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Michael Baes
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1515 Clay St., 16th floor
Oakland, California 94612

Comments on Proposed Hexavalent Chromium PHG

Dear Mr. Baes,

Environmental Working Group (EWG) is a non-profit public health and environmental research and advocacy organization with offices in Oakland and Sacramento, California, as well as in Ames, Iowa and Washington, DC. We focus much of our scientific research on potential health risks from chemical contamination of water, food, consumer products, and the environment. At the same time, we work to expose industry corruption that places public health in jeopardy. The Natural Resources Defense Council (NRDC) is a national environmental non-profit with offices around the country and 1.3 million members. NRDC's mission is to safeguard the Earth: its people, its plants and animals and the natural systems on which all life depends.

Thus, our organizations' special concern regarding the heavy metal contaminant, hexavalent chromium, is two-fold: A well-known inhalation carcinogen, the oral carcinogenic properties of this substance were obscured by industry manipulation of scientific data (EWG 2005). Subsequent appropriate analysis of these human exposure data, in conjunction with results of a recent National Toxicology Program (NTP) study on the effects of oral exposures of hexavalent chromium in rats and mice (NTP 2007a), has clearly established the carcinogenic potential of hexavalent chromium in drinking water.

EWG and NRDC applaud the Office of Environmental Health Hazard Assessment's (OEHHA) proposed Public Health Goal (PHG) for hexavalent chromium in drinking water of 0.06 parts per billion (ppb), based on a lifetime cancer risk threshold of one in one million (OEHHA 2009). We were, however, disappointed that OEHHA overlooked several important factors in terms of protecting sensitive sub-populations, and hope to see the agency correct these oversights in the final PHG.

Because regulation of this extremely common contaminant is long overdue, EWG and NRDC urge prompt finalization of this PHG, and rapid movement towards establishment of a mandatory drinking water standard for this potent carcinogen.

CALIFORNIA OFFICES
2201 Broadway, Suite 308 Oakland, CA 94612 | P: 510.444.0973 F: 510.444.0982
1107 9th Street Suite 340 Sacramento, CA 95814 | P: 916.333.0566 F: 916.442.3610

OEHHA acts on clear evidence that hexavalent chromium is an oral carcinogen. At the request of the State of California, federal toxicologists recently completed a study of the carcinogenic effects of hexavalent chromium administered to rats and mice in drinking water (NTP 2007a). The study revealed statistically significant, dose-related increases in tumors of the duodenum and small intestine in male and female mice exposed to the substance, and statistically significant increases in tumors of the oral cavity in male and female rats. The NTP Board of Scientific Counselors reviewing the research concluded that it presented *clear evidence of carcinogenic activity* of hexavalent chromium in the laboratory animals exposed (NTP 2007b).

These results are consistent with a modern re-analysis of an earlier study on hexavalent chromium that was marred by a number of study limitations, including outbreak of a viral infection in the mice under study (Borneff 1968). OEHHA's new statistical analysis of the data reveals a statistically significant increase in stomach tumors associated with exposure to hexavalent chromium despite the limitations plaguing the study, none of which are thought to be capable of inducing a false positive outcome (2009a).

Given that the International Agency of Research on Cancer considers hexavalent chromium a known human carcinogen via inhalation (IARC 1990), as well as the well-documented genotoxic properties of hexavalent chromium (OEHHA 2009a), it is not surprising that the chemical would prove carcinogenic via oral exposure. Initial reasoning suggested that *all* hexavalent chromium consumed orally might be converted to the poorly absorbed essential nutrient trivalent chromium within the acidic environment of the stomach, thus rendering it harmless. While a significant quantity of hexavalent chromium is reduced to trivalent chromium in the stomach, there is substantial evidence indicating oral exposure to hexavalent chromium results in absorption of some portion of this harmful chemical into the body. For example, if all hexavalent chromium were converted to the trivalent form, oral exposure of the two forms of chromium would produce equivalent results in test subjects. Instead, studies in animals and humans show orally administered hexavalent chromium leads to elevated chromium tissue levels, increased urinary half-life, and increased toxicity compared to orally administered trivalent chromium.

