DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Agency for Toxic Substances
and Disease Registry

Memorandum

Date: July 11, 2019

From: Alan Yarbrough, Acting DCHI ADS

Subject: Interim Guidance--Using California EPA's (CalEPA) oral cancer potency information for hexavalent chromium (Cr^{+6}) and Other Considerations

To: ATSDR DCHI and APPLETREE State Health Assessors

Many sites ATSDR or state partners evaluate have hexavalent chromium in either drinking water or soil. Currently, ATSDR has only non-cancer comparison values (CVs) for hexavalent chromium in drinking water and soil. The current environmental media evaluation guide (EMEG) comparison values for children are 6.3 parts per billion (ppb) for water and 47 parts per million (ppm) for soil. However, ATSDR has no oral water or soil cancer risk evaluation guides (CREGs). Several states have adopted California EPA's (CalEPA) oral cancer slope factor (CSF) and calculate theoretical cancer risks for hexavalent chromium in drinking water or soil.

DCHI derives its cancer-based CV, referred to as CREGs, by using cancer potency values from the EPA Integrated Risk Information System (IRIS) database. Pending the final release of EPA's IRIS reassessment of the carcinogenic effects of hexavalent chromium, an EPA oral CSF is not available. DCHI Associates for Science investigated alternative sources to determine an interim basis for hexavalent chromium cancer potency and recommend the use of California EPA's oral CSF in calculating ATSDR CREGs.

Basis for Interim CREG for Hexavalent Chromium

Until EPA finalizes their cancer re-assessment, ATSDR's interim drinking water and soil CREGs will be derived from the CalEPA oral CSF of 0.5 $(mg/kg/day)^{-1}$. CalEPA's CSF is based on an NTP study (2008) showing increases in oral and stomach tumors in mice following hexavalent chromium administration in drinking water. Health assessors should use the CalEPA oral cancer slope factor to calculate site-specific cancer risks from oral exposure to hexavalent chromium. The CalEPA cancer potency information is currently the basis for EPA's Regional Screening Levels (RSLs) (https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables).

The table below summarizes the interim comparison values that health assessors should use as they evaluate hexavalent chromium in drinking water and soil.

Interim Comparison Values for Soil and Drinking Water		Intended Use
Drinking Water CREG	0.024 ppb*	Screening phase to select contaminants of concern
Soil CREG	0.22 ppm	Screening phase to select contaminants of concern
Oral CSF	0.5 $(mg/kg/day)^{-1}$	Calculating site-specific cancer risk

ppb: parts per billion; ppm: parts per million; mg/kg/day: milligram per kilogram per day

* DCHI recognizes that the source of Cr+6 in drinking water supplies in the U.S can be from natural or anthropogenic sources and that this CREG would require we evaluate more sites (exposures). As with all DCHI comparison values, the proposed interim CREG for Cr+6 is only intended as a screen to determine if further evaluation is needed by health assessors. Once selected, health assessors will need to provide perspective as to whether the detections are related to the site or similar to background in the area. Moreover, per ATSDR's health assessment process, both a quantitative and qualitative evaluation would need to be completed to determine the potential for site-specific exposure to have an increased risk of cancer. The public health implications of oral carcinogenic risk for hexavalent chromium is currently an evolving subject. Health assessors should coordinate with their branch ADS to ensure that the most current and applicable scientific literature is applied to the in depth evaluation.

Since hexavalent chromium is considered by EPA to be a mutagen, the soil and water CREGs include age-dependent adjustment factors (ADAF). The Public Health Assessment Site Tool, or PHAST, incorporates the ADAF approach when calculating cancer risk from exposure to hexavalent chromium. EPA's age-specific ADAF approach, which accounts for increased cancer risk from early life exposure, is described in the Soil and Drinking Water Exposure Dose Guidance (EDG) document. The resultant CREGs that already incorporate ADAFs, are 0.024 ppb in drinking water and 0.22 ppm in soil. These CREGs are now the recommended CVs for screening hexavalent chromium in these media. The non-cancer EMEGs will also remain for assessing potential non-cancer health effects.

