

October 11, 2013

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Via regulations@cdph.ca.gov

Re: CDPH-11-005 (Hexavalent Chromium)

Dear Mr. McKibben,

Thank you for this opportunity to comment on the Department of Public Health's proposed maximum contaminant level (MCL) of 10 micrograms per liter ($\mu\text{g}/\text{L}$) for hexavalent chromium. We write to strongly oppose the proposed standard and urge the Department to move to a health protective standard because:

- The proposed MCL fails to meet the Department's statutory obligations to set the MCL as close as possible to the Public Health Goal and to place primary emphasis on public health. The Department has proposed a standard that, if implemented, will result in California residents consuming drinking water that poses a significant risk of cancer and liver toxicity because the standard is 500 times greater than the state's Public Health Goal 0.02 $\mu\text{g}/\text{L}$ for cancer risks and is above the non-cancer Public Health Goal of 2 $\mu\text{g}/\text{L}$.
- The proposed MCL is not sufficiently health protective. Under a 10 $\mu\text{g}/\text{L}$ standard, more than 85% of the state's known hexavalent chromium contaminated water sources will not be addressed, leaving millions of Californians at risk, including vulnerable populations. Our calculations indicate that 24 million Californians may continue to drink chromium-contaminated water under the Department's proposed standard. At these levels, hexavalent chromium is a potent carcinogen and is also linked to other serious health impacts, including liver damage.
- The Department's cost-benefit analysis is flawed. The Department inflates the anticipated costs associated with the MCL by presuming that all sources will in fact require expensive treatment. The reality is that some larger systems will rely on blending over treatment to lower their concentrations of hexavalent chromium. At the same time, the Department fails to account for benefits associated with a stronger MCL, including the avoidance of non-cancer health risks. It also fails to account for potential co-benefits of treatment technology.

The answer to high costs for some water systems is not to allow people to be exposed to hexavalent chromium or other potent toxins at unsafe levels in their drinking water and to pretend that the water is safe. Instead, the Department must establish health-protective standards and focus on ensuring that those water systems that do not have the resources to meet health-protective standards have access to necessary funding, expertise, and support so that they can provide their communities with truly safe water.

We provide more detail below.

The Proposed Maximum Contaminant Limit (MCL) Does Not Comport with the Law

The proposed MCL fails to place primary emphasis on public health as required by law, both by failing to give adequate emphasis to protection of public health and by giving greater weight to treatment costs at the expense of prioritizing public health. The Department also fails to adequately explain how its proposed MCL places primary emphasis on public health and why the lower MCLs considered are economically and technically infeasible.

California Health and Safety Code § 116365 requires the Department to set the MCL “at a level that is as close as feasible to the corresponding public health goal.” While it requires the Department to consider the “technological and economic feasibility of compliance with the proposed primary drinking water standard,” it also requires the Department to “plac[e] primary emphasis on the protection of public health.”¹ The Department did not follow this statutory directive in proposing a MCL for hexavalent chromium of 10 µg/L.

While the federal Safe Drinking Water Act explicitly allows for a balancing of costs against benefits in which costs can determine the decision in certain circumstances, the California Health and Safety Code clearly tips the balance in favor of public health, designating cost a secondary consideration.² This is in keeping with the Legislature’s stated intent, in enacting the California Safe Drinking Water Act, to improve on federal safe drinking water requirements.³

The Department’s proposed standard flips the mandated balance of public health and costs on its head. At the proposed level of 10 µg/L—500 times greater than the Public Health

¹ *Id.* § 116365(a), (b).

² Compare 42 U.S.C. § 300g-1(6)(A) (“[I]f the Administrator determines . . . that the benefits of a maximum contaminant level . . . would not justify the costs of complying with the level, the Administrator may . . . promulgate a maximum contaminant level for the contaminant that maximizes health risk reduction benefits at a cost that is justified by the benefits”) with Cal. Health & Safety Code § 116365(a) (“Each primary drinking water standard adopted by the department shall be set at a level that is as close as feasible to the corresponding public health goal placing primary emphasis on the protection of public health . . .”).

