Chromium

Potential Designated Chemical

March 27, 2014 Meeting of Scientific Guidance Panel (SGP)
Biomonitoring California[1]

Chromium (Cr) is an element that occurs in nature. The two environmentally relevant forms of chromium are trivalent chromium (Cr(III)) and hexavalent chromium (Cr(VI)). Cr(III) is considered an essential nutrient. Cr(VI) is the toxic form.

The current document provides a brief overview of information relevant to the Scientific Guidance Panel's consideration of chromium as a potential designated chemical. The primary focus of this document is on Cr(VI). There is an extensive body of literature on Cr(VI) (ATSDR, 2012). The Office of Environmental Health Hazard Assessment (OEHHA) developed Reference Exposure Levels (OEHHA, 2001) and a Public Health Goal (OEHHA, 2011) for Cr(VI). OEHHA (2009a) also reviewed the developmental and reproductive toxicity of Cr(VI).

If the Scientific Guidance Panel recommends adding chromium to the list of designated chemicals for Biomonitoring California, this listing would cover any form of chromium. Adding chromium to the list of designated chemicals would mean that Biomonitoring California could consider it for measurement in Program studies. The Program would determine the most appropriate methods for biomonitoring chromium.

Exposure or potential exposure to the public or specific subgroups:

This section summarizes information on use, import/production volume, and exposure to Cr(VI) via air, water or other sources. Regulatory status for Cr(VI) in air and water and related reference values are also provided.

Uses and import/production volume

Chromium is used to manufacture stainless steel and nonferrous metal alloys (ATSDR, 2012). Adding chromium to alloys increases hardness and improves resistance to corrosion. Chromium compounds are used in pigments (green, orange, red, and yellow); for textile dyes, paints, and inks; for chrome-plating; as corrosion inhibitors; in catalysts; and for leather tanning. Nanoparticles of chromium compounds have a variety of applications, including dyes (chromium oxide nanoparticles) and protective coatings (chromium carbide nanoparticles). Chromated copper arsenate was widely used as a wood preservative in the past, but has been largely phased out.

[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.

The U.S. Geological Survey (USGS, 2014) reported that imports of chromium in various forms, such as chromite ore, chromium chemicals, chromium ferroalloys, chromium metal, and stainless steel, totaled 554 thousand metric tons (~1.2 billion pounds) in 2012. Recycling produced an additional 146 thousand metric tons (~320 million pounds) of chromium in the U.S. USGS (2014) also provided estimates for 2013, predicting a drop in imports (459 thousand metric tons) and an increase in recycling (236 thousand metric tons). The U.S. Environmental Protection Agency (U.S. EPA, 2012) summarized data submitted under the 2012 Chemical Data Reporting Rule, reporting a U.S. import/production volume of chromium of 3.7 billion pounds (U.S. EPA, 2012). The reason for the discrepancy between the USGS and the U.S. EPA import/production volumes for chromium was unclear.

Cr(VI) in air

Cr(VI) is regulated as a toxic air contaminant (TAC) in California. The Cr(VI) unit risk value, which is an estimate of cancer risk per unit air concentration, is 0.15 $(\mu g/m^3)^{-1}$ (OEHHA, 2009b). The chronic Reference Exposure Level for Cr(VI) and "soluble hexavalent chromium compounds (except chromic trioxide)" is 0.2 $\mu g/m^3$, to protect the respiratory system (OEHHA, 2001). The Occupational Safety and Health Administration (OSHA, 2007) set an 8-hour time-weighted average (TWA) exposure limit for Cr(VI) compounds of 5 $\mu g/m^3$.

Chrome-plating was a major source of releases to air in California in the past. The California Air Resources Board has worked to reduce Cr(VI) emissions from chrome-plating shops and is continuing those regulatory efforts (see http://www.arb.ca.gov/toxics/chrome/chrome.htm). The California statewide average ambient air concentration of Cr(VI) was 0.04 ng/m^3 in 2012 compared to 0.27 ng/m^3 in 1992 (see http://www.arb.ca.gov/adam/toxics/statepages/cr6state.html).

A study of fumes generated during welding of steel found that most of the airborne chromium was Cr(VI) (Edmé et al., 1997). Steel dust from erosion of subway rails was identified as a source of chromium exposure for transit workers and commuters in New York (Chillrud et al., 2004; 2005). Chillrud et al. did not speciate chromium, but speculated that a portion of the steel particulate would be Cr(VI) based on the study by Edmé et al.

