





April 25, 2023

Office of Environmental Health Hazard Assessment 1001 | Street Sacramento, CA 95814

Submitted electronically at https://oehha.ca.gov/comments

RE: Second Data Call-In for the Hexavalent Chromium Public Health Goal Update

To Whom It May Concern:

The undersigned organizations appreciate the opportunity to offer recommendations to the Office of Environmental Health Hazard Assessment (OEHHA) in response to the second data call-in for updating the Public Health Goal for hexavalent chromium, or Cr(VI), in drinking water. Members of our organizations serve the vast majority of drinking water consumers in California, and have a strong interest in the toxicity of Cr(VI) when ingested orally. We are aware of a growing body of scientific research on this subject, including relevant studies published before and after the 2016 call-in period. We support OEHHA's decision to include in this PHG review many published reports that were also previously available for the 2016 review.

The announcement for this data call-in indicates that OEHHA will also consider studies cited in the U.S. Environmental Protection Agency's (EPA's) draft IRIS toxicological review of Cr(VI). With reference to that review, we recommend OEHHA consider the letter submitted by AWWA¹ that poses serious concerns about the process EPA followed, leading to flawed conclusions as to the Mode of Action (MOA). We raise this point to emphasize that OEHHA must undertake a completely original and independent review: one that is based on the quality of the scientific works reviewed, their relevance to human health, and indifference to the source of funding for the research. However, if OEHHA does look to external evaluations of the literature on Cr(VI) toxicity via drinking water ingestion, the analysis of other national bodies should be considered along with that of the EPA. Specifically, OEHHA should consider the technical analysis published by Health Canada in 2016.² Since the Canadian action, similar conclusions were made by the regulatory body in Japan,³ by the Texas Commission on Environmental Quality,⁴ and by the World Health Organization.⁵ Contradicting the EPA position, strongly suggesting that the thesis of a mutagenic MOA for cancer has been, and should be supplanted on the basis of more recent scientific data.

A convincing body of research conducted since 2016 builds on earlier works available to OEHHA for the last PHG review, and adds substantially more clarity on the crucial question of what happens in the human body when Cr(VI) is ingested at doses comparable to the concentrations found in drinking water. The linear dose response previously posited, which OEHHA relied on in setting the 2011 PHG, is not supported. Rather, there is now more authoritative evidence of a non-linear, threshold MOA for carcinogenic effects. This body of scientific research, largely produced and published by the researchers at ToxStrategies, also point to non-cancer effects, such as intestinal hyperplasia, that would be the appropriate marker for OEHHA to use in updating a non-cancer PHG. Moreover, the dose producing intestinal hyperplasia would be sufficiently protective against cancer, supporting the reasoning for other health regulatory authorities cited above to adopt threshold based toxicity criteria for Cr(VI).

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On the pages that follow, we have attempted to list the important publications that OEHHA should analyze, starting with a clean slate to establish a PHG for hexavalent chromium. Our list begins with the most recent publications, and we additionally include studies published before 2016 that will help to inform the necessary PHG review.

Our organizations appreciate this opportunity to add to the public record for such an important task. The PHG serves as a foundation for a Maximum Contaminant Level in drinking water. With naturally occurring Cr(VI) found widely throughout California in groundwater and even surface water, these two regulatory determinations potentially bear a combined impact in the hundreds of millions of dollars for water treatment. Those costs will ultimately be passed to consumers through water rates, intensifying the challenge to keep drinking water affordable to residents with low and moderate financial means.

If we can be of any further support to OEHHA in its risk assessment effort, please contact any of the undersigned at the email addresses shown.

Sincerely,

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Enclosures (2)

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¹ AWWA, Comment letter regarding "Draft IRIS Toxicological Review of Hexavalent Chromium, Docket No. EPA-HQ-ORD-2014-0313," December 19, 2022.

² Health Canada, "Guidelines for Canadian Drinking Water Quality: Guideline Technical Document - Chromium," March 2016. Accessed at https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-chromium.html, April 19, 2023.

