK model and to account for residual susceptibility differences such as variation in gastric pH not captured by the model.

**5. ADDITIONAL CONSIDERATIONS -** Reviewers were asked to consider the following: 1) whether OEHHA has adequately addressed all important scientific issues relevant to Cr(VI) and to the methods applied in the derivation of the HPC based on noncancer effects; 2) whether a relevant study useful for assessing dose-response relationships or otherwise informing the HPC development was missed; and 3) whether the HPC for Cr(VI) is adequately protective of sensitive populations.

**Comment (PR.5.1):** Reviewers 1 and 4 suggested that variability due to early life stage was not modeled and Reviewer 4 suggested an additional calculation for “actual current life expectancy, that is more towards the 80s than the 70s.”

**Response (PR.5.1):** Sufficient data to quantify or confidently model variability due to early life stage were not identified. However, one aspect of the increased susceptibility of infants and children was addressed through the application of lifetime weighted drinking water consumption rates to calculate the Cr(VI) HPC. When age-specific drinking water intake rates were normalized to body weight, ingestion rates per unit

body weight were higher in infants than adults, thus accounting for disproportionately higher exposures in that population.

It is OEHHA standard practice that a life expectancy of 70 years should be used for HPC and PHG assessments (OEHHA, 2008).

**Comment (PR.5.2):** Reviewer 1 states that human studies appear to be via the inhalation route – text on exposure route for each study should be included.

**Response (PR.5.2):** Most of the human studies could not isolate a single route of exposure. Furthermore, human studies (regardless of exposure route) are not suitable for Cr(VI) dose-response analysis as quantitative data for Cr(VI) are not available.

**Comment (PR.5.3):** Reviewer 4 suggests adding a comparative table describing why values from other agencies are different from OEHHA's, along with a parameter for uncertainty.

**Response (PR.5.3):** The various government values listed in this document are based on the same study (NTP, 2008). In response to this reviewer's comment, the *Other Regulatory Standards and Guidance Values* section has been expanded to shed light on the approaches used by those agencies (pages 37-38).

# RESPONSES TO PUBLIC COMMENTS

To facilitate organization as well as comparison of public comments and associated responses with the peer reviewers' comments, public comments and responses to them were segregated into categories that align with the peer reviewer comments. Public comments outside of those categories are addressed below under "Additional Considerations". The categories are: 1) Critical study selection, 2) Critical endpoint, 3) Dose-response assessment, 4) Toxicokinetics and uncertainty factors, and 5) Any additional considerations.

## 1. CRITICAL STUDY SELECTION

No Public comments.

## 2. CRITICAL ENDPOINT

**Public Comment (PC.2.1)**: Commenter 5 contends that OEHHA demonstrated "inconsistent application of scientific methods (e.g., benchmark dose (BMD) modeling, allometric scaling) to multiple adverse effects to determine which endpoint is the most sensitive and relevant basis for the HPC derivation."

OEHHA has not demonstrated that the effects in the liver are more sensitive than the mouse intestine. "Based on allometric scaling principles, the above-mentioned doses in rats and mice are much more comparable - 0.2 mg/kg-day in rats is equivalent to ~0.05 mg/kg-day in humans and 0.38 mg/kg-day in mice is equivalent to ~0.054 mg/kg-day in humans." This indicates that mice (hyperplasia) are likely more sensitive to Cr(VI) than rats (liver toxicity) and that OEHHA's determination of the most sensitive species and non-cancer effect (chronic liver inflammation in rats) was incorrect.

**Response (PC.2.1):** The allometric scaling presented by Commenter 5 divided the rodent LOAEL doses by generic allometric adjustment factors of 4 for rats and 7 for mice (US EPA, 2002):

$$Human\ Equivalent\ Dose = animal\ dose / species\ adjustment\ factor$$

(US EPA 2002)

Rat to human

$$\frac{0.24\,\frac{\text{mg}}{\text{kg}-\text{day}}}{4} = 0.060\,\frac{\text{mg}}{\text{kg}-\text{day}}$$

Mouse to human

$$\frac{0.38\,\frac{\text{mg}}{\text{kg}-\text{day}}}{7} = 0.054\,\frac{\text{mg}}{\text{kg}-\text{day}}.$$

Rather than using the generic allometric conversion factors of 4 and 7, OEHHA used the NTP (2008) study data in the updated noncancer Cr(VI) HPC document. These data provided the time-weighted body weight averages of 0.274 kg for female rats and 0.0525 kg for female mice. OEHHA calculations included a human bodyweight of 70 kg:

$$\text{Human Equivalent Dose} = \text{animal dose X}\left(\frac{\text{BW}_{\text{animal}}}{\text{BW}_{\text{human}}}\right)^{1/4}$$ US EPA (2011).