³ Cal. Health and Safety Code § 116270(f) (“It is the intent of the Legislature to improve laws governing drinking water quality, to improve upon the minimum requirements of the federal Safe Drinking Water Act Amendments of 1996, to establish primary drinking water standards that are at least as stringent as those established under the federal Safe Drinking Water Act, and to establish a program under this chapter that is more protective of public health than the minimum federal requirements.” (emphasis added)).

Goal of 0.02 µg/L set by the Office of Environmental Health Hazard Assessment (OEHHA)—the proposed MCL is very far removed from placing primary emphasis on the protection of public health and being as close as feasible to the Public Health Goal. Under the proposed MCL, more than 85% of the state’s water sources known to be contaminated at levels above the Public Health Goal will go unaddressed.

A comparison to acceptable risk levels adopted by other bodies further proves the point. In setting risk benchmarks for a “safe or acceptable” contamination for carcinogens, EPA uses a widely accepted risk range of 1 in 1,000,000 lifetime risk of cancer at the lower end of the range to 1 in 10,000 cancer risk at the upper end.⁴ The upper end of the range translates to a lifetime cancer risk of 100 in a 1,000,000. By comparison, the lifetime cancer risk at the Department’s proposed MCL is 500 in 1,000,000. Similarly, under Proposition 65, a manufacturer must post warnings to the public about carcinogens in products and companies may not discharge carcinogenic chemicals into sources of drinking water unless risk is below a lifetime cancer risk of 1 in 100,000.⁵ This risk level translates to a lifetime cancer risk of 10 in 1,000,000 as compared to the 500 in 1,000,000 lifetime cancer risk associated with the Department’s proposed MCL. The significantly higher risk associated with the proposed MCL when compared to other determinations of acceptable health risk associated with carcinogens suggests that the Department gave public health short shrift.

The Department’s proposed MCL also fails to protect the public against non-cancer health risks associated with hexavalent chromium exposure in drinking water at levels above 2 µg/L. And, the Department fails to account in its cost-benefit analysis for the benefits to public health from reduction of non-cancer health risks (see below for a fuller discussion).

In addition to failing to adequately consider the benefits of a lower MCL, the Department also inflates costs by failing to account in its cost assessments for alternatives to full treatment that larger water systems are likely to utilize. For instance, while noting that “[s]ome of these water systems may be able to meet the MCL by blending their drinking water supplies as already occurs during drinking water distribution, at minimal cost,” the Department assesses costs assuming the use of the more expensive treatment technology for all water systems.⁶ This has the effect of giving greater weight to costs at the expense of public health.

Accounting for the lower costs some larger systems may achieve would not only reduce the aggregate cost of compliance, but might also suggest alternate possibilities for addressing costs for that subset of systems that have limited resources and might face a higher cost.

⁴ See, e.g., US Environmental Protection Agency (US EPA), *Envirofacts: Benchmarks*, at <http://www.epa.gov/enviro/facts/radnet/benchmarks.html> (last updated July 11, 2013); see also Office of Environmental Health Hazard Assessment, *MCL Review in Response to PHGs* (“Public health and environmental regulatory agencies generally consider risks within the 10⁻⁶ to 10⁻⁴ cancer risk range to be ‘acceptable.’”), at <http://www.cdph.ca.gov/certlic/drinkingwater/Pages/MCLReview2013.aspx> (last modified 3/1/2013).

⁵ OEHHA, *Proposition 65 in Plain Language*, at <http://oehha.ca.gov/prop65/background/p65plain.html> (last updated February 2013).

⁶ Initial Statement of Reasons 19.