³ FSCJ. Risk Assessment Report Hexavalent Chromium (Beverages). Food Safety Commission of Japan. 2019;7(2):56-57.

⁴ TCEQ. Hexavalent Chromium Oral Reference Dose: Development Support Document (Final). 2016.

⁵ WHO. Chromium in Drinking Water: Background Document for Development of WHO Guidelines for Drinkingwater quality. 2020;WHO/HEP/ECH/WSH/2020.3.

RECOMMENDED DATA SOURCES

Published Present to 2017

- 1. Chappell G, Wolf JC, Thompson CM (2022) Crypt and villus transcriptomic responses in mouse small intestine following oral exposure to hexavalent chromium. *Toxicological Sciences* 186:43-57.
- 2. Proctor DM, Bhat V, Suh M, Reichert H, Jiang X, Thompson CV. 2021. Inhalation cancer risk assessment for environmental exposure to hexavalent chromium: Comparison of margin-of-exposure and linear extrapolation approaches. *Regulatory Toxicology and Pharmacology*, https://sci-hub.se/10.1016/j.yrtph.2021.104969.
- 3. Thompson CM, Aardema MJ, Heintz MM, MacGregor JT, Young RR. 2021. A review of mammalian in vivo genotoxicity of hexavalent chromium: Implications for oral carcinogenicity risk assessment. *Critical Reviews in Toxicology* 51:820-849.
- 4. Chappell GA, Wikoff DS, Thompson CM. 2021. Assessment of mechanistic data for hexavalent chromium-induced rodent intestinal cancer using the key characteristics of carcinogens. Toxicol Sci 180(1):38-50, https://doi.org/10.1093/toxsci/kfaa187.
- 5. Bhat VS, Cohen SM, Gordon EB, Wood CE, Cullen JM, Harris MA, Proctor DM, Thompson CM. 2020. An adverse outcome pathway for small intestinal tumors in mice involving chronic cytotoxicity and regenerative hyperplasia: A case study with hexavalent chromium, captan, and folpet. Crit Rev Toxicol (open access), https://doi.org/10.1080/10408444.2020.1823934.
- 6. Thompson CM, Donahue DA, Hobbs C, Costecalde Y, Franzen A, Suh M, Proctor DM, Harris MA. 2020. Exposure to environmentally-relevant concentrations of hexavalent chromium does not induce ovarian toxicity in mice. Regul Toxicol Pharmacol 116, open access: https://doi.org/10.1016/j.yrtph.2020.104729.
- 7. Aoki, Y, Matsumoto, M, Matsumoto, M, Masumura, K, Nohmi, T. 2019. Mutant frequency is not increased in mice orally exposed to sodium dichromate. Food Safety (Tokyo) March 13; 7(1): 2-10. https://pubmed.ncbi.nlm.nih.gov/31998582/.
- 8. Suh, M., D. Wikoff, L. Lipworth, M. Goodman, S. Fitch, L. Mittal, C. Ring, and D. Proctor. 2019.

 Hexavalent chromium and stomach cancer: A systematic review and meta-analysis. *Critical Reviews in Toxicology* 49(2):140-159.

 https://www.tandfonline.com/doi/abs/10.1080/10408444.2019.1578730?journalCode=itxc20
- Rager, J.E., M. Suh, G.A. Chappell, C.M. Thompson, and D.M. Proctor. 2019. Review of transcriptomic responses to hexavalent chromium exposure in T lung cells supports a role of epigenetic mediators in carcinogenesis. *Toxicology Letters*. 305: 40-50. https://www.sciencedirect.com/science/article/pii/S0378427419300128?via%3Dihub
- 10. Chappell G, Rager J, Wolf J, Babic M, Leblanc, Ring C, Harris MA, Thompson CM. 2019. Comparison of gene expression responses in the small intestine of mice following exposure to three carcinogens using the S1500+ gene set informs a potential common adverse outcome pathway. Toxicol Pathol 47(7):851–864, https://doi.org/10.1177/0192623319873882.
- 11. Moffat, I., N. Martinova, C. Seidel, and C.M. Thompson. 2018. Hexavalent chromium in drinking water. *Journal AWWA*. 110(5): E22-E35.