Rat to human

$$0.24\,\frac{\text{mg}}{\text{kg}-\text{day}}\ \text{X}\left(\left(\frac{0.274\text{kg}}{70\text{kg}}\right)^{0.25}\right) = 0.0600\,\frac{\text{mg}}{\text{kg}-\text{day}}$$

Mouse to human

$$0.38\,\frac{\text{mg}}{\text{kg}-\text{day}}\ \text{X}\left(\left(\frac{0.0252\text{kg}}{70\text{kg}}\right)^{0.25}\right) = 0.0629\,\frac{\text{mg}}{\text{kg}-\text{day}}.$$

Using the actual rodent body weights from the studies (rather than generic allometric scaling factors in the preliminary analyses offered by Commenter 5) results in a human equivalent LOAEL for liver inflammation that is lower than that for epithelial hyperplasia in the small intestine and histiocytic infiltration in the liver.

As described in the noncancer Cr(VI) HPC document, modeling of gastric reduction of Cr(VI) was used to convert the animal POD (BMDL) to an internal animal dose (i.e., the amount of Cr(VI) released into the animal small intestine). Body weight scaling was subsequently applied to convert the animal internal dose to a human internal dose. Finally, gastric reduction modeling was used to convert the human internal dose to a human equivalent dose (HED). These calculations are summarized in Tables 4 and 5 below.

These analyses indicate that chronic liver inflammation in rats is the most sensitive and therefore is the appropriate endpoint for calculation of the Cr(VI) noncancer HPC.

Table 4: 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)<br>Female<br>F-344/N rats<br>(50/dose)<br>2 years | 0<br>0.24<br>0.94<br>2.44<br>7.00 | Chronic liver inflammation | 12/50<br>21/50*<br>28/50*≠<br>35/50*≠<br>39/50*≠ | LOAEL: 0.24 | 0.11/0.065<br>0.37<br>Log-logistic |
| NTP (2008a)<br>Female<br>B6C3F1 mice<br>(50/dose)<br>2 years | 0<br>0.38<br>1.36<br>3.14<br>8.73 | Histiocytic infiltration of the liver | 2/49<br>15/50*≠<br>23/50*≠<br>32/50*≠<br>45/50*≠ | LOAEL: 0.38 | 0.079/0.059<br>0.45<br>Log-logistic |
| NTP (2008a)<br>Male<br>B6C3F1 mice<br>(50/dose)<br>2 years | 0<br>0.38<br>0.91<br>2.44<br>5.93[b] | Diffuse epithelial hyperplasia in the small intestine | 0/41<br>11/45*≠<br>18/46*≠<br>42/48*≠<br>32/41*≠ | LOAEL: 0.38 | 0.072/0.059<br>0.53<br>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 ($Na_2Cr_2O_72H_2O$) 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 Na2Cr2O7 2H2O).

[b] High dose (5.93 mg/kg-day) omitted from BMD modeling to achieve acceptable model fit.

Table 5. Calculation of $POD_{HED}$ from rodent POD

| 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)<br>Female<br>F-344/N rats<br>(50/dose)<br>2 years | Chronic liver inflammation | 0.065 | 0.0049 | 0.00123 | 0.020 |
| NTP (2008a)<br>Female<br>B6C3F1 mice<br>(50/dose)<br>2 years | Histiocytic infiltration of the liver | 0.059 | 0.0088 | 0.00146 | 0.024 |

| 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) Male B6C3F1 mice (50/dose) 2 years | Diffuse epithelial hyperplasia in the small intestine | 0.059 | 0.0088 | 0.00146 | 0.024 |

Even with the inclusion of diffuse epithelial hyperplasia in the small intestine, these analyses (and subsequent analyses presented in Table 6 of the HPC document) indicate that chronic liver inflammation in rats is the appropriate critical effect and species on which to base the Cr(VI) noncancer HPC. No changes were made to the HPC document based on these comments.

