April 26, 2023

Via U.S. Mail and Website (https://oehha.ca.gov/comments)

Attention: PHG Program
Office of Environmental Health Hazard Assessment
P. O. Box 4010
Sacramento, CA 95812-4010

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

To Whom It May Concern:

The undersigned organizations appreciate the Office of Environmental Health Hazard Assessment's (OEHHA) recent action to open a second data call-in period to inform OEHHA's update of the public health goal (PHG) for hexavalent chromium (Cr(VI)) in drinking water. In commencing this second data call-in period, OEHHA appropriately recognizes the need to consider the many studies and reviews that have been published in the over six years since OEHHA initiated the process to update the PHG for Cr(VI) in 2016. Because OEHHA's March 27, 2023 public notice states that OEHHA will consider information previously submitted in response to the 2016 data call-in for the Cr(VI) PHG update, this submission focuses on new scientific data and authoritative reviews published after the close of that first data call-in period on December 13, 2016.[1]

Many new studies have been published since 2016 that add substantially to the weight of evidence supporting a non-linear threshold mode of action (MOA) for carcinogenic effects for Cr(VI). These studies demonstrate the MOA for Cr(VI) involves a sequence of key events that includes intestinal hyperplasia, which is also the most sensitive non-cancer effect demonstrated to date in the scientific literature.[2] The post-2016 scientific data validates decisions by other public health regulatory bodies,

[1] We incorporate by reference the previous submissions by the American Chemistry Council (ACC) on December 12, 2016, and ToxStrategies, Inc. (TSI) on December 13, 2016. As emphasized in this prior correspondence, we continue to urge OEHHA to also thoroughly review and analyze the scientific data and authoritative reviews published between 2011 and December 2016, which also support a threshold MOA for carcinogenic effects for Cr(VI). We can again provide hard or electronic copies of this correspondence to OEHHA upon request.

[2] The best available science indicates intestinal hyperplasia is the effect that OEHHA should use as the basis for an updated non-cancer PHG. See TSI, Recent Research and Developments in Risk Assessment Methods Necessitate Update of Non-Cancer Public Health Goal for Hexavalent Chromium (Feb. 11, 2021), enclosed with a previous February 12, 2021 submission by ACC and the California Manufacturers & Technology Association (CMTA), which we

including Health Canada,[3] the World Health Organization,[4] and the Food Safety Commission of Japan[5] to set health protective guidelines and standards for ingestion of Cr(VI) based on the published literature supporting a threshold MOA for carcinogenic effects.[6] In Appendix A, enclosed, we provide a more detailed summary of this recently published literature.[7]

OEHHA also states that it will review the data cited by the United States Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) in support of its draft 2022 IRIS Toxicological Review of Hexavalent Chromium (Draft IRIS Review).[8] As OEHHA is aware, USEPA's Science Advisory Board (SAB) is currently evaluating the Draft IRIS Review, and the draft review may be revised based on public comments submitted to USEPA[9] and the SAB[10] and recommendations

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incorporate by reference. We can again provide hard or electronic copies of this correspondence to OEHHA upon request.

[3] Health Canada. 2016. Guidelines for Canadian Drinking Water Quality: Guideline Technical Document — Chromium. In: Water and Air Quality Bureau HEaCSB, ed. Vol (Catalogue No H144-36/2017E-PDF). Ottawa, Ontario.

[4] WHO (World Health Organization). 2020. Chromium in drinking water: Background document for development of WHO guidelines for drinking-water quality. Available at: Microsoft Word - GDWQ.2ndEdit.Chromium.doc (who.int).

[5] Food Safety Commission of Japan. 2019. Risk assessment report: Hexavalent chromium (beverages). Food Safety Commission of Japan 7(2):56–57.

[6] Neither these evaluations, nor the underlying scientific research, were addressed in the July 6, 2022, Memorandum from Dr. Vincent Cogliano, Deputy Director, Division of Scientific Programs, OEHHA, to Darrin Polhemus, Deputy Director, Division of Drinking Water, State Water Resources Control Board concerning OEHHA's five-year review of the PHG for Cr(VI). In this regard, we also incorporate by reference the letter submitted by TSI scientists to Dr. Lauren Zeise, Director, OEHHA, on August 29, 2022, responding to the July 6, 2022 OEHHA Memorandum.

[7] We also incorporate by reference the previous submissions by ACC, the California Chamber of Commerce, and CMTA on November 16, 2022, and TSI on August 29, 2022, discussing post-2011 information, studies, and data establishing a threshold cancer MOA for Cr(VI). We can again provide hard or electronic copies of this correspondence to OEHHA upon request.

[8] IRIS, USEPA, Chromium (VI), IRIS Toxicological Review of Hexavalent Chromium (External Review Draft, 2022), https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=355226.

[9] We incorporate by reference the following comments submitted to the USEPA IRIS Docket:
Comment from TSI, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2014-0313-0045; Comment from ACC, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2014-0313-0051; Comment from Dr. Sam Cohen, available at: https://www.regulations.gov/comment/EPA-HQ-ORD-2014-0313-0038.