- Thompson, C.M., M. Suh, D.M. Proctor, and M.A. Harris. 2018. Letter to the Editor Regarding Banu et al. (2018). Chromium Accumulation on Human Placental Oxidative Stress and Apoptosis. Toxicological Sciences. 165(2): 269-271. https://academic.oup.com/toxsci/article/165/2/269/5032764
- 13. Thompson, C.M., C.R. Kirman, S. Hays, M. Suh, S. Harvey, J.E. Rager, L.C. Haws, and M.A. Harris. 2018. Integration of mechanistic and pharmacokinetic information to derive oral reference dose and margin-of-exposure values for hexavalent chromium. *Journal of Applied Toxicology* 38: 351-365. https://onlinelibrary.wiley.com/doi/full/10.1002/jat.3545
- 14. Thompson, C.M., R.R. Young, H. Dinesdurage, M. Suh, M.A. Harris, A.C. Rohr, and D.M. Proctor. 2017. Assessment of the mutagenic potential of hexavalent chromium in the duodenum of Big Blue® rats. *Toxicology and Applied Pharmacology* 330: 48-52. http://www.sciencedirect.com/science/article/pii/S0041008X1730282X
- 15. Thompson, C.M., J. Wolf, A. McCoy, M. Suh, D.M. Proctor, C. Kirman, L.C. Haws, and M.A. Harris. 2017. Comparison of toxicity and recovery in the duodenum of B6C3F1 mice following treatment with intestinal carcinogens captan, folpet, and hexavalent chromium. *Toxicologic Pathology.* 45(8): 1091-1101. http://journals.sagepub.com/doi/10.1177/0192623317742324
- 16. Thompson, C.M., M. Suh, D.M. Proctor, L.C. Haws, and M.A. Harris. 2017. Ten factors for considering the mode of action of Cr(VI)-induced gastrointestinal tumors in rodents. *Mutation Research*. 823: 45-57. https://www.sciencedirect.com/science/article/pii/S1383571817301365
- 17. Kirman, C.R., M. Suh, D.M. Proctor, and S. Hays. 2017. Improved physiologically based pharmacokinetic model for oral exposures to chromium in mice, rats, and humans to address temporal variation and sensitive populations. *Toxicology and Applied Pharmacology.* 325: 9-17. http://www.sciencedirect.com/science/article/pii/S0041008X17301370?via%3Dihub
- Rager, J.E., C.L. Ring, R.C. Fry, M. Suh, D.M. Proctor, L.C. Haws, M.A. Harris, and C.M. Thompson. 2017. High-throughput screening data interpretation in the context of in vivo transcriptomic responses to oral Cr(VI) exposure. *Toxicological Sciences*. 158(1): 199-212. https://academic.oup.com/toxsci/article-lookup/doi/10.1093/toxsci/kfx085

Published Pre-2016

- Thompson, C.M., L.C. Haws, M.A. Harris, N.M. Gatto, and D.M. Proctor. 2011. Application of the U.S. EPA Mode of Action Framework for Purposes of Guiding Future Research: A Case Study Involving the Oral Carcinogenicity of Hexavalent Chromium. *Toxicological Sciences*. 119(1): 20-40. Manuscript: http://toxsci.oxfordjournals.org/content/119/1/20/suppl/DC1
 Supplemental data: http://toxsci.oxfordjournals.org/content/119/1/20/suppl/DC1
- Thompson, C.M., D.M. Proctor, L.C. Haws, C.D. Hébert, S.D. Grimes, H.G. Shertzer, A.K. Kopec, J.G. Hixon, T.R. Zacharewski, and M.A. Harris. 2011. Investigation of the Mode of Action Underlying the Tumorigenic Response Induced in B6C3F1 Mice Exposed Orally to Hexavalent Chromium. *Toxicological Sciences*. 123(1): 58-70. Manuscript:
 http://toxsci.oxfordjournals.org/content/123/1/58.full.pdf+html?sid=d185e9e8-71d0-415b-9e2d-97ca5844207c; Supplemental data: http://toxsci.oxfordjournals.org/content/123/1/58/suppl/DC1