**Public Comment (PC.2.2):** Commenters 7and 8 stated that the revised noncancer draft HPC document provides, “An insufficient demonstration that liver inflammation in rats is an adverse effect of Cr(VI) exposure, or that it is relevant to humans.”

**Response (PC.2.2):** In the revised noncancer HPC document, OEHHA strengthened the support for the human significance of liver inflammation observed in rats in the NTP (2008) studies. Liver inflammation can lead to serious complications that affect not only the liver but also the whole body. The liver's vital functions, including detoxification, protein synthesis, and production of biochemicals necessary for digestion, can be severely compromised when inflammation occurs. This can result in symptoms such as jaundice, abdominal pain, and dark urine, among others. If the inflammation is allowed to persist, it can lead to liver scarring, cirrhosis, liver failure, and even liver cancer (Cleveland Clinic, 2025; Mayo Clinic, 2025). Liver inflammation in rats is an adverse effect as mild/modest liver inflammation has been shown to markedly increase sensitivity to the hepatotoxic effects of xenobiotic agents (Ganey and Roth, 2001; Luyendyk et al., 2002; Luyendyk et al., 2003) (added to *Health-Protective Drinking Water Concentration* section, page 35).

US EPA (2024) conducted a systematic review to characterize hepatic toxicity associated with oral exposure to Cr(VI). US EPA concluded, “Overall, Cr(VI) likely causes hepatic effects in humans Cr(VI) contributes to oxidative stress in the liver, causes inflammation, increased fat storage and substantial increases in serum ALT and AST” (US EPA, 2024).

Su et al. (2024) observed a positive dose-response relationship between blood chromium vs. systemic inflammation and liver injury in humans who were occupationally

exposed to (Cr(VI) as chromate, $CrO_4^{-2}$. They concluded that blood chromium impacts the target organ (e.g., liver), causing oxidative stress and a variety of effects including target organ inflammation. Their findings provide evidence of a link between inflammation and the harmful effects of chromate on the liver, indicating that Cr(VI)-induced liver inflammation can occur in humans.

## 3. DOSE-RESPONSE ASSESSMENT

**Public Comment (PC.3.1):** Commenter 5 stated, "The model results reveal a flaw in OEHHA's policy to use a default 5% benchmark response (BMR) instead of EPA's default 10% BMR for POD derivation. In this case, the $BMDL_{05}$ is more than 3-fold lower than the lowest non-zero dose of 0.24 mg/kg-day. This indicates uncertainty in the $BMDL_{05}$ value because it is below the range of empirical observation. Alternatively, OEHHA could have used the default 10% BMR typically used by the USEPA (U.S. EPA, 2012). Figure 1 also shows the high 24% background incidence of liver inflammation in unexposed female rats mentioned previously. Taken together, the available evidence warrants use of a different model or a 10% BMR in deriving the POD."

**Response (PC.3.1):** In multiple studies, OEHHA has demonstrated that the lower 95% confidence bound on the $BMD_{05}$ typically appears equivalent for risk assessment purposes to a NOAEL in well designed and conducted animal studies where a quantal (dichotomous) measure of toxic response is reported. Therefore, OEHHA uses a default 5% response rate for determination of the BMC or BMD from quantal data in animal studies unless there is a sufficient justification to select an alternate benchmark response (OEHHA, 2008). As such, the OEHHA BMD analyses of liver inflammation in female rats (NTP, 2008) used 5% extra risk as the BMR. Benchmark dose modeling can generate BMDL values that are below the range of the experimental doses, especially when the lowest non-zero dose is the LOAEL as is the case in the NTP (2008) studies, because the models take the entire dose-response curve into account when determining BMDs and BMDLs. The model selection logic automatically applied in US EPA's Benchmark Dose Software (BMDS) checks to see if the BMDL is lower than the lowest dose. If the BMDL is at least 10x lower than the lowest dose, the model is moved to the "Questionable" bin. In this case, the ratio of the lowest dose (0.24 mg/kg-day) to the BMDL (0.065 mg/kg-day) is less than 10, indicating that the relationship between the lowest dose and the BMDL is acceptable.