Cr(VI) is found in tobacco smoke, and indoor air concentrations of Cr(VI) can be orders of magnitude higher, due to smoking, compared to outdoor air concentrations (ATSDR, 2012).

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Cr(VI) in water

Cr(VI) is currently regulated in California drinking water under the Maximum Contaminant Level (MCL) of 50 µg/L for total chromium. CDPH (2013a) proposed a MCL for Cr(VI) of 10 µg/L, and expects to establish an MCL in 2014. The Public Health Goal (PHG) for Cr(VI) is 0.02 ppb (0.02 µg/L), derived using an oral cancer slope factor of 0.5 $(mg/kg\text{-}day)^{-1}$ (OEHHA, 2011). The PHG is also protective of the non-carcinogenic effects of Cr(VI).

Cr(VI) can occur naturally in groundwater in California and as a result of industrial use (California Department of Public Health [CDPH], 2013a). In a USGS study, Izbicki et al. (2008) found naturally occurring Cr(VI) at concentrations greater than 50 µg/L (the current MCL) in groundwater from aquifers in the western Mojave Desert in Southern California. Cr (VI) contamination of groundwater has occurred in California as a result of industrial activities, such as manufacturing of textile dyes, wood preservation, and anti-corrosion processes (CDPH, 2013a).

Cr(VI) was identified as an "unregulated chemical requiring monitoring" (UCMR[2]) in California drinking water under 22 CCR §64450, regulations that were repealed in 2007. For UCMR monitoring of Cr(VI), California used a 1 µg/L detection limit. Drinking water systems in some counties continued to monitor their sources even after the UCMR regulations were repealed. CDPH (2013b) summarized results of the 2000 to 2012 monitoring in drinking water sources, which included both raw and treated sources. The results are for only those sources that reported more than a single detection of Cr(VI) and do not represent final concentrations in drinking water. Cr(VI) was detected at or above 1 µg/L in about one third of 7,000 drinking water sources. CDPH (2013b) summarized the counties that reported the greatest numbers of detections in specified ranges of Cr(VI) concentrations, as shown in the table below.

[2] Acronym used by CDPH. See http://www.cdph.ca.gov/certlic/drinkingwater/Documents/UCMR/ucmrguidance.pdf

Cr(VI) range (µg/L)	Detected in		Counties with most detections, 2000-2012 (number of drinking water sources)												
	Drinking water sources	Counties	San Bernardino	Los Angeles	Fresno	Sacramento	Riverside	Kern	San Joaquin	Stanislaus	Yolo	Merced	Solano	Santa Cruz	Santa Barbara
1 – 5	1,596	39	228	218	164	131	126	123	84	--[1]	--	--	--	--	--
6 – 10	496	31	66	98	--	78	49	25	31	26	--	--	--	--	--
11 – 20	247	27	32	41	--	18	48	--	--	--	19	--	16	--	--
21 – 30	66	14	11	9	--	--	6	--	--	--	16	6	6	--	4
31 – 40	17	6	1	4	--	--	--	--	--	--	4	6	--	1	1
41 – 50	5	3	1	2	--	--	--	--	--	--	2	--	--	--	--
>50	4	2	--	3	--	--	--	--	--	--	--	--	--	--	1

1. The dash means that CDPH did not summarize the number of detections for that county in the specified range of Cr(VI) concentrations. The dash does not necessarily mean there were no detects in that county for that range. CDPH's summary listed only the top counties with detections in a given range.

Other Cr(VI) exposures

Merritt and Brown (1995) found that corrosion of orthopedic implants made from stainless steel and cobalt-chromium alloys releases chromium, with Cr(VI) as the predominant species.

Known or suspected health effects

Cr(VI) compounds were in the original set of chemicals listed under Proposition 65 in 1987 as known to the state to cause cancer (http://www.oehha.ca.gov/prop65/prop65_list/files/P65single013114.pdf). The International Agency for Research on Cancer (2012) classified Cr(VI) as a human carcinogen, based on sufficient evidence of carcinogenicity in humans and animals. Cr(VI) compounds are also listed under Proposition 65 as known to cause male and female reproductive toxicity, and developmental toxicity, supported by findings in humans and animals (OEHHA, 2009). Cr(VI) is a respiratory toxicant and can adversely affect the hematopoietic system (OEHHA, 2001).