- Thompson, C.M., D.M. Proctor, M. Suh, L.C. Haws, C.D. Hébert, J.F. Mann, H.G. Shertzer, J.G. Hixon, and M.A. Harris. 2011. Comparison of the Effects on Hexavalent Chromium in the Alimentary Canal of F344 rats and B6C3F1 Mice Following Exposure in Drinking Water: Implications for Carcinogenic Modes of Action. *Toxicological Sciences*. 125(1): 79-90.
 Manuscript: http://toxsci.oxfordjournals.org/content/125/1/79/suppl/DC1
 http://toxsci.oxfordjournals.org/content/125/1/79/suppl/DC1
- 4. Thompson, C.M., D.M. Proctor, and M.A. Harris. 2012. Duodenal GSH/GSSG Ratios in Mice Following Oral Exposure to Cr(VI). *Toxicological Sciences*. 126(1): 287-288. Letter to Editor: http://toxsci.oxfordjournals.org/content/126/1/287.full.pdf+html
- Kopec, A.K., S. Kim, A.L. Forgacs, T.R. Zacharewski, D.M. Proctor, M.A. Harris, L.C. Haws, and C.M. Thompson. 2012. Genome-wide gene expression effects in B6C3F1 mouse intestinal epithelia following 7 and 90 days of exposure to hexavalent chromium in drinking water. *Toxicology and Applied Pharmacology*. 259(1): 13-26. Manuscript: http://www.sciencedirect.com/science/article/pii/S0041008X11004480
- Kopec, A.K., C.M. Thompson, S. Kim, A.L. Forgacs, and T.R. Zacharewski. 2012. Comparative toxicogenomic analysis of oral Cr(VI) exposure effects in rat and mouse small intestinal epithelia. *Toxicology and Applied Pharmacology*. 262(2): 124-138. http://www.sciencedirect.com/science/article/pii/S0041008X12001731
- 7. Thompson, C.M., J.G. Hixon, D.M. Proctor, L.C. Haws, M. Suh, J.D. Urban, and M.A. Harris. 2012. Assessment of Genotoxic Potential of Cr(VI) in the Mouse Duodenum: An In Silico Comparison with Mutagenic and Nonmutagenic Carcinogens Across Tissues. *Regulatory Toxicology and Pharmacology*. 64(1): 68-76. http://www.sciencedirect.com/science/article/pii/S0273230012001134?v=s5
- 8. Proctor, D., M. Suh, L.L. Aylward, C.R. Kirman, M.A. Harris, C.M. Thompson, H. Gürleyük, R. Gerads, L.C. Haws, and S.M. Hays. 2012. Hexavalent Chromium Reduction Kinetics in Rodent Stomach Contents. *Chemosphere*. 89 (5): 487-493. http://www.sciencedirect.com/science/article/pii/S0045653512005978.
- Thompson, C.M., Y. Federov, D.D. Brown, M. Suh, D.M. Proctor, L. Kuriakose, L.C. Haws, and M.A. Harris. 2012. Assessment of Cr(VI)-Induced Cytotoxicity and Genotoxicity Using High Content Analysis. *PLoS ONE*. 7(8): e42720. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0042720
- Kirman, C.R., S.M. Hays, L.L. Aylward, M. Suh, M.A. Harris, C.M. Thompson, L.C. Haws, and D.M. Proctor. 2012. Physiologically Based Pharmacokinetic Model for Rats and Mice Orally Exposed to Chromium. *Chemico-Biological Interactions*. 200(1): 45-64. http://www.sciencedirect.com/science/article/pii/S0009279712001548?v=s5
- 11. Thompson, C.M., D.M. Proctor, M. Suh, L.C. Haws, C.R. Kirman, and M.A. Harris. 2013. Assessment of the Mode of Action Underlying Development of Rodent Small Intestinal Tumors Following Oral Exposure to Hexavalent Chromium and Relevance to Humans. *Critical Reviews in Toxicology*. 43(3): 244-274. http://informahealthcare.com/doi/abs/10.3109/10408444.2013.768596

