August 30, 2011

Vincent Cogliano
Integrated Risk Information System (IRIS)
c/o EPA Docket Center, Mail Code 28221T
Environmental Protection Agency – West Building
1301 Constitution Avenue, NW
Washington, DC 20005

Re: Hexavalent Chromium – EWG Response to Reviewer Post-Meeting Comments

Dear Mr. Cogliano,

Environmental Working Group is a research and advocacy nonprofit with considerable expertise in water quality and water contaminants. Our goal is to bring the best data and science to bear to inform the development of policy to protect our nation's source waters and provide safer drinking water to all Americans. To this end, our December 2010 study documenting the presence of hexavalent chromium in drinking water from 31 of 35 U.S. cities (ewg.org/chromium6-in-tap-water) brought significant attention to the ongoing federal process of assessing the public health risks of this potent and ubiquitous water contaminant.

EWG felt compelled to write the Environmental Protection Agency at this time after reading the July 2011 comments provided by EPA-appointed peer reviewers of the agency's 2010 draft toxicological review of hexavalent chromium. It was clear to us that a number of criticisms made by a subset of reviewers were simply scientifically inappropriate and unreasonable. We wish to provide our own formal response to these criticisms, which were also effectively rebuked by the California EPA on July 27, 2011, when the agency finalized a public health goal for hexavalent chromium in drinking water of 0.02 ppb (OEHHA 2011).

It should be noted that three peer reviewers provided comments that were largely supportive of the draft assessment, and many of the reviewers brought up a variety of interesting and relevant scientific points and corrections that the EPA should incorporate in revisions. We urge the agency to focus on comments that will produce a robust and defensible toxicological review, while dealing effectively and succinctly with comments that deviate from strict scientific principles.

Key issues we will address in this letter are as follows:

- The statistical necessity of extrapolating from risks associated with high doses in animal studies to those associated with lower, environmentally relevant doses;
- The weight of evidence favoring a mutagenic mode of action relative to other hypothesized modes of action;
- The dangerous precedent suggested by delaying risk assessment activities to allow incorporation of as-yet unpublished, industry-funded research; and

- The abundance of existing data to support a designation of hexavalent chromium in drinking water as "likely to be carcinogenic to humans."

High-dose studies are widely accepted as an efficient means of establishing toxicity. While in an ideal world, we would like carcinogenicity and other toxicity studies that evaluate risks associated with environmentally-relevant, low-dose exposures to substances under investigation, such studies would require thousands upon thousands of laboratory animals to establish statistically significant levels of chemical exposures associated with adverse health effects. For decades, real-world toxicologists working with practical resource constraints and striving for humane treatment of lab animals have conducted high-dose studies of the carcinogenic and toxic effects of chemicals using far fewer lab animal test subjects and controls, then extrapolated the results to calculate potential risks posed by lower doses, especially those relevant to humans. In keeping with this accepted practice, industry's own ongoing assessment of the safety of hexavalent chromium uses typical numbers of lab animals and thus cannot provide any additional information specific to low-dose exposures. Comments from reviewers that imply the lack of low-dose studies is a fundamental flaw in this toxicological review appear to be an unreasonable indictment of the entire study of toxicology in its present form.

While some chemicals exhibit unusual potency at low-dose exposures relative to medium- or high-dose exposures, creating a U-shaped dose-response curve, at this time there is no evidence to suggest hexavalent chromium has these properties. Therefore, extrapolation of low-dose risks based on a high-dose study is an appropriate means of establishing risk, similar to the extrapolation of human risks based on animal studies when limited epidemiological data are available.

Available evidence largely supports a mutagenic mode of action. In the draft toxicological review, EPA scientists have documented dozens of studies indicating hexavalent chromium damages DNA *in vitro* and *in vivo*. The wealth of evidence accumulated in recent decades is clearly consistent with a mutagenic mode of action. While these studies frequently use doses of the chemical higher than typical environmental levels, extrapolation of low-dose risks from high-dose laboratory studies is appropriate and necessary in the field of toxicology, as described previously.

We call attention to a thoughtful and well-researched review of hexavalent chromium carcinogenicity by peer reviewer Dr. Anatoly Zhitkovich (2011). Zhitkovich's paper provides a balanced treatment of the evidence supporting the mutagenic mode of action and alternatives. Zhitkovich finds a mutagenic mode of action to be strongly supported by the body of available science and can find no firm evidence to justify use of a threshold to extrapolate risk:

> Extensive formation of DNA adducts, clear positivity in genotoxicity assays with high predictive values for carcinogenicity, the shape of tumor-dose responses in mice, and a biological signature of mutagenic carcinogens (multispecies, multisite, and trans-sex tumorigenic potency) strongly support the importance of the DNA-reactive mutagenic mechanisms in carcinogenic effects of Cr(VI). Bioavailability results and kinetic considerations suggest that 10-20% of ingested low-dose Cr(VI) escapes human gastric inactivation. The directly mutagenic mode of action and the incompleteness of gastric detoxification argue against a threshold in low-dose extrapolation of cancer risk for ingested Cr(VI).