[10] We incorporate by reference the following comments submitted to during the SAB Hexavalent Chromium Review Panel Meeting on March 29-31, 2023:
Statement of Dr. Sam Cohen, available at:
https://sab.epa.gov/ords/sab/f?p=100:0:3569388626601:APPLICATION_PROCESS=MEETING_FILE:::MM_ID:6218;
Oral Statement from ACC, available at:
https://sab.epa.gov/ords/sab/f?p=100:0:3569388626601:APPLICATION_PROCESS=MEETING_FILE:::MM_ID:6217;
Statement from Dr. Chad Thompson, TSI, available at:
https://sab.epa.gov/ords/sab/f?p=100:0:3569388626601:APPLICATION_PROCESS=MEETING_FILE:::MM_ID:6220;
Statement from Drs. Thompson and Wikoff, TSI, available at:
https://sab.epa.gov/ords/sab/f?p=100:0:3569388626601:APPLICATION_PROCESS=MEETING_FILE:::MM_ID:6192.

from the SAB. We strongly encourage OEHHA to independently evaluate the published literature cited by USEPA, and to question USEPA's rationale for discounting several state of the art studies that reduce uncertainty in the evidence supporting a threshold MOA for Cr(VI) and would support a more accurate risk assessment.

Finally, given OEHHA's renewed commitment to complete the PHG update process prescribed in the California Safe Drinking Water Act (Act), and the potential for this process to result in revising the Cr(VI) PHG, the State Water Resources Control Board should temporarily suspend its development of a new maximum contaminant level (MCL) for Cr(VI). The Act requires periodic updates of PHGs to ensure that corresponding MCLs are based on the most current scientific data, principles, practices, and methods. As the many publications and public comments cited in this and prior correspondence attest, the 2011 PHG for Cr(VI) is no longer an appropriate foundation for an enforceable drinking water standard.

We look forward to working with OEHHA as it develops a new Cr(VI) risk assessment, and to future opportunities to comment on draft technical support documents for an updated PHG. If you have any questions, please do not hesitate to contact Tim Shestek with ACC at 916-448-2581 or tim_shestek@americanchemistry.com.

Sincerely,

Tim Shestek
American Chemistry Council

Rob Spiegel
California Manufacturers & Technology Association

Brenda Bass
California Chamber of Commerce

Trudi Hughes
California Food Producers

We also incorporate by reference the following comments submitted during the SAB Hexavalent Chromium Review Panel Meeting on February 15, 2023:
Oral Statement from Neepa Choksi, TSI, available at:
https://sab.epa.gov/ords/sab/f?p=114:0:6093780410622:APPLICATION_PROCESS=MEETING_FILE:::MM_ID:6188;
Slide Presentation from Dr. Chad Thompson, TSI, available at:
https://sab.epa.gov/ords/sab/f?p=114:0:6093780410622:APPLICATION_PROCESS=MEETING_FILE:::MM_ID:6189;;
Statement from ACC, available at:
https://sab.epa.gov/ords/sab/f?p=114:0:6093780410622:APPLICATION_PROCESS=MEETING_FILE:::MM_ID:6161.

Enclosure

cc: Christine Hironaka, Deputy Cabinet Secretary, Governor's Office (via email)
Yana Garcia, Secretary for Environmental Protection, CalEPA (via email)
Clare Mendelsohn, Deputy Secretary for Public Policy, CalEPA (via email)
Anna Naimark, Deputy Secretary and Special Counsel for Water Policy, CalEPA (via email)
Dr. Lauren Zeise, Director, OEHHA (via email)
Dr. David Edwards, Chief Deputy Director, OEHHA (via email)
Dr. Vincent Cogliano, Deputy Director, Division of Scientific Programs, OEHHA (via email)
Eileen Sobeck, Executive Officer, SWRCB (via email)
Darrin Polhemus, Deputy Director, Division of Drinking Water, SWRCB (via email)
Jonathan Bishop, Chief Deputy Director, SWRCB (via email)

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Appendix A

Summary of Published Literature Establishing the Mode of Action for Hexavalent Chromium

Published literature indicates that many carcinogens induce *in vivo* genotoxicity at lower doses and earlier timepoints than carcinogenicity.[1,2] This is expected if genotoxicity is a precursor in a sequence of events leading to cancer. When genotoxicity cannot be observed *in vivo,* or is detected only at doses exceeding carcinogenic effects, then those effects are most likely driven by non-genotoxic modes of action (MOA).[3,4] With respect to Cr(VI), and as discussed in a recent article in *Critical Reviews in Toxicology*,[5] the majority of oral *in vivo* genotoxicity studies on Cr(VI) are negative, and all of the studies conducted in the target tissues where tumors were observed in the National Toxicology Program (NTP) 2-year Cr(VI) drinking water cancer bioassay[6] (small intestine and oral mucosa) are negative.[5]