The background incidence in the control group is inconsequential to the BMD analyses as the BMDL estimate is based on 5% extra risk, i.e., 5% above the background (control) incidence. NTP (2008) did evaluate concurrent controls, so incidences significantly higher than background are likely indicative of a true effect.

As the BMD method employed by OEHHA is not limited to the experimental doses, the BMDL may be outside of the dose range. No changes were made to the document based on this comment.

## 4. TOXICOKINETICS AND UNCERTAINTY FACTORS

**Public Comment (PC.4.1):** Commenter 5 stated, “An inexplicable *increase* in the total uncertainty factors applied to the same endpoint *after* using physiologically-based pharmacokinetic (PBPK) models to reduce uncertainty in interspecies extrapolation and intraspecies variability.” The commenter goes on to say, “Absent further explanation and given OEHHA’s use of a 10-fold UFH in 2011 in the absence of data from PBPK models, the change in UFH policy seems intended to counteract the effects of using updated risk assessment methods such as BMD modeling, allometric scaling, and use of PBPK models.”

**Response (PC.4.1):** A comparison of uncertainty factors in the 2011 Cr(VI) PHG document and the noncancer Cr(VI) HPC document indicate that the composite uncertainty factor ($UF_C$) has been reduced from 1,000 (LOAEL to NOAEL:10, $UF_H$:10, $UF_A$:10) to 60 ($UF_H$:20, $UF_A$:√10).

To calculate the human POD in the noncancer Cr(VI) HPC document, a toxicokinetic model and allometric scaling of internal dose were used to quantitatively account for interspecies differences in toxicokinetics. Because of this, an interspecies uncertainty factor ($UF_A$) of √10 was applied to account for differences in toxicodynamics when extrapolating these data from animal studies to humans ($UF_{A\text{-}K}$:1, $UF_{A\text{-}D}$: √10).

For the intraspecies uncertainty factor ($UF_H$), OEHHA applied √10 ($UF_{H\text{-}D}$) for the toxicodynamic component and 6 ($UF_{H\text{-}K}$) for the toxicokinetic component. OEHHA typically applies an intraspecies toxicokinetic uncertainty factor ($UF_{H\text{-}K}$) of √10 when there are some toxicokinetic data (e.g., PBPK models for adults). 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 simulations, 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 neonates (stomach pH ≈ 5.5 - 6.5 for about 1-2 hours after feeding) fall outside of the pH range included in this model (Laine et al., 2008; Neal-Kluever et al., 2019; Omari and Davidson, 2003). Delving into the output of the Monte Carlo simulations permitted OEHHA to better assess the populations that are included or excluded from the current modeling approach (compared to OEHHA (2011)).

Based on these insights, OEHHA incorporated an additional uncertainty factor of 2 (rendering an overall intraspecies toxicokinetic uncertainty factor ($UF_{H-K}$) of 6 (2 × √10)) to account for residual uncertainty related to pH that was not adequately captured by the gastric reduction model. The combined intraspecies uncertainty factor ($UF_H$) is 20 (rounded). Thus, the $UF_H$ of 30 ($UF_{H-K}$:10, $UF_{H-D}$:√10), which is the current OEHHA standard practice (pages 4-5 and 33 in noncancer Cr(VI) HPC document) was reduced to $UF_H$ of 20 due to the use of the PBPK model. Therefore, the composite uncertainty factor ($UF_C$) is 60 (20 ($UF_H$) × √10 ($UF_A$)) compared to the $UF_C$ of 1,000 in the 2011 PHG due to the application of updated methodologies that decreased uncertainty. No changes to the document were made based on this comment.

**Public Comment (PC.4.2)**: Commenter 7 stated, **"**Application of a 6-fold UFHk that is not consistent with OEHHA (2008) guidance, US EPA guidance, the use of available PBPK models, or available biological evidence." Commenter 8 stated, "Application of an arbitrary 2-fold factor, in addition to a UFHk = √10 (3) that already more than adequately accounts for residual uncertainty, results in double counting uncertainties."

**Response (PC.4.2):** Guidance set forth in OEHHA (2008) states, "The uncertainty factor used to account for intraspecies (inter-individual) variability in the human population ($UF_H$) has previously been assigned a default value of 10. Investigators have proposed subdividing the intraspecies uncertainty factor into √10 for toxicokinetic ($UF_{H-k}$) and √10 for toxicodynamic ($UF_{H-d}$) subfactors. However, it appears that a default toxicokinetic value of √10 may not be adequate for all chemicals, routes of elimination, or for the entire population, in particular the subpopulation of infants. A toxicokinetic subfactor of 10 is therefore recommended to protect infants, unless data are available to indicate that this subpopulation is not at higher risk due to differences in toxicokinetics."