For instance, if costs are lower for larger water systems (and the majority of people affected), the Department could focus on assisting resource-strapped smaller water systems that might face higher costs (including through funding assistance and facilitation of connections to regional water systems to achieve economies of scale). This could help these small water systems address not only hexavalent chromium but other contaminants as well. Such scenarios are expressly contemplated by the California Health & Safety Code.⁷ Moreover, in doing so, the Department would be providing constructive assistance to cash-strapped water systems instead of simply relying on the costs facing such systems as a rationale for failing to ensure safe drinking water supplies.

The Department also fails to take into account any potential co-benefits of treatment technology, thus again potentially overestimating treatment costs. Weak base anion exchange treatment systems, which form the basis of the Department's cost estimates, can also remove several other contaminants such as uranium, nitrate, arsenate, and selenite,⁸ and might thus reduce the costs of treatment for other contaminants. Moreover, some water systems already have such treatment systems in place and are incidentally removing hexavalent chromium.⁹ Taking these existing systems into account would also affect the Department's analysis of costs.

Finally, we note that, in the Initial Statement of Reasons, the Department has failed to explain *how* its proposed MCL places primary emphasis on public health or *why* the costs presented render lower MCLs economically or technically infeasible other than to state that that is the case.¹⁰

The Proposed MCL May Leave Millions Exposed to Contaminated Drinking Water that Threatens Their Health

The Department's own calculations show that setting the MCL at 10 µg/L will leave more than 85 percent of the water sources in California with known hexavalent chromium contamination issues untreated (CDPH 2013).

⁷ See, e.g., *id.* § 116425(d), (e) (discussing financial assistance and agreements to become part of a regional public water system).

⁸ See US EPA, Chemical Contaminant Removal, at <http://www.epa.gov/nrmrl/wswrd/dw/smallsystems/ccr.html> (last updated January 16, 2013).

⁹ Based on his experience with water systems and treatment, Mr. Robert Bowcock of Integrated Resource Management, Inc., and one of the authors of these comments, notes that several water systems already have anion exchange systems in place, and that some of them are already removing hexavalent chromium. Mr. Bowcock also notes that, based on his experience, presently, drinking water treatment system manufacturers and resin suppliers are quoting water utilities approximately \$0.50 per 1,000 gallons or between \$100 and \$200 per acre-foot of treated water; \$80.00 per acre-foot for Operation and Maintenance and \$80.00 to \$100.00 per acre foot for capital costs and resale estate acquisition. The US EPA reports the average family of four uses 400 gallons of water every day (at <http://www.epa.gov/watersense/pubs/indoor.html> (last updated September 19, 2013)), or as much as 12,000 gallons per month. At \$0.50 per 1,000 gallons, the average family would see an increase of \$6.00 per month, which is significantly lower than the Department's estimates.

¹⁰ See Initial Statement of Reasons 12-27.

Hexavalent chromium is a carcinogen, with increasing risks as the MCL goes further above the public health goal of 0.02 µg/L. According to the Department’s own calculations, by choosing to set a MCL at 10 µg/L versus 1 µg/L, it will allow about 1,379 additional cancers. The Department’s assessment found that the following potential MCLs are associated with the corresponding number of avoided cancers:

- MCL= 1 µg/L: 2,207 cancers avoided
- MCL =5 µg/L: 1,350 cancers avoided
- MCL = 10 µg/L: 828 cancers avoided.¹¹

Moreover, since the detection limit used to assess which active water sources were contaminated with hexavalent chromium is 1 µg/L (and therefore fifty times higher than 0.02 µg/L), it is unclear how many people may be at increased risk due to exposures above the Public Health Goal but below the detection limit.¹²

Hexavalent chromium also may cause liver inflammation in adults and children and hematopoietic effects in children at levels below the proposed MCL of 10 µg/L (as discussed further below).

