EXTERNAL SCIENTIFIC PEER REVIEW COMMENTS ON THE PROPOSED HEALTH-PROTECTIVE CONCENTRATION FOR 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

This document contains the comments received from the external scientific peer review of the Office of Environmental Health Hazard Assessment's Proposed Health-Protective Concentration for Noncancer Effects of Hexavalent Chromium in Drinking Water. The draft document was released for public comment on November 24, 2023, and pursuant to Health and Safety Code section 116365(c)(3)(D), was submitted for scientific peer review following the closure of the comment period.

The peer review was coordinated by the CalEPA External Scientific Peer Review Program (the Program) via an agreement with the University of California, in accordance with Health and Safety Code section 57004. Reviewers identified by the University of California and approved by the Program were asked to review and comment on the draft document's scientific assumptions, findings, and conclusions as summarized in Attachment 2 of the peer review request (provided below).

Reviewers:

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2. Carly Hyland, MS, Ph.D.
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Attachment 2: Scientific Assumptions, Findings, and Conclusions to Review

Reviewers are asked to determine whether the scientific work product is "based upon sound scientific knowledge, methods, and practices."

OEHHA requests that you make this determination for the chemical assessed in the draft document, *Public Health Goal – Proposed Health-Protective Concentration for the Noncancer Effects of Hexavalent Chromium in Drinking Water*. An explanatory statement is provided below for focusing the review.

Chromium is a naturally occurring metal that can enter ground water by leaching from soil, but there are also many anthropogenic sources such as electroplating factories, leather tanneries, and textile manufacturing facilities that can contribute to drinking water contamination. Chromium in water can exist as either the trivalent form, Cr(III), or the hexavalent form, Cr(VI). Cr(VI) is the more toxic of the two forms of chromium, while Cr(III) is an essential trace element in the diet.

The current PHG for Cr(VI) is 0.02 parts per billion (ppb) or micrograms per liter (µg/L) in drinking water. This is based on the occurrence of small intestinal tumors in male mice exposed to Cr(VI) in drinking water for two years (NTP, 2008). A noncancer HPC of 2 ppb was also identified based on liver toxicity (mild chronic inflammation, fatty changes) in female rats exposed to Cr(VI) in drinking water for two years (NTP, 2008). As part of the review and update of the 2011 Cr(VI) PHG, OEHHA has developed a proposed HPC of 5 ppb for noncancer effects. The HPC based on cancer is in development and will be submitted later for a separate peer review.

Assumptions, Findings, and Conclusions

1. **Critical study - 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 proposed noncancer HPC.**

   An evaluation of the scientific literature published after 2011 did not identify any new studies that would be more suitable for derivation of the HPC for noncancer effects. The NTP (2008) studies were well conducted, chronic in duration, and were more sensitive than other studies, which made them the best choice for HPC derivation.

   The sections of the product that pertain to this conclusion include:

- Literature search – animal studies (starting on pg. 2)
- Basis for the 2011 Noncancer PHG (starting on pg. 6)

- Updated Toxicological Review – Toxicological Effects in Animals (starting on pg. 16)

2. **Critical endpoint - After reviewing the literature on hexavalent chromium, or 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.**

   While there have been numerous studies published on the toxicity of Cr(VI) since the 2011 PHG, OEHHA concluded that liver toxicity remains the most sensitive noncancer health effect associated with exposure to Cr(VI). Two endpoints were evaluated for point of departure determination: chronic liver inflammation in female rats and histiocytic infiltration of the liver in female mice.

   The sections of the product that pertain to this conclusion include:

- Basis for the 2011 Noncancer PHG (starting on pg. 6)

- Updated Toxicological Review – Toxicological Effects in Animals (starting on pg. 16)

3. **Dose-response assessment – OEHHA is applying benchmark dose modeling to derive the point of departure from the two-year drinking water studies.**

   To derive the HPC, the data were modeled with Benchmark Dose Software (BMDS; US EPA, version 3.3) using a benchmark response of 5%, which is OEHHA's policy as outlined in its peer reviewed guidelines (OEHHA, 2008).

   The sections of the product that pertain to this conclusion include:

- Dose-response assessment (starting on pg. 28)

- Appendix 3 (starting on pg. 79)

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).