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. However, adults medicated with proton pump inhibitors (stomach pH ≈ 6) and infants (stomach pH ≈ 5.5 - 6.5 for about 1-2 hours after feeding) fall outside of the pH range included in this model (added to *Acceptable Daily Dose* section, page 33).

OEHHA determined that a $UF_{H-K}$ of √10 would not be sufficiently protective because the kinetics model did not account for the gastric pH of infants following feeding. Considering the OEHHA (2008) guidance cited above, the pH of infant stomach, and the pH range of the applied kinetics model, OEHHA applied a factor of 2 to account for residual uncertainty related to pH that was not adequately captured by the gastric reduction model, resulting in a $UF_{H-K}$ of √10 × 2 ≈ 6. This value falls between the current OEHHA recommendations of $UF_{H-K}$ of 10 (to allow for diversity, including infants and children, with no human kinetic data) and $UF_{H-K}$ of √10 (for residual susceptibility

differences where there are some toxicokinetic data (e.g., PBPK models for adults only). The process used to determine the $UF_{H-K}$ of 6 is consistent with intent of the OEHHA (2008) guidelines and does not introduce double counting of factors. No changes were made based on these comments.

**Public Comment (PC.4.3):** Commenters 7, and 8 stated, "Mischaracterization of the human PBPK modeling and failure to consider strong biological evidence indicating minimal pharmacokinetic differences between adults and infants/children, both of which support a UFHk of 1, consistent with EPA (2024)."

**Response (PC.4.3):** Current OEHHA guidance specifies a $UF_{H-K}$ of 1 for human studies including sensitive subpopulations (e.g., infants and children), or where a PBPK model is used and accounts for measured inter-individual variability. The modeling approach used in developing the updated noncancer Cr(VI) HPC does not fully account for adults and infants. As such, a $UF_{H-K}$ of 1 would not adequately protect some sensitive populations. No changes to the document were made based on this comment.

**Public Comment (PC.4.4):** Commenters 7, and 8 stated, "The purported justification for OEHHA's default 30-fold UFH is inconsistent with uncertainty factor policies employed by many other regulators, including EPA, and protection of infants and children can be adequately addressed in most cases, including for Cr(VI), by proper endpoint selection and application of traditional UF values."

Commenter 6 requested that OEHHA explain the rationale for changing the toxicokinetic adjustment factor for intraspecies differences from 10 to 30, as noted in footnote b to Table 4, page 33 (First draft). Note: this is table 6, page 37 in the final Cr(VI) noncancer HPC document.

**Response (PC.4.4):** OEHHA's Water Toxicology Section adopted UF values adopted in the OEHHA Technical Support Document for Non-Cancer Exposure Levels (OEHHA, 2008). In this document (Table 4.4.2), OEHHA summarizes the PK UF values indicated by the PBPK modeling of various test chemicals by OEHHA and others. Of the 25 chemicals presented in this document, 13 have $UF_{H-K}$ greater than $\sqrt{10}$. This results primarily from the differences in toxicokinetics between infants and adults, resulting in higher internal dosages of the compounds and longer clearance half-lives. OEHHA's risk assessment methods aim to adequately protect all populations of concern, including infants and children. Based on this analysis, OEHHA deemed it appropriate to increase the default $UF_{H-K}$ from its previous value of $\sqrt{10}$ to a $UF_{H-K}$ value of 10 resulting in an intraspecies uncertainty factor of 30 (10 ($UF_{H-k}$) X $\sqrt{10}$ ($UF_{H-d}$)). As such, the uncertainty factors align with OEHHA guidance and no changes regarding this matter were made to the HPC document.

**Public Comment (PC.4.5):** Commenters 5, 7, and 8 expressed that the application of a composite 60-fold UF consisting of a 3-fold $UF_A$ and 20-fold $UF_H$ results in an HPC of 5 ppb Cr(VI). Correction of the $UF_H$ to 3 would result in a composite UF of 10, equating to a 6-fold reduction in the composite UF and therefore a 6-fold increase in the HPC to 30 ppb. This value would be derived in a manner consistent with OEHHA guidance and would be protective of all life stages.