- Kirman, C.R., L.L. Aylward, M. Suh, M.A. Harris, C.M. Thompson, L.C. Haws, D.M. Proctor, W. Parker, and S.M. Hays. 2013. Physiologically Based Pharmacokinetic Model for Humans Orally Exposed to Chromium. *Chemico-Biological Interactions*. 204(1): 13-27. http://www.sciencedirect.com/science/article/pii/S0009279713000823
- O'Brien, T.J., H. Ding, M. Suh, C.M. Thompson, B.L. Parsons, M.A. Harris, L.C. Haws, W.A. Winkelman, J.C. Wolf, J.G. Hixon, A.M. Schwartz, M.B. Myers, L.C. Haws, and D.M. Proctor. 2013. Assessment of K-Ras mutant frequency and micronucleus incidence in the mouse duodenum following 90-days of exposure to Cr(VI) in drinking water. Mutation Research. 754: 15-21. http://www.sciencedirect.com/science/article/pii/S1383571813000752
- 14. Thompson, C.M., C.R. Kirman, D.M. Proctor, L.C. Haws, M. Suh, S.M. Hays, and M.A. Harris. 2014. A Chronic Oral Reference Dose for Hexavalent Chromium—Induced Intestinal Cancer. *Journal of Applied Toxicology*. 34: 525-536. http://onlinelibrary.wiley.com/store/10.1002/jat.2907/pdf; Supplemental Information: http://onlinelibrary.wiley.com/store/10.1002/jat.2907/asset/supinfo/jat_2907_Supplemental%20Material_Appendices.docx?v=1&s=64762ef5f64f32afac1581e845f27ebcc9eeed1e
- Suh, M., C.M. Thompson, C.R. Kirman, M.C. Carakostas, L.C. Haws, M.A. Harris, and D.M. Proctor. 2014. High Concentrations of Hexavalent Chromium in Drinking Water Alter Iron Homeostasis in F344 Rats and B6C3F1 Mice. Food and Chemical Toxicology. 65: 381-388. Manuscript: http://www.sciencedirect.com/science/article/pii/S027869151400012X;
 Supplemental data: <a href="http://www.sciencedirect.com/science/MiamiMultiMediaURL/1-s2.0-S027869151400012X/-s2.0-S027869151400012X/-mmc1.docx/271257/FULL/S027869151400012X/5820684ed005bb81f0302625060aa258/mmc1.docx
- 16. Proctor, D.M., M. Suh, S.L. Campleman, and C.M. Thompson. 2014. Assessment of the mode of action for hexavalent chromium-induced lung cancer following inhalation exposures. *Toxicology*. 325: 160-179. http://www.sciencedirect.com/science/article/pii/S0300483X14001681
- 17. Thompson, C.M., J. Seiter, M.A. Chappell, R.V. Tappero, D.M. Proctor, M. Suh, J.C. Wolf, L.C. Haws, R. Vitale, L. Mittal, C.R. Kirman, S.M. Hays, and M.A. Harris. 2015. Synchrotron-Based Imaging of Chromium and γ-H2AX Immunostaining in the Duodenum Following Repeated Exposure to Cr(VI) in Drinking Water. *Toxicological Sciences*. 143(1): 16-25. http://toxsci.oxfordjournals.org/content/early/2014/10/31/toxsci.kfu206.full.pdf+html
- 18. Thompson, C.M., J.C. Wolf, R.H. Elbekai, M.G. Paranjpe, J.M. Seiter, M.A. Chappell, R.V. Tappero, M. Suh, D.M. Proctor, A. Bichteler, L.C. Haws, and M.A. Harris. 2015. Duodenal crypt health following exposure to Cr(VI): micronucleus scoring, γ-H2AX immunostaining, and synchrotron X-ray fluorescence microscopy. *Mutation Research*. 789-790, 61-66. http://www.sciencedirect.com/science/article/pii/S1383571815001205
- Cullen, J.M., J.M. Ward, and C.M. Thompson. 2015. Reevaluation and classification of duodenal lesions in B6C3F1 mice and F344 rats from 4 studies of hexavalent chromium in drinking water. <u>Toxicologic Pathology</u>. 44(2): 279-289.
 http://tpx.sagepub.com/content/early/2015/11/13/0192623315611501.full.pdf

