Hexavalent Chromium Carcinogenic to Humans:

Comments from Environmental Working Group on the EPA's Integrated Risk Information System Toxicological Review for Hexavalent Chromium

June 9, 2014

Re: IRIS Toxicological Review for Hexavalent Chromium; Cr(VI) Docket EPA-HQ-ORD-2014-0313

Environmental Working Group is a research and advocacy nonprofit organization working to protect our nation's waters from pollution and ensure safe drinking water for all Americans. We are submitting comments on the Environmental Protection Agency's Preliminary Materials for the Integrated Risk Information System toxicological review of hexavalent chromium, which would be discussed at the IRIS Public Science Meeting on June 25-27, 2014.

As a group with significant expertise in water quality, EWG has worked on the issue of hexavalent chromium pollution since 2004. EWG's December 2010 study documented the presence of hexavalent chromium in drinking water from 31 of 35 U.S. cities and brought renewed public attention to the health risks of this potent and ubiquitous contaminant. Through research reports and comments submitted to federal and state agencies, EWG has been calling for a strong, health-protective water quality standard for hexavalent chromium in drinking water, which is urgently needed given frequent occurrence of chromium pollution nationwide.

EWG finds that carcinogenicity data from human epidemiological studies and the National Toxicology Program studies on laboratory mice and rats support a designation of hexavalent chromium as carcinogenic to humans and that the weight of evidence favors a mutagenic mode of action for hexavalent chromium. We advise EPA to consider jointly carcinogenic and non-carcinogenic effects of hexavalent chromium in the finalized IRIS assessment and to rely on the NTP 2-year study of chromium exposure in drinking water rather than the 90-day subchronic exposure studies promoted by the industry.

In support of our recommendations, we provide responses to specific science issues raised in the EPA Preliminary Materials for IRIS review of hexavalent chromium, including:

- Cancer classification, mode of action and dose response analysis for hexavalent chromium;
- Gastrointestinal, hematological and hepatic toxicity findings in animal studies;
- Use of chronic, rather than sub-chronic, exposure data for establishing a safety threshold for hexavalent chromium in drinking water.

Details and the rationale for our recommendations are provided below.

1. Carcinogenicity findings in people and laboratory animals and mode of action data support a designation of hexavalent chromium as carcinogenic to humans.

As the National Toxicology Program two-year study demonstrated, drinking water exposure to hexavalent chromium (given as sodium dichromate dihydrate) induces oral cancers in rats and cancer of

the small intestine in mice (NTP 2008; Stout 2009). Consistent with the animal study findings, in epidemiological studies people drinking chromium-polluted water had an elevated risk of multiple types of cancer, including lung, stomach, kidney and genitourinary cancers (Beaumont 2008; Linos 2011).

In the preliminary materials prepared for the June 2014 IRIS Public Science meeting, EPA raised two science issues related to hexavalent chromium carcinogenicity: cancer classification for hexavalent chromium (issue 1), which will be discussed in this section; and relationship between anemia and oral tumors in rats (issue 6) which will be discussed in section 2 of our comments.

Hexavalent chromium has been classified as a "known human carcinogen by the inhalation route of exposure" by federal, state and international health agencies, including the EPA. This classification is based on extensive evidence from occupational studies that inhalation of chromium causes lung cancer in humans (EPA 2014; NIOSH 2013). EPA is now proposing to update the dose-response assessment for carcinogenic effects of hexavalent chromium; to identify susceptible subpopulations and lifestages; and to determine if a mutagenic mode of action is operative in hexavalent chromium carcinogenicity.

EWG strongly supports this plan. In our 2011 comments to we pointed out to EPA that hexavalent chromium exposure via oral route, from drinking water, meets and exceeds the EPA 2005 Guidelines for Carcinogen Risk Assessment criteria for the descriptor "likely to be carcinogenic to humans", as an agent that has tested positive in animal experiments in more than one species (mice and rats), sex (males and females), and site (oral and intestinal) (EWG 2011).

EWG now finds that data from human and animal studies for both inhalation and drinking water exposure routes, together with strong evidence on the mutagenic mode of action for hexavalent chromium carcinogenicity merit a single, uniform descriptor of hexavalent chromium as "carcinogenic to humans".

As demonstrated by numerous studies, once chromium enters human cells, it causes DNA damage and mutagenesis (McCarroll 2010; Zhitkovich 2011). The weight of evidence favors a mutagenic mode of action for hexavalent chromium carcinogenicity. In the 2010 external review draft assessment for hexavalent chromium, EPA scientists documented dozens of studies indicating hexavalent chromium damages DNA in vitro and in vivo (EPA 2010). In a 2013 review, National Toxicology Program scientists highlighted the "abundance of evidence for genotoxicity" of hexavalent chromium (Witt 2013).