The proposal to use CalEPA's hexavalent chromium cancer potency factor and age-dependent adjustment factors (ADAFs) is a reasonable approach for evaluating cancer risks for chromium (VI) exposure. CalEPA derived its cancer slope factor based on the increased incidences of adenomas and carcinomas in the small intestine of male mice exposed via drinking water in a well-conducted and peer-reviewed 2-year study. The CalEPA derivation is well-documented (CalEPA 2011) and uses methods that are consistent with generally accepted risk assessment practices. The use of age-dependent adjustment factors is supported by numerous studies that provide evidence that hexavalent chromium is a mutagenic carcinogen (CalEPA 2011; McCarroll et al. 2010). Chemicals that act through a mutagenic mode of action may also pose a greater lifetime risk of cancer to children exposed prenatally or during childhood than to individuals similarly exposed during adulthood (USEPA 2005). Additional information on the basis for the hexavalent chromium CSF is available on the CalEPA Office of Environmental Health Hazard Assessment website at:
https://oehha.ca.gov/media/downloads/water/chemicals/phg/cr6phg072911.pdf

Although ATSDR believes that the use of the CalEPA CSF is a reasonable approach for calculating these interim CVs, much debate remains about the mode-of-action of hexavalent chromium in initiating cancer through the oral exposure route. EPA has developed a "white paper" that addresses many of the issues they are currently evaluating in their reassessment (USEPA 2018). Until EPA completes it reassessment of hexavalent chromium carcinogenesis, the issues discussed in this EPA paper should be considered when evaluating the cancer risk posed by oral exposure to hexavalent chromium in our health assessment documents.

Additional Guidance:

Health assessors should also consider the following guidance when evaluating oral exposures to hexavalent chromium at their sites:

1. **Source and Fate and Transport.** Health assessors are often provided with water and soil sampling data for total chromium and not speciated chromium. Fate and transport studies of hexavalent chromium in the environment shows that hexavalent chromium is readily reduced to trivalent chromium, which is less toxic. One of the most important factors is to determine the source of the chromium. If the facility released chromium, then some percentage of it may have been in the hexavalent form and some proportion of the total chromium concentration may remain as hexavalent chromium. Health assessors should consult the facility's emissions inventory to determine whether chromium was emitted and what percent of total chromium was hexavalent (e.g., EPA and state regulators have facility-specific estimates of the hexavalent-to-trivalent-chromium ratio in air emissions). If hexavalent chromium was likely released at the site, then health assessors should assume the total chromium to be in the hexavalent form and, if the exposure is determined to be a hazard, should indicate that additional sampling with speciation is needed to verify the hazard. If evidence indicates hexavalent chromium releases to the environment are unlikely, then the health assessor may assume that chromium in soil and water is predominantly in the trivalent form and should be evaluated as such.

2. **Absolute Bioavailability**. Because the study used to derive the CalEPA CSF and the ATSDR minimal risk levels (MRLs) were based on an administered dose, health assessors **should not** adjust their exposure point concentrations nor their calculated doses to account for bioavailability due to reduction of hexavalent chromium to trivalent chromium in the GI tract.

3. **Evaluation of Sample Results.** Sample results should include both filtered and unfiltered results. Dissolved samples are considered more mobile and bioavailable and better for evaluating the public health implications of exposure. When presented with both total chromium and hexavalent chromium results, health assessors should carefully evaluate the detection limits as they may differ (the total chromium detection limits may be lower than those for hexavalent chromium).

Karl Markiewicz, PhD, Senior Toxicologist, from ATSDR's Region 3 office is available to discuss the evaluation of hexavalent chromium public health issues in our assessments, especially in relation to evaluating the cancer risk. He can be reached via e-mail at kvm4@cdc.gov or by phone at 215-814-3149.

This interim guidance represents the best currently available science on cancer potency. After EPA completes it reassessment of the carcinogenic effects of hexavalent chromium, DCHI will review and update the interim CREGs and CSF as warranted.

If you have questions about how to apply this guidance at a site, please contact me at txf5@cdc.gov or 770-488-3737.

References

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