Research on oral exposures of humans to hexavalent chromium extends beyond simple tissue absorption studies to examine increased cancer risk. Investigation of an exposed population of villagers, whose drinking water became contaminated with hexavalent chromium released from an alloy plant in the Liaoning Province of China, revealed an increase in stomach cancer (Zhang 1987). A follow-up report clouded this conclusion by alleging the increase in cancer was unrelated to this exposure (Zhang 1997); this paper was later retracted amid allegations of conflict of interest (Brandt-Rauf 2006). OEHHA's thoughtful analysis of the data demonstrates a statistically significant rate ratio for stomach cancer among the exposed villagers relative to the Province population (1.69 (1.12 – 2.44), $p = 0.013$; Beaumont 2008), despite several study limitations.

Given the weight of the evidence, OEHHA draws a clear conclusion (OEHHA 2009a):

> The findings of available human, animal, genotoxic, and toxicokinetic studies all indicate that hexavalent chromium is a possible human carcinogen by the oral route. Given these observations and until more human and/or animals studies become available, it is prudent to consider this hazard in the development of a proposed PHG.

Perhaps one of the reviewers of the PHG (Dr. R. Gwiazda) summed it best when he stated simply that "Overall, the document convincingly demonstrates that indeed there is a relationship between exposure to CrVI via the oral route and the development of cancer in the gastrointestinal tract" (Gwiazda 2008).

Finally, it bears mentioning that while there may not be scientific consensus on the exact mechanism(s) of carcinogenesis, this should not be used as any kind of reason to delay finalizing the PHG or setting a drinking water standard. It's not as if there are no studies showing DNA damage, rather, as OEHHA notes in its document, hexavalent chromium "induces a wide range of DNA damage, including DNA adducts, DNA-protein crosslinks, DNA-DNA crosslinks, mutations, DNA strand breaks, abasic sites, oxidized DNA bases, chromosomal aberrations, sister chromatid exchanges, and micronuclei" (OEHHA 2009). In fact, the lack of scientific consensus is to be expected given that there are likely multiple mechanisms of DNA damage. The bottom line is that when there is widespread exposure, human and animal studies demonstrating oral carcinogenicity, and a broad range of studies showing genotoxicity, it would be foolish to delay action for any amount of time to clarify any mechanistic questions further.

<u>OEHHA's proposed PHG should be revised to more adequately protect sensitive populations.</u> While EWG and NRDC are supportive of the proposed PHG, we note that the proposal falls short in addressing the issue of sensitive populations and ensuring their adequate protection. This should be corrected in the final PHG document.

Conversion of hexavalent to trivalent chromium can be impaired in individuals with low-acid stomachs, a condition brought about by several widely used medications, like antacids and proton pump inhibitors, which treat disorders including gastroesophageal reflux disease, peptic ulcer disease, and chronic gastritis. Other health conditions that can result in reduced stomach acid production include pernicious anemia, pancreatic tumors, infection with *Helicobacter pylori*, mucolipidosis type IV, and some autoimmune diseases. In fact, increased absorption of hexavalent chromium was measured in people affected by pernicious anemia relative to controls (Donaldson 1966). Thus, a susceptible subpopulation united by a variety of common to rare medical conditions face a greater risk from oral exposure to hexavalent chromium.

One of the peer reviewers (Dr. R. Gwiazda) aptly noted how OEHHA had overlooked some of these concerns in its proposed PHG in the following statement: "There are two sensitive populations that are not included in the estimate of the one in a million lifetime cancer risk: carriers of Helicobacter pylori and people with anomalous stomach pH regulation" (Gwiazda 2008). Dr. Gwiazda went on to detail how including these sensitive populations would lower the PHG:

> It is noted that animals in the NTP 2007 study were free of H. Pylori. As noted at the end of the document, a more realistic scenario, at least to evaluate the oral carcinogenicity of CrVI in carriers of H. pylori would utilize infected animals. This study would most likely yield a lower point of departure for linear extrapolation to zero and result in a lower PHG estimate.... At this point there is no sufficient information to quantify the higher risks that these populations may be exposed to due to CrVI in drinking water. The only certainty is that their inclusion in the cancer risk estimate would yield a lower protective level of CrVI in drinking water than the current one that does not incorporate them specifically. (Gwiazda 2008).