**Response (PC.4.5):** As outlined in Table 6 (page 36, 37) and appendix 4 of the HPC document, OEHHA applied an interspecies UF of √10 (animal observation in nonhuman primates). For the intraspecies UF, OEHHA applied √10 for the toxicodynamic component (studies focusing on human populations). For the intraspecies toxicokinetic UF, OEHHA applied a value of 6. OEHHA typically applies an intraspecies toxicokinetic UF of √10 when there are some toxicokinetic data (e.g., PBPK models for adults only but no reason to suspect additional susceptibility of children). 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.

For this study, 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 (stomach pH ≈ 5.5 - 6.5 for about 1-2 hours after feeding) fall outside of the pH range included in this model (Laine et al., 2008; Neal-Kluever et al., 2019; Omari and Davidson, 2003). Post-ingestion is likely the critical time period as stomach/intestinal exposure to Cr(VI) is associated with ingestion and elevated stomach pH. As such, OEHHA has reason to believe that there is additional susceptibility for infants and the correct intraspecies toxicokinetic UF is between √10 and 10.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 (C × 2). The combined intraspecies UF is 20 (rounded). Therefore, the composite UF is 60 ($UF_A$ (√10) X $UF_H$ (20) = 60.

This Public Comment (PC.4.5) suggests that both the intraspecies and interspecies UF should be √10 which would render a composite UF of 10. While OEHHA agrees that an interspecies UF of √10, is appropriate, an intraspecies UF of √10 requires that there is no reason to suspect additional susceptibility of children (Appendix 4, HPC document). As explained above, OEHHA has determined that there is reason to suspect additional susceptibility of children. As such, the proposed value of √10 for intraspecies UF is

inadequate. The proposed √10 intraspecies UF is not consistent with OEHHA guidance and would not be protective of all life stages.

## 5. ADDITIONAL CONSIDERATIONS

**Public Comment (PC.5.1):** Commenter 5 stated, “Unexplained and seemingly unjustified presumption that intestinal lesions are more relevant to the cancer PHG assessment than the non-cancer PHG.”

**Response (PC.5.1):** Analysis of intestinal lesions (epithelial hyperplasia) is included in the final draft of the noncancer Cr(VI) HPC (see Peer Review Response PR.2.2).

**Public Comment (PC.5.2):** Commenter 9 stated, “Decreasing chromium standards from 10 ppb to 5 ppb is necessary to ensure the risk of cancer decreases in California. These steps will pave the road for more stringent remediation methods. I urge you to not only lower the acceptable concentrations but also support scientific research that would aid in finding technologies that could better remove these chemicals from our water. These levels are concerning and should urge you to protect your residents.”

**Response (PC.5.2):** The noncancer HPC derived in the Cr(VI) document is based “exclusively on public health considerations…” as required by the Safe Drinking Water Act (SDWA), Health and Safety Code section 116365(c)(1) and is not a regulatory standard. Regulatory standards, called Maximum Contaminant Levels (MCLs), are set by the State Water Resources Control Board (SWRCB) which considers the PHG, any primary drinking water standard for this chemical adopted by the US EPA, and the “technological and economic feasibility of compliance with the proposed drinking water standard. (Health and Safety Code section 116365(b)). Changes to MCLs and technologies to remove chemicals from water are outside of the scope of the HPC.

**Public Comment (PC.5.3)**: Commenters 5, 6, 7, and 8 suggested that the process used to update the MCL for Cr(VI) departed from the statutory requirements of the SDWA and State Water Resources Control Board’s (SWRCB) past practices. The commenters suggest that OEHHA is seeking to reestablish the existing MCL by using predetermined conclusions. They continue that the Cr(VI) MCL should not be established until the conclusion of the Cr(VI) cancer and noncancer HPC analyses and CR(VI) PHG. And that this PHG is based on the 2011 PHG, which provides an inadequate scientific basis.