Potential to biomonitor

Chromium can be measured in a wide variety of biological samples, including blood (whole blood, serum, plasma, erythrocytes [red blood cells]), urine, saliva, hair, breast milk, and joint synovial fluid. Urine is the primary route of excretion for absorbed chromium. Measurements in blood and urine are considered most reliable for detecting elevated exposures to chromium (ATSDR, 2012).

Cr(VI) is more readily absorbed than Cr(III) and this increase in absorption is reflected in increased plasma and erythrocyte levels, increased amount excreted in the urine, and prolonged plasma and urinary half-lives (OEHHA, 2011). It was previously thought that Cr(VI) is efficiently reduced to Cr(III) in the body, but studies have shown that this is not always the case (OEHHA, 2011 and references cited therein; Collins et al., 2010; Zhitkovich, 2011).

Cr(VI), but not Cr(III), can be taken up by red blood cells (RBCs). Cr(VI) is reduced inside the RBC to Cr(III), which can remain there for the life of the cell. Measuring chromium in RBCs, and determining the ratio with levels in plasma/serum, may be a more specific indicator for Cr(VI) exposure. However, non-specific binding of Cr(III) to proteins on the outside of RBCs can be significant, particularly at higher concentrations (OEHHA, 2011). Furthermore, Barceloux (1999) noted,

> "Substantial differences in the ability of individuals to reduce chromium in plasma complicates the interpretation of chromium concentrations in erythrocytes. Individuals, who reduce Cr (VI) quickly, have relatively high urinary chromium levels and relatively low blood chromium levels compared with slow reducers."

To separate plasma/serum from RBCs, fresh (preserved but never frozen) blood has to be available.

Because Cr(VI) is largely reduced to Cr(III) in the body, speciation of chromium is not useful. Elevated levels in blood or urine can be indicative of Cr(VI) exposures, but other factors may complicate interpretation (Paustenbach, 1997; Bukowski et al., 1991). For example, individuals who take Cr(III) supplements can have elevated levels of urinary chromium (Gargas et al., 1994; Fagliano et al., 1997). To interpret elevated chromium urinary and/or blood levels, additional information, such as from an exposure questionnaire, is necessary.

Past biomonitoring studies

A large number of studies that measured chromium levels in biological samples from various populations were identified. Biomonitoring results from selected studies using whole blood, serum, or urine samples are outlined below.

In a study by the Centers for Disease Control & Prevention (CDC), levels of trace metals were analyzed in urine (Paschal et al.,1998). Chromium was detected in 54% of the 496 participants, with a geometric mean urinary concentration of 0.13 µg/L (0.12 µg/g creatinine) and an arithmetic mean concentration of 0.22 µg/L (0.21 µg/g creatinine). The 95th percentile concentration was 0.70 µg/L (0.60 µg/g creatinine).

Ikeda et al. (2011) reported a geometric mean chromium blood level of 0.55 µg/L in samples from 1,420 Japanese women. The geometric mean blood level of chromium

varied among prefectures, ranging from 0.40 to 0.94 µg/L. The highest blood level measured was 41.8 µg/L.

The Alberta Biomonitoring Program (2008) measured a range of organic compounds, metals and mineral micronutrients in blood of pregnant women. Serum samples were randomly drawn from more than 50,000 samples collected in 2005. Pooled samples were developed to represent geographic region (Northern, Central, Southern Alberta) and age (≤ 25 years, 26-30 years, and 31+). The report provided the range of mean chromium concentrations, which was 0.9 µg/L to 4.6 µg/L.

Fagliano et al. (1997) studied urinary chromium levels of people living or working near Cr(VI) waste sites in New Jersey versus a comparison group. The average levels were slightly higher for the residents/workers relative to the comparison group. The largest difference between residents and the comparison group was found in children age 1 to 5 (0.35 µg/L [n = 52 residents] vs. 0.19 µg/L [n = 18, comparison group]). In this age group, being a resident in the area targeted by the study was a statistically significant predictor for urinary chromium, after adjusting for urine diluteness, weight, sex and household smoking (which was also associated with urinary chromium levels). Stern et al. (1998) found that dust was the likely source of exposure for these children.