The point of departure from the animal studies were converted to corresponding human equivalent doses (POD_{HED}) using rodent and human physiologically-based pharmacokinetic (PBPK) models and a body weight scaling adjustment. The lowest POD_{HED} of 0.020 mg/kg-day for chronic liver inflammation in female rats was selected for HPC derivation.

The body weight scaling adjustment and PBPK modeling were applied to address the uncertainty around toxicokinetics when extrapolating a human equivalent dose from an animal dose. To derive the HPC, OEHHA applied the following uncertainty factors (UFs) (OEHHA, 2008):

- an interspecies UF of $\sqrt{10}$ to account for toxicodynamic differences between animals and humans;
- an intraspecies UF of $\sqrt{10}$ for toxicodynamic variability in humans; and
- an intraspecies UF of 6 for toxicokinetic variability in humans.

OEHHA reduced the toxicokinetic component of the intraspecies UF from 10 (the default value when using animal toxicity studies) to 6 instead of 1, to (i) account for interindividual differences in toxicokinetics and Cr(VI) dose to the intestine not captured by the adult human PBPK model, and (ii) to account for residual susceptibility differences such as variability in stomach pH and life stages (e.g. infants and children) not addressed by the PBPK model. Individuals and populations with a higher stomach pH (such as newborns, fed infants, and individuals taking proton pump inhibitors or medications that raise the gastric pH) will have a decreased capacity to reduce Cr(VI), thus increasing absorption and the potential for toxicity. The combined intraspecies UF is 20 (rounded). Therefore, the composite UF is 60.

Applying the composite UF of 60 to the POD_{HED} of 0.020 mg/kg-day (based on chronic liver inflammation in female rats) resulted in an acceptable daily dose of 0.34 µg/kg-day. To calculate the HPC, a drinking water intake rate of 0.053 L/kg-day, which is time-weighted over a 70-year lifetime and incorporates the higher water intake rates of infants and children, and a relative source contribution of 0.8 were applied, resulting in the noncancer HPC of 5 ppb.

The sections of the product that pertain to this conclusion include:

- Toxicokinetics (starting on pg. 6)
- Dose-Response Assessment (starting on pg. 28)

- Health-Protective Drinking Water Concentration (starting on pg. 31)
- Appendix 4 (starting on pg. 85)

5. Additional considerations

Reviewers are not limited to addressing only the specific topics presented above, and are asked to consider the following in their review:

(a) For the proposed HPC, please comment on 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.

(b) For the chemical reviewed (Cr(VI)), please comment on whether a relevant study useful for assessing dose-response relationships or otherwise informing the HPC development was missed.

(c) HPCs must be protective of known sensitive populations. Please comment on whether HPC for Cr(VI) is adequately protective of sensitive populations.

Gary Ginsberg, PhD
Professor, Yale School of Public Health
Feb 29, 2024

Subject: Review Comments of California OEHHA draft document entitled "Proposed Health-Protective Concentration for the Noncancer Effects of Hexavalent Chromium in Drinking Water, Public Review Draft, Nov 2023"

Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I could review with confidence and listed and responded to below.

Overall Charge Question

Reviewers are asked to determine whether the scientific work product is "based upon sound scientific knowledge, methods, and practices."

The methods and practices appear to be sound in this OEHHA draft document but the document may be able to make further use of scientific knowledge in the form of human plasma chromium (Cr) data in studies involving human ingestion of water containing hexavalent chromium (CrVI).

Conclusion 1: Choice of Study

The 2008 drinking water NTP study in rats is appropriate for dose response modeling of a variety of CrVI-related toxic effects; the study is well conducted, has extensive QA/QC and provides dose-related effects . USEPA 2022 also relied on NTP 2008 as the primary data source for RfD derivation.

Conclusion 2: Choice of Endpoint

Liver inflammation in female rats appears to be a reliable and sensitive endpoint, making distributional sense that the liver would be particularly targeted due to its first pass location for orally absorbed CrVI. The dose response data for other endpoints, including intestinal hyperplasia in mice (an endpoint used by ATSDR) does not appear to result in any greater sensitivity.

Conclusion 3: Dose Response Assessment: OEHHA's method of deriving the acceptable daily dose from the rodent POD (BMD modeling, 5% response level), then deriving the

rodent internal POD from the gastric reduction model, estimating the HED internal POD and backing out the human external dose POD all represent reasonable logic and standard, sound scientific methodology. The net result is a similar derivation of the "RfD" as derived by USEPA based upon the same endpoint - rat liver inflammation – EPA 0.7 ug/kg/d, OEHHA: 0.34 ug/kg/d

Conclusion 4: Toxicokinetics and Uncertainty Factors

The application of toxicokinetic (TK) modeling and Uncertainty Factors (UF) needs further consideration by OEHHA.