Transgenic rodent (TGR) *in vivo* mutation assays primarily detect DNA damage comprised of point mutations and small lesions. Intraperitoneal studies in TGR models have shown increases in mutant frequency (MF) in non-target tissues;[5] and although such exposures lack human relevance, they demonstrate that Cr(VI) is *capable* of inducing DNA damage when it reaches relevant cell populations at sufficient levels. As such, TGR models are valid for assessing the mutagenicity of Cr(VI) in target tissues following oral exposure to carcinogenic concentrations. In the mouse intestine, two TGR assays of different durations were negative.[7] In the rat intestine, a TGR assay was negative.[8] Although rats did not develop intestinal tumors, Big Blue® TGR rats contain genes capable of detecting mutations in every tissue, including the small intestine, as evidenced by the increased MF in the intestine caused by the positive controls in these studies. In the rat oral cavity, a TGR assay was negative.[9] Taken together, these data indicate that Cr(VI) does not induce mutational DNA damage in target tissues following oral exposures up to 180 parts per million (ppm).

The micronucleus (MN) assay is ideal for measuring larger clastogenic DNA damage. Intraperitoneal studies have reported increases in bone marrow MN following Cr(VI) exposure.[5] Such exposure routes lack human relevance but demonstrate that Cr(VI) is *capable* of inducing MN when it reaches relevant cell populations at sufficient levels. Micronucleus assays are best conducted in highly proliferating tissues such as the bone marrow and intestine. Cr(VI) unequivocally reaches the small intestine.[10-12] In fact, intestinal toxicity is the basis of the United States Environmental Protection Agency's (USEPA) proposed oral reference dose. In a 7-day MN study published in *Mutation*

Research,[12] exposure to ≤180 ppm Cr(VI) did not increase MN in crypts where stem cells reside and progeny cells undergo proliferation. In contrast to Cr(VI), exposure to the positive control cyclophosphamide significantly increased MN in crypts. In addition, immunostaining for DNA damage using γ-H2AX antibodies marked aberrant crypt enterocytes in mice exposed to cyclophosphamide but not Cr(VI). These results indicate that γ-H2AX is a secondary marker of genotoxicity in crypts. Notably, staining for γ-H2AX in mice exposed to 180 ppm Cr(VI) for 90 days exhibited no aberrant crypt enterocytes—indicating a lack of genotoxicity in crypts.[11] In a 90-day MN study published in *Mutation Research*,[13] exposure to ≤180 ppm Cr(VI) did not increase MN in crypts. Taken together, these data indicate that Cr(VI) does not induce clastogenic DNA damage in the intestine following oral exposures up to 180 ppm.

The negative genotoxicity results in the intestine are consistent with x-ray fluorescence imaging demonstrating that the majority of chromium in the intestine following ingestion is in the villous enterocytes and not in the crypt compartment.[11,12] Thus, while chromium reaches the intestine, it does not reach relevant cell populations at doses sufficient to induce genotoxicity. Given that genotoxic carcinogens typically induce genotoxicity at and below carcinogenic doses, the data for Cr(VI) are inconsistent with a mutagenic MOA. Instead, Cr(VI) has been demonstrated to induce villus cytotoxicity and crypt proliferation within just 7 days of exposure,[12-14] by several metrics[15] including hyperplasia, increases in crypt length, increases in crypt enterocyte counts, changes in crypt area, and transcriptomics.[11-14,16] Taken together, the lack of genotoxicity in the intestine and evidence for proliferation meet the criteria for an adverse outcome pathway for intestinal tumors in rodents that involves cytotoxicity-induced regenerative hyperplasia.[17]

Several regulatory authorities have reviewed the available science for Cr(VI) and determined that protection against intestinal hyperplasia is sufficient to protect against cancer, and therefore developed threshold-based toxicity criteria for Cr(VI).[18-21] USEPA's conclusion that the oral tumors are the result of a mutagenic MOA is a minority opinion that results from mischaracterization of the evidence supporting a threshold MOA, including findings of "low confidence" for numerous peer-reviewed *in vivo* genotoxicity studies. The rationale for these conclusions has been discredited in comments submitted to the Science Advisory Board (SAB) reviewing USEPA's draft 2022 IRIS Toxicological Review of Hexavalent Chromium. Comments submitted to USEPA and the SAB also highlight critical discrepancies in 1) the use of dose to score genotoxicity but not other endpoints (e.g., reproductive toxicity) and 2) the use of dose in scoring studies for other chemistries (e.g., ethylbenzene). Finally, we note that the SAB asked EPA to reconsider the strong evidence for and incorporate low-dose non-linearities in the dosimetry of Cr(VI).[22] In short, USEPA's draft toxicological review is flawed and unreliable for purposes of establishing a scientifically sound PHG that serves as the foundation for a drinking water regulatory standard. Rather, the best available data necessitate a *de novo* risk assessment and a revised PHG.

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