An alternate hypothesis raised by industry suggests that the carcinogenic action of hexavalent chromium is driven not by mutagenicity but by broader cell toxicity, which could cause necrosis followed by regenerative proliferation that might result in spontaneous mutations leading to tumors. Such a mode of action would result in a steep, sublinear dose dependence with a threshold below which cell death, followed by cell proliferation and the potential for tumors, would not occur.

There is insufficient evidence to support this alternate, industry-promoted hypothesis at this time. There were no signs of necrosis in the intestines of mice in the 2-year NTP study (2008), and the supralinear dose-response pattern observed is more consistent with the process of eliminating genetically damaged cells by apoptosis, a well-established protective mechanism that organisms use to fight cancer (Zhitkovich 2011). Initial results of an industry-funded, 90-day study of mice exposed to hexavalent chromium demonstrated that significantly more animals exhibited cell proliferation than apoptosis at each dosage level (Thompson 2011). The greater sensitivity of cell proliferation than cell death with exposure to hexavalent chromium is not at all consistent with a mode of action whereby cell death triggers cell proliferation, as suggested in industry's alternative hypothesis. Furthermore, the apoptosis observed could again be interpreted as part of the natural process by which an organism replaces chromium-mutated cells as a defense against cancer (Zhitkovich 2011), rather than as a result of chromium-induced cell toxicity only.

There is also insufficient evidence to provide a rationale to discount the wealth of data currently supporting a mutagenic mode of action in favor of the alternate hypothesis. A single study suggesting an absence of DNA damage in the intestines of mice orally exposed to hexavalent chromium (DeFlora 2008) used biomarkers that lacked sufficient sensitivity to detect such damage (Zhitkovich 2011). One of these biomarkers (8-hydroxydeoxyguanosine) was also used in the more recent industry-funded 90-day study of mice (Thompson 2011), despite its short lifetime and established lack of sensitivity for this purpose (Zhitkovich 2011). Use of an insensitive biomarker of oxidative DNA damage prevents any useful conclusions about the potential for chromium-induced mutation from this study. Meanwhile, industry advocates who attempt to discount the mutagenic mode of action by emphasizing the weakly mutagenic properties of hexavalent chromium DNA adducts seem to ignore the strongly mutagenic properties of widely-observed DNA adducts that include both chromium and ascorbate or other common organic molecules found in cells.

While we continue to seek out more and better data concerning the carcinogenic mode of action of hexavalent chromium, there is no longer any debate that the chemical causes cancer in lab animals through oral exposure and could cause cancer to people as well. While we do not yet possess a complete molecular understanding of the specific pathway by which tumors form as a result of exposure to hexavalent chromium, the same could be said for many other known human carcinogens currently regulated by the EPA. At this time, we have significant evidence to support a mutagenic mode of action for the contaminant and little to no evidence to support an alternative mode of action.

Late to the table, industry's studies should not dictate the schedule for this or any other IRIS process. Peer reviewer Monica Nordberg, Ph.D., summarized this point best in her comments to EPA:

> During the workshop a number of ongoing studies were presented and it was suggested that they be paid attention to. It is always an advantage to get more and more information and research is always going on.

> In my opinion it is however important to set recommendations for exposure to toxic agents in order to protect humans from developing adverse health effects. It is a human right to be protected from unwanted exposure which also will cause unnecessary worry during the time from alert to protection. People expect regulatory agencies to make evaluations and set exposure limits. Studies underway even if published in peer review scientific journals should be carefully evaluated and scrutinized by EPA's working group to determine if presented data is reliable e.g., based on a number of factors such as, just to mention a few, how large are the studies and what is the power of the study, analytical procedures that include quality control so data is validated and to be trusted. Based on experience it takes time before data will be available even for ongoing studies. I recommend that IRIS, EPA sets a recommendation based on information presented in the draft document. In case important information which can change any evaluation shows up in time, such data can be included in the final document as an appendix or addendum. It is important in Risk Assessment to keep in mind that any recommendation set for exposure levels values needs to be reevaluated over time because by new techniques e.g., rapid development of usage of "omics" has to be considered. In view of said it is important to draw conclusions now and on data available now and not to wait.

Should EPA choose to delay finalizing its review to include an as-yet unpublished, industry-funded study on hexavalent chromium, it would set a disturbing precedent for industry manipulation of the IRIS process. Simply put, any industry with a vested interest in a chemical facing IRIS scrutiny could launch its own study, provide preliminary data, and advocate a delay in the review process while promising to publish the study in a peer-reviewed journal as soon as possible. The EPA simply cannot cede control of IRIS timelines to well-funded industries in this way.

Hexavalent chromium easily meets IRIS criteria for designation as a probable human carcinogen. Hexavalent chromium is clearly "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans" (EPA 2005), thus meriting the descriptor "likely to be carcinogenic to humans."

While a few peer reviewers suggested an alternate designation of "suggestive evidence of carcinogenic potential," the level of available data on hexavalent chromium carcinogenicity clearly exceeds that detailed in EPA's Guidelines for Carcinogen Risk Assessment for this descriptor: "a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system" (EPA 2005).

We hope agency scientists find this letter a useful document as they work to revise the draft toxicological review for hexavalent chromium in drinking water. We appreciate the time and dedication of EPA staff working to accurately assess the risks of this dangerous chemical and look forward to reading the final review document in the near future.

Sincerely,

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