With the great deal of data generated to inform cross species comparison of gastric reduction of hexavalent chromium post oral ingestion (references by DeFloria, Proctor, Sasso Kirman as cited in the draft document) it is appropriate for Cal OEHHA to focus upon this factor in constructing physiological models of chromium absorption. The ex vivo gastric fluid reduction studies are useful to gain some understanding of this cross-species difference. However there may be uncertainties and limitations with this approach, and with the further allometric scaling adjustment to internal dosimetry, that are not evaluated in the draft document.

Limited Human Evidence:

Data for human toxicokinetic modeling come largely from ex vivo gastric fluid studies. The kinetics of gastric reduction of CrVI are complex, being dependent upon gastric pH, emptying time, recent dietary intake, levels of various reducing agents, and potentially a host of pharmacologic and physiologic factors. The role of the gastric microbiome in this process is unexplored. Against this backdrop Kirman et al. 2013 provide evidence of more complete human reduction of CrVI in humans as compared to mice (primarily at low doses) and similar or slightly more effective than in rats (Kerwin et al. 2013, 2014. The ex vivo human data are from an experiment in which gastric fluid was collected from 10 fasted preoperative subjects, pooled and then adjusted to different pH values. This small study using a compositing approach and employing the fasted state does not begin to explore the wide range of human variability in gastric fluid content with respect to reducing equivalents that may be possible across ages, dietary patterns and disease states. Use of the fasted state in humans would be expected to provide low rates of reduction as De Flora (2016) found approximately twice the reducing capacity in gastric fluid from the fed state. The Kirman et al. study did adjust separate gastric aliquots to different pHs (1, 4 or 7) and given the importance of pH on gastric reduction of CrVI (lower pH, greater reduction), this was an important relationship to establish. These researchers also explored whether patients on proton pump inhibitors would have a different capacity to reduce CrVI. The

draft OEHHA document could be benefitted by further elaboration of the limitations of such data and the uncertainties in using it to provide in vivo simulations useful for intraspecies and cross-species extrapolations.

Toxicokinetic Modeling across Species based upon Ex Vivo Studies/Allometric Scaling:

Allometric Scaling instead of Systemic PBPK Modeling: conceptually it is fine for the draft document to choose scaling over multicompartment PBPK modeling in the interest of keeping the approach simpler and focused upon where the cross-species differences are believed to be pivotal. The net result when OEHHA calculated the PODs in both rats and humans was a POD_{HED} that is 3.25 lower than the rat POD (OEHHA, Table 4). This would suggest that the internal levels of Cr species (CrIII+CrVI) would be modestly higher in humans than mice. However, according to the reality cross-check presented in the table below, actual (not modeled) human plasma levels across 2 studies involving a total of 5 volunteers receiving oral CrVI in drinking water is on the order of 3.4 to 48 fold greater than the plasma level achieved in rats for a similar dose level. A quick review of the human urinary data compared to rodents shows humans excreted substantially more Cr (higher percentage of dose) in urine than rats. Thus, slower excretion would not appear to be the cause for higher Cr in plasma in humans than rodents by more than the allometric scaling factor (approx. 4 fold).

The reason for these apparent differences is unclear but given that both the plasma concentration and urinary excretion of Cr are greater in humans than in rodents, it would seem that the bioavailability of CrVI may be greater in humans than rats. This is not what is suggested by the gastric fluid modeling approach. Thus, even if CalOEHHA believes the PBPK modeling is unnecessariy complex and too uncertain, I recommend that they perform the screening cross-check exemplified in the following table to determine whether the cross species toxicokinetics predicted by gastric modeling is consistent with the underlying systemic data that are available.

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 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 lAUC as a key dose metric for cross-species TK extrapolation.