Perhaps more importantly, OEHHA did not follow its own guidelines when it comes to assessing early-in-life susceptibility to carcinogens. As the agency notes in its May, 2009 document *In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures* OEHHA was directed by the California legislature in 2000 to "to assess methodologies used in addressing early-in-life risk, compile animal data to evaluate those methods, and develop methods to adequately address carcinogenic exposures to the fetus, infants, and children" (OEHHA 2009b).

In 2001, the agency assessed the standard cancer risk assessment approaches and concluded that these "did not adequately address the possibility that risk from early-in-life exposures may differ from that associated with exposures occurring in adulthood." OEHHA subsequently undertook an 8-year investigation of this issue and published its findings and related guidelines in the May, 2009 document cited above and briefly summarized as follows:

> Taken together, these results indicate that early lifestages are generally more sensitive to carcinogen exposure than adults, and that cancer risk assessment practices should take increased sensitivity of the young into account. When data on age-at-exposure related susceptibility are lacking for a specific carcinogen, these analyses indicate that increased susceptibility of the young is a scientifically justifiable assumption. This early-life susceptibility can be addressed by applying adjustments such as ASFs [age sensitivity factors] to the adult cancer potency slope factor when estimating cancer risk associated with early life exposures.

OEHHA further details how "The U.S. EPA and existing California practice does not estimate contributions from prenatal carcinogen exposure when estimating lifetime cancer risk. *This is an implicit assumption in risk calculation that risk from prenatal exposure is zero. As shown in the multi-lifestage exposure studies analysis presented here, this assumption is inconsistent with the available evidence. Moreover, the analysis presented here suggests that a prenatal adjustment factor to the adult potency is needed*; a factor of 10 falls roughly at the 70th percentile for the prenatal multi-lifestage exposure studies; the mean value is 21" (OEHHA 2009b; emphasis added).

From the excerpts above, it is clear that OEHHA should revise its proposed hexavalent chromium PHG to reflect the agency's own recently published guidelines to take into account the special concerns about early-life susceptibility to carcinogens.

<u>OEHHA makes careful choices to protect the health of Californians</u>. In formulating its draft public health goal, OEHHA has wisely chosen to target hexavalent chromium specifically, rather than examining total chromium, an outdated approach still used by many public health agencies. Because hexavalent chromium is more water soluble, more readily absorbed into living cells, and more toxic than trivalent chromium, an adequate evaluation of the health threat posed by hexavalent chromium must differentiate exposures to these two very different compounds.

In drafting its public health goal, OEHHA used well-respected public health conventions to arrive at an appropriate, health-protective outcome. The Office made careful and consistent choices in developing oral and inhalation cancer slope factors, assessing human exposures via multiple routes, and using a linear extrapolation to pinpoint the level of a one in one million lifetime cancer risk (OEHHA 2009). OEHHA's use of conservative and highly defensible risk assessment techniques has resulted in a public health goal beyond reproach – with the exception needing some adjustments in order to account more fully for the concerns of sensitive sub-populations.

OEHHA's health protective choices are especially important for hexavalent chromium, given the widespread nature of contamination in the state of California. California Department of Health Services tests of drinking water have detected hexavalent chromium in 1,997 out of over 6,400 water sources analyzed as of April 6, 2004 (detection limit 1 ppb; CDHS 2004). About 10% of the water sources tested had levels of 5 ppb or more. In addition, according to municipal water system records compiled by EWG, more than 500 California communities and 30 million state residents drank water contaminated with hexavalent chromium at levels above 0.1 ppb between 1998 and

2003 (EWG 2009). Such broad contamination clearly argues for establishment of a strict goal to protect public health.

OEHHA and other agencies must move quickly – hexavalent chromium regulation is long overdue. California is already 5 years late in establishing a drinking water standard for hexavalent chromium, as mandated by the state legislature. OEHHA's proposed public health goal is intended to help guide the California Department of Public Health in developing a Maximum Contaminant Level for hexavalent chromium in drinking water, as defined in the California Safe Drinking Water Act. The Act specifically requires OEHHA to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations.