At the 10 µg/L proposed MCL, millions of people will continue to be exposed to both the cancer and non-cancer risks. An Environmental Working Group analysis of the Department’s drinking water monitoring data found that if the Department moves ahead with its proposed MCL, almost **24 million Californians** may continue to drink water from more than 950 water systems that have known hexavalent chromium contamination. Certain communities, of course, will be hit harder than others. In particular, the 10 counties listed below will bear a disproportionate burden of the untreated contamination that will result from the proposed standard. This is simply unacceptable.

10 Counties will be Disproportionately Impacted by the High Proposed Standard

County Name	Population affected	Number of water systems with hexavalent chromium detections between 1 and 10 ppb
Los Angeles	7,492,045	109
Riverside	1,978,938	38
San Bernardino	1,948,006	57
Orange	1,878,119	19

¹¹ From the Rulemaking File document “Procedure for CBA of HC” prepared by Sharon M. Wong, dated August 4, 2013, Table Titled: *Estimated Annual Cost per Theoretical Excess Cancer Cases Reduced for Evaluated HC MCLs*. Total cancers listed above= (annual SWS cases + annual LWS cases) * 70 years.

¹² We note that the Department has relied on a 1 µg/L detection limit even though hexavalent chromium can be detected at levels at much lower levels. *See, e.g.*, US EPA, EPA’s recommendations for enhanced monitoring for Hexavalent Chromium (Chromium-6) in Drinking Water (“By following EPA Method 218.7, laboratories are capable of attaining a detection limit as low as 0.005 micrograms per liter µg/L (ppb) and can support a reporting limit of 0.03 µg/L (ppb).”), at <http://water.epa.gov/drink/info/chromium/guidance.cfm#ten> (last updated February 11, 2013).

Santa Clara	1,707,277	23
Sacramento	1,371,635	25
Fresno	779,198	55
Kern	698,839	70
San Joaquin	634,623	76
Ventura	566,445	18

The Proposed MCL Fails to Protect Against Non-Cancer Health Effects and Underestimates the Public Health Benefits of an MCL by Doing So

The proposed MCL fails to protect public health not only against cancer risks but also against the risk of non-cancer health effects of hexavalent chromium in drinking water. In its analysis supporting the proposed MCL, the Department fails to consider these risks and fails to account in its cost-benefit analysis for the benefits of avoided non-cancer health effects.

Of particular concern is the potential for hexavalent chromium to cause liver inflammation and damage as well as hematopoietic toxicity at the proposed MCL. Notably, the proposed MCL of 10 µg/L is above OEHHA’s Public Health Goal (PHG) for non-cancer effects of 2 µg/L and should not be considered sufficiently protective against the non-cancer endpoints of liver inflammation in adults and children and effects on blood forming tissues in children. This may put people at increased risk. Below, we describe in greater detail the health effects and some of the studies addressed in the Public Health Goal for non-cancer effects that the Department failed to consider in setting the proposed MCL.

In a 2008 National Toxicology Program (NTP) study, liver inflammation was significantly higher in the group of female rats receiving the lowest dose of hexavalent chromium tested in drinking water (14.3 mg/L) when compared to the control group. Therefore, it is probable that adverse effects would also occur at lower doses, and the researchers could not establish a No Observed Adverse Effect Level (NOAEL) for this endpoint. Additional studies are consistent with these results and also report kidney toxicity (Acharya 2001, Chopra 1996). Liver effects were observed at both subchronic and chronic exposure levels.

The liver was also identified by the NTP as a site of histiocytic infiltration in rodents, which can lead to organ damage when exposure is chronic and severe. This effect was also observed in the duodenum and pancreatic lymph nodes (NTP 2007). There were significant increases in histiocytic cellular infiltration of the liver in all exposed groups of female mice and of the mesenteric lymph node in all exposed groups of male and female mice (NTP 2008). Therefore, it is probable that these adverse effects would also be observed at lower doses.