Reality Cross-Check Rat vs Human Internal Dosimetry from Drinking Water Studies

Species	Dose/Duration	Biomarker	Conc	Human/Rat[1]	Notes
Rats	2.9 mg/kg/d x 90d	Plasma Cr	0.15 mg/L	---	N=5
Rats	7.2 mg/kg/d x 90d	Plasma Cr	0.20 mg/L	---	N=5
Rats	20.5 mg/kg/d x 90d	Plasma Cr	0.30 mg/L	---	N=5
Humans	0.057 mg/kg/d x 17d	Plasma Cr	0.01 mg/L	3.4-12	N=1
Humans	0.071 mg/kg/d x 1 d	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, Fig 7A 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. They report that:

> *Daily variation in gastric emptying is also expected to occur. Gastric emptying half time of liquids in non-fasted individuals is typically higher than 35 min, while in fasted individuals it may be as low as 4–12 min (DeSesso and Jacobson, 2001; Mudie et al., 2010, 2014). The default value used for the gastric emptying rate in this model corresponds to an emptying half-time in the stomach of 35 min.*

It also doesn't appear that Sasso and Schlosser evaluated the influence of variability in emptying time on CrVI flux to intestine, but this is not clear from their statement on this:

> *The human extrapolation using the kinetics presented in this paper (Table 1) did not combine data for both sexes and multiple individual small intestine segments, did not utilize a whole-body PBPK model, and did not perform simulations for different human lifestages or circadian variation.*

Similarly, it is unclear how OEHHA modeled human variability in gastric reduction of CrVI from the two statements I could find describing this modeling in the draft document:

An estimated daily Cr(VI) dose to achieve the 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.

AND

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}).

Several suggestions that OEHHA can consider in modeling intrahuman variability are:

1. Present the full variability analysis done by OEHHA in an appendix. It would be particularly of interest to see the ratio of the median to the 1st percentile HED doses.
2. Model variability in gastric emptying time if not already done
3. Evaluate whether other influential parameters have sufficient information to enable their contribution to model variability.
4. Consider whether any adjustments made affect the estimate of 1st percentile HED dose.

Decreased IntraspeciesToxicokinetic Uncertainty Factor:

OEHHA decreased this default UF from 10 to 6 fold and offered the explanation provided below. However its still unclear how the factor of 6 was chosen (perhaps in some policy document or perhaps I missed it in this draft document) but additional explanation would be helpful. I would assume that picking a conservative point on the Monte Carlo distribution would normally lead to a TK UF of 1 and then somehow the following considerations bring this UF to 6.

For the intraspecies UF, OEHHA applied √10 for the toxicodynamic component and reduced the toxicokinetic component from a full factor of 10 (the default) to 6, to (i) account for interindividual differences in toxicokinetics and dose to the intestine of Cr(VI) not captured by the human adult PBPK model, and (ii) to account for residual susceptibility differences such as variability in stomach pH and life stages (e.g. infants and children) not addressed by the PBPK model. Individuals and populations with a higher stomach pH (such as newborns, fed infants, and individuals taking proton pump inhibitors or medications that raise the gastric pH) will have a decreased capacity to reduce Cr(VI), thus increasing absorption and the potential for toxicity. The combined intraspecies UF is 20 (rounded). Therefore, the composite UF is 60.

Additional Considerations

(a) For the proposed HPC, please comment on 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.
This is a complex analysis that OEHHA merits kudos for using a simplified TK modeling approach to achieve reasonable cross-species extrapolation. As described above there are a few suggestions for how OEHHA can cross-check their results and perhaps adjust modeling procedures to enhance cross-species extrapolation and analysis of intrahuman variability.

(b) For the chemical reviewed (Cr(VI)), please comment on whether a relevant study useful for assessing dose-response relationships or otherwise informing the HPC development was missed.
No, I am not aware of any keys studies that were missed.

(c) HPCs must be protective of known sensitive populations. Please comment on whether HPC for Cr(VI) is adequately protective of sensitive populations.

The Kirman 2013 study describes the potential for infants to have less reduction due to a milk-based diet leading to higher gastric pH but this could be counteracted by slower gastric emptying with the net outcome not obvious. It doesn't appear that variability due to early lifestage was formally modeled and this should be further discussed. In addition, the support for reducing the intrahuman TK variability UF to 6 fold needs further consideration and support.

Additional Comment – many of the human studies described under updated toxicological review (pages 13-15) appear to by the inhalation exposure route. However, dose route is not mentioned in these study summaries except in the summary table. The text should describe exposure route in each case and I would recommend organizing this summary by exposure route given that for this PHG analysis the oral route of exposure is far more relevant.