- 20. Thompson, C.M., R.R. Young, M. Suh, H. Dinesdurage, R.H. Elbekai, M.A. Harris, A.C. Rohr, and D.M. Proctor. 2015. Assessment of the mutagenic potential of Cr(VI) in the oral mucosa of Big Blue® transgenic F344 rats. *Environmental and Molecular Mutagenesis*. 56: 621-628. http://onlinelibrary.wiley.com/doi/10.1002/em.21952/abstract
- 21. Young, R.R., C.M. Thompson, H.R. Dinesdurage, R.H. Elbekai, M. Suh, A.C. Rohr, and D.M. Proctor. 2015. A robust method for assessing chemically induced mutagenic effects in the oral cavity of transgenic Big Blue(R) rats. *Environmental and Molecular Mutagenesis*. 56: 629-636. http://onlinelibrary.wiley.com/doi/10.1002/em.21951/abstract
- 22. Thompson, C.M., A. Bichteler, J. Rager, M. Suh, D. Proctor, L. Haws, and M. Harris. 2016. Comparison of In Vivo Genotoxic and Carcinogenic Potency to Augment Mode of Action Analysis: Case Study with Hexavalent Chromium, *Mutation Research*. 800-801: 28-34. http://www.sciencedirect.com/science/article/pii/S1383571815300334
- 23. Thompson, C.M., J.E. Rager, M. Suh, C.L. Ring, D.M. Proctor, L.C. Haws, R.C. Fry, and M.A. Harris. 2016. Transcriptomic responses in the oral cavity of F344 rats and B6C3F1 mice following exposure to Cr(VI): Implications for risk assessment. *Environmental and Molecular Mutagenesis*. 57(9): 706-716. http://onlinelibrary.wiley.com/doi/10.1002/em.22064/epdf
- 24. De Flora, S., A. Camoirano, R.T. Micale, S. La Maestra, V. Savarino, P. Zentilin, E. Marabotto, M. Suh, and D.M. Proctor. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. I. Chemical reduction and mitigation of mutagenicity. *Toxicology and Applied Pharmacology*. 306: 113-119. http://www.sciencedirect.com/science/article/pii/S0041008X16301788?via%3Dihub
- 25. Kirman, C.R., M. Suh, S.M. Hays, H. Gurleyuk, R. Gerads, S. De Flora, W. Parker, S. Lin, L.C. Haws, M.A. Harris, and D.M. Proctor. 2016. Reduction of hexavalent chromium by fasted and fed human gastric fluid. II. Ex vivo gastric reduction modeling. *Toxicology and Applied Pharmacology*. 306: 120-133. http://www.sciencedirect.com/science/article/pii/S0041008X16301764?via%3Dihub
- Proctor, D.M., M. Suh, L. Mittal, S. Hirsch, R.V. Salgado, C. Bartlett, C. Van Landingham, A. Rohr, and K. Crump. 2016. Inhalation cancer risk assessment of hexavalent chromium based on updated mortality for Painesville chromate production workers. *Journal of Exposure Science and Environmental Epidemiology*. 26: 224-231. http://www.nature.com/jes/journal/vaop/ncurrent/full/jes201577a.html