Hematopoietic effects have also been observed in a series of NTP studies. Hypochromic anemia and changes in erythrocyte levels, platelet concentrations, mean cell volume and hemoglobin occurred in male rats administered the lowest dose of hexavalent chromium in

their drinking water (NTP 2007). Decreased red blood cell size (MCV) was observed in the F₁ generation (first generation produced by a cross) of female mice at the lowest dose level (NTP 1997). Consistent with these results, exposure-related anemia and effects on other hematological parameters including erythrocyte microcytosis was observed for male rats in a 2-year chronic study (NTP 2008). The health protective concentration OEHHA calculates for a child, based on the hematopoietic endpoints reported for the LOAEL in the 2007 NTP study, is below 10 µg/L. This raises concerns that children may not be sufficiently protected from blood-related health effects at the currently proposed MCL.

In summary, multiple adverse effects on different biological systems were recorded for the lowest doses tested in the NTP studies. These include non-cancer endpoints that the Department did not account for in assessing the benefits of the MCL. The 2011 OEHHA PHG report calculated health protective concentrations for hexavalent chromium for non-cancer endpoints based on 6 studies conducted by the NTP and independent researchers (Table 17). The LOAELs for these studies were based on endpoints for liver and hematopoietic toxicity, with the exception of the limited MacKenzie study where OEHHA noted the thoroughness of the toxicological investigation was unclear (OEHHA 2011). For all but one of the studies (MacKenzie 1958) the proposed MCL of 10µg/L exceeds the health protective concentrations calculated for children, and it exceeds the health protective concentrations calculated for adults in half the studies (OEHHA 2011). Based on the 2008 NTP study, OEHHA finalized a health protective concentration for the non-cancer endpoint of liver inflammation of 2 µg/L, which is five times lower than the current proposed MCL.

Simply put, OEHHA's calculations indicate that an MCL above 2 µg/L will not be sufficiently protective against liver toxicity and damage. This is particularly concerning given how common liver disease is in the population: the Liver Foundation estimates that 1 in 10 Americans have some form of liver disease. If the Department moves forward with a 10 µg/L standard, not only will many Californians remain at elevated risk for cancer, they will face elevated risk of liver toxicity.

In addition to ignoring the effects on the liver and the blood that may be expected at concentrations below 10 µg/L, it is also worth noting that the Department has also ignored the potential developmental and reproductive effects of hexavalent chromium in its cost-benefit calculations.

Hexavalent chromium has exhibited a number of reproductive and developmental effects in laboratory animals following oral exposure at higher doses in numerous studies. These effects included reduced litter size and fetal weights, birth defects, delayed onset of puberty, decreased ovarian follicle number, impaired estrous cycle, adverse effects on sperm count and seminiferous tubules, and effects on hormones (Banu 2008, Li 2001, OEHHA 2009, OEHHA 2011). Reductions in sperm count and other reproductive effects have also been observed for men occupationally exposed via inhalation, but there is a lack of data regarding hexavalent chromium reproductive toxicity in orally exposed people (OEHHA 2009; Li 2001).

Concern over these high dose findings was significant enough for hexavalent chromium to be listed as a reproductive toxicant in both men and women pursuant to the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). OEHHA has calculated the Maximum Allowable Dose Level (MADL) for hexavalent chromium as 8.2 µg/day by the oral route, and the concentration in drinking water that would yield that level of exposure is 3.6 µg/L (OEHHA 2011). This was based on the NOAEL for reduction of ovarian follicles in mice (Murthy 1996). The fact that the proposed MCL exceeds the MADL for reproductive effects for hexavalent chromium is further evidence that the proposed standard may not be sufficiently protective of public health.

The non-cancer health effects provide additional reason for the MCL to be set as close to the PHG as possible to protect public health. Furthermore, by ignoring the non-cancer health endpoints, the Department significantly underestimates the potential benefits of a lower MCL.