Berkeley
UNIVERSITY OF CALIFORNIA

February 29, 2024

Dr. Carly Hyland
Assistant Professor
Environmental Health Sciences, School of Public Health
University of California, Berkeley

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

Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I would review in confidence, including the critical endpoint (point 2) and dose-response assessment (point 3).

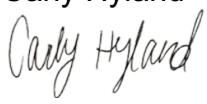
I have reviewed the Public Health Goals (PHG) for hexavalent chromium in drinking water from OEHHA's 2011 assessment and the draft review for the current assessment, dated November 2023. OEHHA has conducted a thorough review of all new epidemiologic and toxicological studies on the potential non-carcinogenic effects of hexavalent chromium since its 2011 review and adequately summarized the findings of these studies in their report. After this thorough review, OEHHA concluded that chronic liver inflammation remained the most sensitive endpoint, based on findings with female rats. Further, OEHHA retained a 2008 report from the National Toxicology Program (NTP) on hexavalent chromium as the critical study for non-cancer endpoints, as was used in the development of the 2011 PHG. I agree with OEHHA's conclusion that data suggest that chronic liver inflammation remains the most sensitive non-cancerous endpoint and agree with their conclusion to retain the 2008 NTP report as the critical study. As noted in their review, several studies that have been published since their 2011 report could not be used for dose-response assessment as only one exposure group was examined (outlined in Tables A2.1-A2.5).

The primary differences in OEHHA's assessment for a PHG for noncancer effects of hexavalent chromium in drinking water in 2011, in which the PHG was set at 2 pbb, to the current recommendation, which is proposed at 5 ppb, are: 1) updating the determination of the Point of Departure (POD) from the Lowest Observed Adverse Effect Level (LOAEL) of 0.02 mg/kg/day, obtained from the 2008 NTP report, to a benchmark dose lower confidence limit (BMDL) of 0.065 mg/kg/day; 2) updating the toxicokinetic adjustment for interspecies and intraspecies differences; and 3) updating the estimated Daily Water Intake (DWI) from 0.067 L/kg/day to 0.053 L/kg/day. While I do not have the appropriate expertise to evaluate the toxicokinetic adjustments used to derive the Uncertainty Factors, I believe that OEHHA was justified in updating the POD to a BMDL of 0.065 mg/kg/day, particularly given the lack of dose-response data in the literature, particularly for epidemiologic studies. While LOAELs and BMDLs each have advantages and disadvantages, the use of BMDLs seems appropriate in the current context, as it can better account for variability or uncertainty in studies and is less

dependent on dose spacing, for which there appears to be insufficient literature for hexavalent chromium.
It is notable that in its 2011 report, OEHHA documented a Health Protective Concentration (HPC) of 0.0024 mg/L, or 2.4 ppb, for children based on the same 2008 NTP report (Table 17). On page 30 of the current recommendation, OEHHA noted that they applied a combined intraspecies UF of 20 to account for "residual susceptibility differences such as variability in stomach pH and life stages (e.g., infants and children) not addressed by the PBPK model. Individuals and populations with a higher stomach pH (such as newborns, fed infants, and individuals taking proton pump inhibitors or medications that raise the gastric pH) will have a decreased capacity to reduce [hexavalent chromium], thus increasing the potential for toxicity". I do not have the appropriate expertise to evaluate the PBPK modeling and toxicokinetic adjustments, and request that others with this expertise weigh in on this assessment in order to confirm the HPC is protective of the most sensitive populations, such as infants and children.

In conclusion, I agree with OEHHA's assessment to retain chronic liver inflammation as the most sensitive endpoint and the 2008 NTP report as the critical study in its determination of a PHG for noncancer effects of hexavalent chromium in drinking water. I believe OEHHA is justified in its decision to update its 2011 assessment from using a NOAEL to a BMDL, which can be advantageous in cases such as this where there is a lack of dose-response data, particularly from epidemiologic literature. I do not have the expertise to evaluate OEHHA's toxicokinetic adjustments to account for intraspecies differences and would request that other reviewers with this expertise provide feedback to ensure the HPC is protective of the most sensitive populations, particularly given 1) the lower HPC identified for children in the 2008 NTP report, and 2) OEHHA's assessment in the current report of the potential increased toxicity of hexavalent chromium among populations such as infants and children.

Please do not hesitate to contact me if you have any further questions or concerns.