Patients with joint replacements have shown elevated levels of chromium in whole blood, RBCs, serum, urine, and other biological samples (Afolaranmi et al., 2008; Sunderman et al., 1989; Mazoochian et al., 2013). Levine et al. (2013) reported on a ten-year follow up of their earlier study (Jacobs et al., 1998) of serum chromium, cobalt and titanium concentrations in patients who had primary total hip arthroplasty compared to control patients at a hospital in Illinois. The original study evaluated 75 patients, including 55 who had received a hip implant and 20 controls. The ten-year follow up study included 40 patients (27 with implants and 13 controls). The patients that received the hybrid or cobalt-chromium total hip arthroplasty had mean chromium levels that were about 4 times higher at 120 months than they were immediately prior to arthroplasty.

Tian et al. (2014) found that urinary chromium excretion was higher in smokers (33.41±14.99 µg/24 hours; n = 193) compared to non-smokers (27.45±10.49 µg/24 hours; n = 58). Urinary levels were 30.88 µg/g creatinine in smokers vs. 26.41 µg/g creatinine in non-smokers. The difference was statistically significant. Urinary chromium was positively correlated with urinary cotinine (correlation coefficient r = 0.51).

Chang et al. (2006) studied blood chromium levels in Taiwanese residents in areas with a high density of electroplating factories. Blood chromium levels were significantly associated with residence and age (decreased with increasing age). The geometric mean (GM) level in the high density areas was 0.38 µg/L (95% confidence interval [CI] = 0.36–0.40; n= 521) compared to the GM of 0.27 µg/L (95% CI = 0.25–0.30; n = 120) in controls.

The mean levels in the high density areas (GM = 0.38 µg/L; arithmetic mean [AM] = 0.47 µg/L]) were about double the mean levels observed in general population studies from the United Kingdom (AM = 0.19 µg/L), Italy (AM = 0.23 µg/L) and Spain (GM = 0.2 µg/L).

Numerous studies of workers exposed to Cr(VI) in various industries, such as welding, chrome-plating, and chromium alloy manufacturing, have found elevated levels of chromium in blood and urine correlated with Cr(VI) exposures (ATSDR, 2012).

Experimental studies

Gube et al. (2013) showed a dose-related relationship between the levels of Cr(VI) in air and total chromium in urine. Twelve healthy males who had no history of welding were exposed for 6 hours (with a short break at 3 hours) to 0, 1 or 2.5 mg/m^3 Cr(VI) in air, generated from a gas metal arc welding process. Before exposure, chromium in urine was below the limit of detection (0.5 µg/L). After exposure to 1 mg/m^3 Cr(VI) in air, the median level of chromium in urine was 0.88 µg/L. After exposure to 2.5 mg/m^3 Cr(VI), the median level of chromium in urine was 1.7 µg/L.

Experimental studies of chromium levels in urine and blood following ingestion of Cr(VI) by volunteers have also been conducted (Kerger et al., 1996; Kerger et al., 1997; Finley et al., 1997). Increased levels of chromium were measured in urine and blood samples post-exposure, indicating that elevated exposures to Cr(VI) via ingestion may be detectable through biomonitoring.

Analytical considerations:

Accurate and precise determination of chromium in urine is challenging due to its presence as a contaminant in analytical labware and the presence of a high level of polyatomic interferences. CDPH's Environmental Health Laboratory (EHL) of Biomonitoring California has developed and validated a unique analytical method for simultaneous determination of twelve metals in urine by Inductively Coupled Plasma - Mass Spectrometry (ICP-MS). Chromium is included in this panel and can be routinely analyzed at the current method detection limit of 0.16 µg/L (ppb). This detection limit is comparable with typical urinary chromium concentrations of approximately 0.2 µg/L found in the general population without occupational exposure (ATSDR, 2012; Paschal et al., 1998). EHL could substantially lower the detection limit with a more sensitive ICP-MS, which the laboratory plans to acquire in the next fiscal year (July 2014).

CDC is considering adding total chromium to its blood metals panel for environmental chemicals (Mowbray, pers comm, 2014). EHL could easily add chromium to the blood metals panel at a negligible incremental cost.

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Need to assess efficacy of public health actions:

No data were located on levels of chromium in blood or urine samples from California residents. Biomonitoring chromium could provide information on exposures across the state.

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