The Proposed MCL Is Not Sufficiently Protective of Vulnerable Populations

OEHHA's cancer and non-cancer PHGs account for the risks to vulnerable populations, and a failure to meet these PHGs puts these populations at risk. This is particularly apparent for children, since the proposed MCL of 10 µg/L exceeds the calculated health protective concentrations for blood and liver effects based on the LOAELs described in 5 studies by NTP and independent researchers (OEHHA 2011). As discussed above, hexavalent chromium exposure from drinking water can cause multiple health effects. This has serious implications for populations that may be more vulnerable to such exposures including the fetus, infants and children, the elderly, and people with preexisting diseases or genetic predispositions for certain types of disease.

Gastric juice acidity is an important detoxification mechanism for hexavalent chromium as it facilitates the reduction of hexavalent chromium to trivalent chromium. As OEHHA notes in its 2011 PHG document, the pH of an infant's stomach is higher than that of adults, and early life exposures to carcinogens may result in a greater lifetime risk. A more basic gastric juice pH reduces the capacity to detoxify hexavalent chromium, which may put infants at a higher risk for health effects. In the same section, OEHHA also notes that certain medications, including antacids that many Americans use, increase the pH of the stomach. Therefore infants and people who take antacids or other medications that raise the gastric pH may be at an increased risk for health effects as their ability to detoxify hexavalent chromium is compromised.

There are also a variety of medical conditions that reduce gastric acid production, including pernicious anemia (a condition also shown to increase the intestinal absorption of hexavalent chromium in people), pancreatic tumors, and some autoimmune diseases and infections (OEHHA 2011). Infections and inflammation reduce the barrier capacity of the intestine, as well as certain diseases such as celiac disease, type 1 diabetes, inflammatory bowel disease, and infectious diarrhea (Visser 2009, EPA 2013). These conditions may increase the biological uptake of hexavalent chromium in the intestine since the barrier capacity is reduced.

People with compromised liver function and those who are genetically susceptible to liver diseases may be more at-risk for potential health problems due to hexavalent chromium. The Mayo Clinic states that there are more than 100 different types of liver diseases that may be genetically inherited (Mayo Clinic 2013). Likewise, those with hematopoietic conditions such as anemia may also be more sensitive to the effects of hexavalent chromium.

Vulnerable populations are not just exposed to hexavalent chromium, of course. They are exposed to many potential carcinogens and other kinds of harmful chemicals every day. This is of particular concern in the case of hexavalent chromium since the liver is the site of metabolism for many xenobiotic agents and is therefore especially susceptible to chemical-induced injury (reviewed in Gu, 2012).

Since people are exposed to chemical mixtures that are metabolized by the liver, allowing a level of hexavalent chromium in drinking water that is not only 500 times higher than the cancer-based PHG, but five times higher than the non-cancer PHG based on liver inflammation, has the potential to exacerbate the cumulative toxic effects of these collective exposures. For example, oxidative damage due to the production of free radicals is a proposed mechanism of action for hexavalent chromium in the liver and other tissues (NTP 2008, OEHHA 2011, Witt 2013). This can contribute to both cancer and non-cancer effects. Other agents that cause oxidative damage in the liver and other organs could compound the effects of hexavalent chromium. In addition, exposure to chemicals that have hematopoietic effects may also increase risk for toxic effects in blood.

The greater risks to vulnerable populations from hexavalent chromium exposure in drinking water is further reason for the Department to set the MCL as close as possible to the PHG.

In conclusion, hexavalent chromium is an extremely toxic contaminant, and as a result of its existence in nature and extensive use in industrial applications, is widespread throughout the state's drinking water supplies. The peer reviewed science that informed California's Public Health Goal has demonstrated a direct connection between both cancer and non-cancer health impacts and exposure through drinking water. The California Legislature clearly wished to protect the public when it required the establishment of a specific MCL for this particular form of chromium by January 2004. It is the Department's responsibility to fulfill this mandate. However, by proposing a standard that will ensure that less than 15 percent of the state's contaminated water sources will be remediated, the Department has failed to fulfill its mission to protect public health. We therefore urge the Department to abandon the 10 µg/L proposal and establish a new MCL that is as close as possible to the Public Health Goal and will be protective of the health of the millions of Californians that would otherwise be at risk from hexavalent chromium in their water.