Carly Hyland

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Haizhou Liu, PhD, PE
Professor of Chemical and Environmental Engineering
Review comments completed on 3/8/2024

Review item:
Draft document titled, *Public Health Goal – Proposed Health-Protective Concentration for the Noncancer Effects of Hexavalent Chromium in Drinking Water.*

Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I could review with confidence:

Conclusion #1: Critical study
The critical study is based upon sound scientific knowledge, methods, and practices. The choice of the two-year drinking water studies in rats and mice performed by the National Toxicology Program (NTP, 2008) is scientifically sound and justified. The literature search is extensive. The critical study also include an extensive updated toxicology reviewer on non-cancer effects in animals. The review was well conducted. Based on the updated review, the choice of the NTP 2008 as the critical study is justified.

Conclusion #2: Critical endpoint
The critical endpoint is based upon sound scientific knowledge, methods, and practices. Using liver toxicity as the most sensitive non-cancer health effect is scientifically sound and justified. The extensive updated toxicological review on the toxicological effects in animals also supports the choice of liver toxicity as the most sensitive non-cancer health effects based on the best available literature.

Conclusion #3: Dose-response assessment
The dose-response assessment is based upon sound scientific knowledge, methods, and practices. The choice of a benchmark response of 5% has been OEHAA's standard policy as outlined in its 2008 guidelines. Using the Benchmark Dose software to conduct the dose-response modeling follows the standard EPA guidelines and sound practices. No other relevant study useful for assessing dose-response relationships was missed based on the reviewer's knowledge.

Conclusion #4: Toxicokinetics and uncertainty factors
The toxcicokinetics and uncertainty factors are based upon sound scientific knowledge, methods, and practices. Specifically, the dose-response assessment is based on EPA and OEHAA's published guidelines and protocols. The calculation of health-protective drinking water concentration is 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). The draft proposal explained the toxcicokinetics in details with sound assumptions and justifications. Two respective health-protective drinking water concentrations based on chronic liver inflammation and histiocytic infiltration of liver were calculated, and the lowest value was chosen. Appendix 4 of the draft proposal explained the modeling and calculation in details. Uncertainty factors reasonably takes account into sensitive populations including infants and children in the modeling. Other uncertainty factors are also based on sound scientifically principles that have been well established and

applied in toxcicokinetics studies. The modeling has adequately addressed all important scientific issues relevant to Cr(VI) and to the methods applied in the derivation of the health-protective drinking water concentration based on noncancer effects. The draft proposal is adequately protective of sensitive populations.

Emanuela Taioli, MD PhD

Icahn School of Medicine at Mount Sinai

New York, NY

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

Based on my expertise and experience, I am reviewing the findings, assumptions, or conclusions I agreed I could review with confidence:

2. Critical endpoint: after reviewing the literature on hexavalent chromium, or Cr(VI), that was published 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.

I have started my review by looking at the literature search (pag 6): I suggest moving the search start date back to September 2010, just to make sure that there are no missing articles. Usually we like to use a little bit of overlap between the old search and the new one, and then discard the articles that are duplicates and already present in the old search. This assures that the field is covered completely.

ADD: a life expectancy of 70 years is used for all the calculations. Although this is ok, I suggest adding some secondary calculations on the side for the actual current life expectancy, that is more towards the 80s than the 70s. We should deal with a real life scenario, in my view, especially going forward, given that this document will be guiding the agency for the next few years.

The agency is relying on three studies on total Cr in the blood, and one study where CrVI measurements are reported. Given the paucity of papers/publications, I suggest to take maximum advantage of these few papers. One option is to ask Sazakli et al to conduct some additional analyses/send the de-identified dataset to the EPA for further analyses. This should not be a big deal, and could actually be a good way to assess dose-response. Another strategy, completely different, is to move the focus to the molecular epidemiology universe and 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. I recognize that this may be a shot in the dark with a lot of uncertainty associated to the results. On the other hand, Sazakli appears all over your tables with measures of several different end-points; my impression is that this may be your best option for getting some dose response data. I would ask for their dataset and make an attempt to re-analyze the data for relevant dose-response curves.