In a 2010 review, researchers from the George Washington University wrote:

> "*Structural genetic lesions produced by the intracellular reduction of Cr(VI) include DNA adducts, DNA-strand breaks, DNA-protein crosslinks, oxidized bases, abasic sites, and DNA inter- and intrastrand crosslinks. The damage induced by Cr(VI) can lead to dysfunctional DNA replication and transcription, aberrant cell cycle checkpoints, dysregulated DNA repair mechanisms, microsatelite instability, inflammatory responses, and the disruption of key regulatory gene networks responsible for the balance of cell survival and cell death, which may all play an important role in Cr(VI) carcinogenesis."* (Nickens 2010).

The California Office of Environmental Health Hazard Assessment also affirmed hexavalent chromium mutagenicity, stating:

> "*Numerous studies demonstrate that Cr VI is both genotoxic and mutagenic. A mutagenic MOA has been fully described and justified. Unless there are data supporting an alternative*

> *mechanism of action, the standard approach for carcinogens operating via a genotoxic or mutagenic MOA is to apply a linearized multistage model to calculate cancer potency*." (OEHHA 2011)

Given that a large body of data points to a mutagenic mode of action for hexavalent chromium, EPA must apply a linear-dose response model for developing a safety threshold for hexavalent chromium exposure from drinking water and by inhalation.

In addition to the question of low dose extrapolation, EPA should also address susceptible populations in its risk assessment for chromium. Existing evidence suggests that newborn babies and millions of Americans that take gastric acid-reducing medications would be particularly susceptible to hexavalent chromium toxicity and carcinogenicity. As discussed in the California Office of Environmental Health Hazard Assessment materials supporting Public Health Goal for hexavalent chromium in drinking water, gastric juice acidity is an important detoxification mechanism for hexavalent chromium as it facilitates the conversion to non-toxic trivalent chromium. A more basic gastric juice pH reduces the capacity to detoxify hexavalent chromium (OEHHA 2011).

The pH of an infant's stomach is higher than that of adults, which may put infants at a higher risk for chromium toxicity. Certain medications, such as antacids or prescription medications to treat gastritis, ulcers, and gastrointestinal reflux disease, increase the pH of the stomach. Gastric acid production is also reduced in certain diseases and medical conditions. One of them is pernicious anemia that increases the intestinal absorption of hexavalent chromium in people, a fact known since 1960s (Donaldson and Barreras 1966).

EPA should develop a safety threshold for chromium that would be sufficiently protective for newborn infants, people with elevated gastric pH and patients with medical conditions that could increase susceptibility to hexavalent chromium toxicity. Given the sensitivity of infants, EWG believes that an additional 10-fold safety factor would be justified for setting the limit for hexavalent chromium exposure.

2. Gastrointestinal, hematological and hepatic toxicity of hexavalent chromium should be considered jointly with carcinogenicity effects.

EPA raised the issue of noncancer hazards of hexavalent chromium (science issue 2), proposing to review its potential for respiratory, gastrointestinal, immunological, hematological, hepatic, reproductive and developmental effects. EWG supports the EPA approach. The concurrent presence of increased cancer risk and toxicity to multiple organs and tissues in the NTP study indicates that carcinogenic and non-carcinogenic toxicity of hexavalent chromium must be considered jointly in the IRIS risk assessment for this chemical.

EWG is particularly concerned about the potential for hexavalent chromium to cause liver damage as well as hematopoietic toxicity. In the NTP study, liver inflammation and histiocytic cellular infiltration of the liver were significantly higher in the female rats receiving the lowest tested dose of hexavalent chromium, 0.38 mg/kg/day, compared to the control group. From the NTP data, it was impossible to establish a No Observed Adverse Effect Level for liver toxicity endpoint, since adverse effects could occur at lower doses. Liver toxicity of hexavalent chromium is of particular concern given that 1 in 10 Americans has some form of liver disease (American Liver Foundation 2009).

Hematopoietic toxicity effects have been observed in a series of NTP studies on hexavalent chromium. 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; NTP 2008). Decreased red blood cell size, measured as mean corpuscular volume, was also observed in the female mice at the lowest dose level tested in the reproductive toxicity study of hexavalent chromium (NTP 1997).

With respect to carcinogenic and non-carcinogenic toxicity of hexavalent chromium, EWG believes that science issues 3 and 6 raised by EPA need to be considered together. In issue 3 EPA posed a question whether gastrointestinal toxicity, observed in mice at the lowest hexavalent dose tested of 0.38 mg/kg/day, could be the driving force of other toxicity effects in mice. In issue 6, EPA posed a question whether anemia, to which rats were more susceptible than mice, could be the driving force for tumor development in rats.

With respect to science issue 3, NTP data and studies by Thompson et al (2011, 2012) indicate that hexavalent chromium is toxic to the intestinal cells in both mice and rats, albeit at different doses, a finding that is not surprising in toxicity assays with two different species. Elevated stomach cancer mortality among people who drank water contaminated with hexavalent chromium indicates that hexavalent chromium causes gastrointestinal toxicity in people as well (Beaumont 2008). While this study, conducted in China, has been critiqued because of data quality issues, California Environmental Protection Agency researchers concluded that the overall data were consistent with increased stomach cancer risk (Beaumont 2008).