Sincerely,



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References

- Acharya S, Mehta K, Krishnan S, Rao CV (2001). A subtoxic interactive toxicity study of ethanol and chromium in male Wistar rats. *Alcohol* 23(2):99-108.
- Banu SK, Samuel JB, Arosh JA, Burghardt RC, Aruldas MM (2008). Lactational exposure to hexavalent chromium delays puberty by impairing ovarian development, steroidogenesis and pituitary hormone synthesis in developing Wistar rats. *Toxicol Appl Pharmacol*. Oct 15;232(2):180-9.
- CDPH (2013). California Department of Public Health. Chromium-6 in Drinking Water Sources: Sampling Results. Available: <http://www.CDPH.ca.gov/certlic/drinkingwater/Pages/Chromium6sampling.aspx>
- Chopra A, Pereira G, Gomes T, Pereira J, Prabhu P, Krishnan S, et al. (1996). A study of chromium and ethanol toxicity in female Wistar rats. *Toxicol Environ Chem* 53:91-106.
- EPA (2013). Scientific Workshop: Factors affecting the reduction of hexavalent chromium in the GI tract and their potential impact on evaluating the carcinogenicity of oral exposures to hexavalent chromium. Disease states and medical factors.
- OEHHA (2009). Reproductive and Cancer Hazard Assessment Section. Evidence On The Developmental And Reproductive Toxicity Of Chromium (hexavalent compounds).
- OEHHA (2011). Public Health Goals For Chemicals In Drinking Water. Hexavalent Chromium (Cr VI).
- Gu X, Manautou JE (2012). Molecular mechanisms underlying chemical liver injury. *Expert Rev Mol Med*. Feb 3;14:e4.
- Li H, Chen Q, Li S, Yao W, Li L, Shi X, Wang L, Castranova V, Vallyathan V, Ernst E, Chen C (2001). Effect of Cr(VI) exposure on sperm quality: human and animal studies. *Ann Occup Hyg*. Oct;45(7):505-11.
- MacKenzie RD, Byerrum RU, Decker CF, Hoppert CA, Langham RF (1958). Chronic Toxicity Studies II. Hexavalent and trivalent chromium administered in drinking water to rats. *AMA Arch Ind Health* 18:232-4.
- Mayo Clinic website (2013). Accessed September 28, 2013 at: <http://www.mayoclinic.org/liver-disease/types.html>
- Murthy RC, Junaid M, Saxena DK (1996). Ovarian dysfunction in mice following chromium (VI) exposure. *Toxicol Lett* 89:147-154.

NTP (1997). Final Report on the Reproductive Toxicity of Potassium Dichromate (Hexavalent) (CAS #7778-50-9) Administered in Diet to BALB/c Mice, Feb 25, 1997, PB97-144919, National Toxicology Program, National Institute of Environmental Health Sciences, North Carolina.

NTP (2007). NTP Technical Report on the Toxicity Study of Sodium Dichromate Dihydrate Administered in Drinking Water to Male and Female F344/N Rats and B6C3F₁ Mice and Male BALB/c and am3-C57BL/6 Mice, Toxicity Report Series, Number 72, January 2007. National Toxicology Program, Research Triangle Park, North Carolina.

NTP (2008). 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,

Visser J, Rozing J, Sapone A, Lammers K, Fasano A (2009). Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes paradigms. *Ann N Y Acad Sci.* May;1165:195-205.

Witt KL, Stout MD, Herbert RA, Travlos GS, Kissling GE, Collins BJ, Hooth MJ (2013). Mechanistic insights from the NTP studies of chromium. *Toxicol Pathol.* Feb;41(2):326-42.