While government delays in developing this PHG did result in inclusion of crucial findings of the NTP animal studies on hexavalent chromium (NTP 2007), as well as appropriate re-analysis of data from a now-retracted human exposure study (Beaumont 2008), now there's not a moment to lose. We urge prompt finalization of OEHHA's PHG for hexavalent chromium, and immediate action on the part of the California Department of Public Health to establish a sound regulatory standard for this toxic carcinogen.

We thank OEHHA for the opportunity to comment on their commendable draft public health goal, and look forward to participation in the development of a strict regulatory standard for hexavalent chromium in drinking water.

Sincerely,

Renée Sharp
Director, California Office
Environmental Working Group
Oakland, CA

Rebecca Sutton, Ph.D.
Senior Scientist
Environmental Working Group
Oakland, CA

Gina Solomon, MD, MPH
Senior Scientist
Natural Resources Defense Council
San Francisco, CA

References

Beaumont J, Sedman R, Reynolds S, *et al*. (2008). Cancer mortality in five villages in China with hexavalent chromium-contaminated drinking water. Epidemiol 19:12–23.

Borneff J, Engelhardt K, Griem W, Kunte H, Reichert J (1968). [Carcinogens in water and soil. XXII. Mouse drinking water experiments with 3,4-benzopyrene and potassium chromate]. Arch Hyg Bakteriol 152(1):45-53.

Brandt-Rauf P (2006). Editorial retraction. J Occup Environ Med 48(7):749.

CDHS (2004). Chromium-6 in Drinking Water: Regulation and Monitoring Update (April 7, 2004). California Department of Health Services, Sacramento, CA. Accessed at: http://www.dhs.ca.gov/ps/ddwem/chemicals/Chromium6/Cr+6index.htm.

Donaldson RM Jr, Barreras RF (1966). Intestinal absorption of trace quantities of chromium. J Lab Clin Med 68(3):484-93.

EWG (2005). Chrome-Plated Fraud: How PG&E scientists-for-hire reversed findings of cancer study. December 2005, http://www.ewg.org/node/8626

EWG (2009). National Tap Water Quality Database. Environmental Working Group, http://www.ewg.org/tapwater/findings.php.

Gwiazda, R (2008). Review of the document: "Public Health Goal for hexavalent chromium in drinking water." Available at: http://oehha.ca.gov/water/phg/chr6draft082009.html

IARC (1990). Chromium and chromium compounds. International Agency for Research on Cancer. IARC Monogr Eval Carcinog Risks Hum 49:49-214.

NTP (2007a). Draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate in F344/N Rats and B6C3F1 Mice. NTP TR 546. NIH Publication No. 07-5887, National Toxicology Program, Research Triangle Park, North Carolina, http://ntp.niehs.nih.gov/files/546_board_web.pdf.

NTP (2007b). Actions on Draft NTP Technical Reports Reviewed by the NTP Board of Scientific Counselors Technical Reports Review Subcommittee, May 16-17, 2007, http://ntp.niehs.nih.gov/files/Actions_TRRS_May_05170final[2].pdf.

OEHHA (2009a). DRAFT: Public Health Goal for Hexavalent Chromium in Drinking Water. Prepared by Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, and California Environmental Protection Agency, August 2009, http://oehha.ca.gov/water/phg/chr6draft082009.html

OEHHA (2009b). In Utero and Early Life Susceptibility to Carcinogens: The Derivation of Age-at-Exposure Sensitivity Measures. , Office of Environmental Health Hazard Assessment Reproductive and Cancer Hazard Assessment Branch, May 2009, http://www.oehha.ca.gov/air/hot_spots/tsd052909.html

Zhang J, Li X (1987). Chromium pollution of soil and water in Jinzhou (Chinese language with English abstract). Zhonghua Yu Fang Yi Xue Za Zhi (Chinese Journal of Preventive Medicine) 21:262-4.

Zhang J, Li S (1997). Cancer mortality in a Chinese population exposed to hexavalent chromium in water. J Occup Environ Med 39(4):315-9.