With respect to science issue 6, EWG agrees that hexavalent chromium-induced anemia was more severe in rats. However, there are no data showing that anemia was the causal agent of oral mucosa tumor development in rats. In the NTP assays, the carcinogenicity effects were observed at a similar dose of hexavalent chromium in different species and sexes of animals, independently of presence or absence of statistically significant hematologic toxicity effects. At the lowest detected effect threshold, oral mucosa squamous cell carcinomas were observed at 2.4 mg/kg/day in female rats and 5.9 mg/kg/day in male rats; small intestine carcinomas and/or adenomas were observed at 1.4 mg/kg/day in female mice and 2.4 mg/kg/day in male mice. Furthermore, both rats and different strains of laboratory mice experienced anemia, indicating that hematologic toxicity of hexavalent chromium is not limited to one species or strain (NTP 2007; NTP 2008; Stout 2009).

EWG finds that these observations, taken together, indicate that hexavalent chromium is toxic to multiple tissues and causes cancer at multiple sites in mice and rats. The diversity of tumor sites should not be considered as the lack of concordance in observations from different laboratory animals. Rather, they indicate multi-site toxicity of hexavalent chromium, which heightens the human health concern for this contaminant. EWG urges EPA to ensure that the exposure threshold developed by IRIS for hexavalent chromium would be protective of gastrointestinal, liver and hematologic toxicity as well as carcinogenicity.

EPA also raised science issue 5 regarding the data quality for studies that examined reproductive and developmental toxicity of hexavalent chromium. Numerous studies have found that heavy metals such as chromium are toxic to reproduction and development, suggesting that these effects could occur in people (Apostoli and Catalani 2011). EWG agrees with EPA that overall NTP data do not show a statistically significantly change in reproductive organ weights or sperm parameters in laboratory animals exposed to hexavalent chromium (NTP 1997; NTP 2007), although other studies pointed to this

possibility (Samuel 2014; Marouani 2012). However, many parameters relevant to reproductive and developmental toxicity assessment of hexavalent chromium, such as the levels of reproductive and thyroid hormones, have not been examined in most studies published to-date. Therefore, the database for reproductive and developmental toxicity for hexavalent chromium is not yet complete and the potential adverse effects of chromium contamination in drinking water on the reproductive system and on the developing fetus need to be taken seriously. The public needs to be protected from the possibility of reproductive harm in the face of database gaps and uncertainty.

3. IRIS assessment should rely on chronic exposure data for establishing a safety threshold for hexavalent chromium in drinking water.

In science issue 4, EPA raised the question of the utility of histopathological data from subchronic exposure studies for assessing the health risks of hexavalent chromium. This issue deals specifically with recently published 90-day studies of hexavalent chromium in rodents conducted by industry consulting firm ToxStrategies. These studies reported toxicity effects in the intestine at high drinking water concentrations, but not at lower concentrations and expended significant effort to defend the non-mutagenic mode of action for hexavalent chromium toxicity (Thompson 2011; Thompson 2012).

EWG finds that, compared to the NTP 2-year exposure studies that are the gold standard of toxicological analysis, 90-day exposure studies published by the industry are unable to provide the comparable degree of insight into the potential for chronic toxicity of hexavalent chromium. In the absence of a strong, health protecting standard limiting hexavalent chromium pollution, people in communities all across the United States are forced to drink water polluted with this toxic contaminant (AwwaRF 2004; EWG 2010; WRF 2012). A subchronic period of exposure in laboratory animals cannot adequately represent the daily lifetime exposure to drinking water contaminants that represents real-world scenarios.

EWG believes that these subchronic toxicological data cannot and should not be used as the basis for the IRIS assessment on the effects of chronic exposure to hexavalent chromium. We also find that the studies promoted by the industry seem to have been conducted and written up with the clear agenda of defending the non-mutagenic mode of action for hexavalent chromium carcinogenesis rather than finding the lowest dose of chromium that could cause adverse health effects.

Industry consultants have stalled and delayed the IRIS assessment process for hexavalent chromium for a long time, as EWG and other environmental organizations highlighted in letters and comments to the EPA and other government agencies (EWG 2011). The time has now come for EPA to move forward with the hexavalent chromium risk assessment. EWG urges the EPA to rely on the chronic exposure data from 2-year NTP study for setting the safety threshold for hexavalent chromium exposure and not on the 90-day subchronic exposure studies.

Conclusion

We appreciate the time and dedication of EPA staff working to accurately assess the risks hexavalent chromium. We urge you to move ahead with finalizing the EPA assessment for this dangerous chemical, so that water providers will have a clear mandate to reduce chromium contamination in drinking water.

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