**Response (PC.5.3):** OEHHA has followed the statutory requirements in the SDWA, including following the scientific requirements proscribed in statute, following the processes for public comment periods, a public workshop, and providing the required

HPC to the SWRCB. Given the complexity of the analysis, the cancer and non-cancer analysis were split. Per the SDWA, the SWRCB develops MCLs factoring different considerations than the PHG process, such as technical and economic feasibility. A PHG is solely based “exclusively on public health considerations” and the best available science including if applicable, adverse effects on sensitive subgroups of the population, like infants, children, and pregnant women. Additionally, the SDWA requires peer review of the draft HPC which provides a statutorily required check on robustness of OEHHA’s analysis. The comments directed at the SWRCB, and the timing of the MCL are outside of the scope of the HPC/PHG process. Further, while OEHHA did use the same point of departure for this update when compared to 2011, it did update other factors, such as the uncertainty factors for consistency with state-of-the-science methodologies. No changes were made to the final document based on this comment.

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## LIST OF UPDATES TO FINAL DRAFT

1. Toxicokinetics section: Expanded explanation of PBPK pH parameters added as suggested by peer reviewer Ginsberg.
2. Table 2: Drinking water concentrations (ppm) were converted to doses (mg/kg-day) for Sánchez-Martín et al. (2015) and Sivakumar et al. (2014). This update facilitates comparison of these studies to the other studies included in this table.
3. Table 3: BMDL for histiocytic infiltration of the liver was changed from 0.059 to 0.058 mg/kg-day, due to a typographical error in the original draft. This update is consistent with the BMDS output in Figure A3.3. This update has no impact on the conclusions of the Cr(VI) noncancer HPC.
4. Table 4: Table 4 lists the PODs (BMDLs) from Table 3, and the POD for histiocytic infiltration of the liver was updated from 0.059 to 0.058 mg/kg-day. This update has no impact on the conclusions of the Cr(VI) noncancer HPC.
5. Acceptable Daily Dose section: The ADD for histiocytic infiltration of the liver in female mice was updated from 0.39 to 0.40 µg/kg-day due to a rounding error. This update has no impact on the conclusions of the Cr(VI) noncancer HPC.
6. Table 5: This table was added to clarify the steps used to derive the HPC. This is in response to peer review comments by peer reviewer Taioli.
7. Table 6: In the 2011 column, the term NOAEL was omitted and the POD value was described as LOAEL/10. In the 2011 doc, LOAEL/10 was listed as the NOAEL for the POD. This clarification is made in response to a peer review comment.
8. Other Regulatory Standards and Guidance Values section: US EPA's oral reference dose (RfD) of 3 µg/kg-day was updated to 0.9 µg/kg-day as US EPA finalized its RfD for Cr(VI) between OEHHA's first draft and final Cr(VI) noncancer HPC document.
9. Other Regulatory Standards and Guidance Values: The California State Water Resources Control Board (SWRCB) adopted an MCL of 10 ppb Cr(VI) in drinking water in 2024, after the release of the first draft HPC noncancer document. The subsequent versions of the noncancer HPC document include mention of the new MCL.
10. Other Regulatory Standards and Guidance Values: Information was added with additional details on how Health Canada derived their Maximum Acceptable Concentration of chromium in drinking water. This update was provided in response to peer reviewer Tailo's request for more details on how other entities derived their regulatory/guidance values for Cr and Cr(VI).

11. Figure A1.1 and Detailed Study Review: Reference corrected to A2.1 – A2,5.

12. References: References were updated or added/deleted in response to comments by peer reviewers and the public.

    a. Updated references: IARC (2018), SWRCB (2024), US EPA (2005), US EPA (2024)

    b. Added in response to peer reviewers: ICRP (2002), ICRP (2006)

    c. Added in response to public comments: Chen and Zhang (2023), Cleveland Clinic (2025), De Flora et al. (2016), Mayo Clinic (2025), Neal-Kluever et al. (2019), Omari and Davidson (2003), Tilg and Moschen (2010)

    d. Deleted in response to public comments: Rahman et al. (2016)

13. Appendix 3: BMDS 3.3.2 was used for the analyses of epithelial hyperplasia data and this was the most current version at that time. Initial dose-response analyses were conducted with US EPA's Benchmark Dose Software (BMDS) 3.3, which was the current version of BMDS at that time. For consistency, other endpoints were rerun using BMDS 3.3.2. PODs (BMDLs) determined by BMDS 3.3.2 were no different than PODS determined by BMDS 3.3.