Animal studies for non-cancer endpoints: I disagree with the conclusion of excluding all the recent studies and rely on the old NTP (2008) study only. The first comment that

comes to mind is that table 2 should have an extra-column where the limitations of each study should be described, so that the reader is oriented and can better appreciate why the studies were eventually dismissed. I suggest something similar to what was done in table A2 for human studies. In addition, an attempt to pool data from comparable studies could be made here, given the number of individual studies reported in table 2; results could then be used as additional supporting documentation, and/or compared to the NTP 2008 study for strengthening the interpretation. There are also some more sparse end-points that may result associated with exposure if the data is pooled and the sample will become large enough to allow for sensitivity analyses and other more refined analyses.
Another aspect that is not clear is the categorization of the GI effects (pancreas, duodenum, mesenteric): are all the GI effects considered pre-neoplastic and thus evaluated in the cancer end-point document, or some of them are just dismissed? This should be clarified. My recommendation is to consider all of them, either here or in the cancer effects review.

To summarize, given the data that are considered and presented in this document, I agree that the liver toxicity remains the most sensitive end-point. However, as I have mentioned above, I would consider the following alternative strategies: use some other human studies to derive blood concentration of CrVI and apply them to the studies that report health endpoints, ask for the Sazakli database and re-analyze it to derive relevant results for the current purpose, try to pool the animal data to derive more information on liver toxicity as well as discover if other end-points are worth our attention.

3. Dose-response assessment: OEHHA is applying benchmark dose modeling to derive the point of departure from the two-year drinking water studies.

There are some aspects in this section that need clarification. For example, why was the POD calculated using the BMDL rodent data, when there were corresponding human data, some of which from the same authors that published the animal data (Sasso and Schlosser)?. Why wasn't the Kirman model used for POD? It is hard to believe that the adjustments for interspecies differences introduce less noise than the uncertainties observed in a human study. Can the results obtained with a simulation based on the human studies be added to table 4, to see how results compare, human versus rodents?

After careful review of all the uncertainty factors as well as table 4, it seems that the main contributing factor to the final results of 5ppb (versus the old 2 ppb) is the use of a corrected NOAEL (divided by 10) versus using the BMDL. BMDL is 3 times higher than NOAEL, and the result (5 versus 2) is in fact 2.5 times higher than the previous one. We need here a very strong, convincing paragraph of why this approach is better than the old one. I have searched through the document very carefully, but I could not find a section strongly advocating for this. If the issue is reduced uncertainty, can we see a figure comparing the uncertainty associated with the two approaches?. I see a section where BMDL is defined as superior to LOAEL, although without a reference, but I don't see a place where it is clearly spelled out why the LOAEL is divided by 10, while the BMDL is not. There is a section that defines mathematically when BMD is considered ok

for inclusion in the calculations and preferred to LOAEL, but the final issue here is that the LOAEL is way lower than the BMDL. We need some explanations here, as I cannot figure out why this is.

Another confusing aspect: since the calculation is conducted on the exact same dataset (NTP 2008), one has to explain why the BMDL was not used in 2011, but it is used now. This approach as currently described is very confusing and hard to follow. Can somebody repeat the calculations with the NOAEL, and show in a column what the HPC would be? Although I am not opposed to using 5 ppb if that is the final value, going from 2 to 5 ppb is a big change, and it requires more details and justifications.

The section on other regulatory standards is even more confusing: looks like many of these agencies have used the same NTP 2008 study used by CalEPA, but came up with completely different limits. Can a comparative table show where the differences in approach that guided the results are? There should be some comments added to explain all these divergent results, how they were obtained and what is the credibility assigned by CalEPA to each of the results. I suggest adding a parameter to assess the level of uncertainty of each HPC, and especially the uncertainty of 2 versus 5 ppb.

It seems to me that a critical juncture is the calculation of the human POD, which was obtained from rodent experiments, but I suspect that it could have been calculated directly from the human experiments (Sasso and Schlosser, Kirman). It seems that this approach would have made everything much simpler because many of the UF could have been eliminated or reduced, but I m not in the position of verifying this and/or proving my statement. I suggest that, if CalEPA choses this venue (rodent experiments for POD), it also gives more details of the advantages of their choice. The reader has to be convinced that this is the best strategy, and right now I am not.

I guess what I would like to see is a more composite table 4, where a step-by-step comparison of the old and the new calculations are reported, to exactly see where the differences kick in, along with a footnote with justifications about each single change from the old calculations to the new proposed calculations.

I am happy to review a revised version of the document, as well as to review supporting documents that can help me navigating the process used for the calculations.