Industry Says Pending Study Shows No Need To Strengthen EPA's Cr6 Limits

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Industry-funded researchers say their soon-to-be published risk research shows that EPA's current drinking water limit for hexavalent chromium (Cr6) is adequately protective, bolstering chemical industry efforts to push EPA to soften its controversial 2010 draft assessment that labeled the metal a human carcinogen and was expected to drive stricter regulatory standards.

The finding is likely to draw criticism from environmentalists, who have criticized EPA for delaying its assessment to allow industry time to complete its study.

The $4 million industry-funded research project is intended to provide the agency additional information about how the metal causes cancer when ingested, information which can vastly change EPA's Integrated Risk Information System (IRIS) assessments because of agency policy on how the cancer portions of the assessments are conducted.

EPA's draft 2010 Cr6 assessment concluded that the metal causes cancer through a mutagenic mode of action (MOA). Under EPA's cancer risk assessment guidelines, assessors are required to use conservative linear modeling -- which assumes no safe level of exposure -- when assessing the cancer risk of chemicals that are mutagenic or those whose MOAs are unknown.

The guidelines do allow the use of non-linear modeling, which assumes that there is some level of exposure below which exposure is safe, in the case of chemicals with a known, non-mutagenic mode of action.

The new Cr6 research, funded by the chemical industry association American Chemistry Council (ACC), proposes that Cr6 is not mutagenic, but instead has a cytotoxic MOA, where cells are repeatedly killed and replaced. As a result, they propose a risk estimate based on non-linear modeling in a risk assessment they are preparing for publication perhaps as early as this month, ToxStrategies consultant Deborah Proctor told reporters during a Feb. 22 briefing held by ACC.

Proctor, who is leading the research project, told reporters during the briefing that the researchers are nearing completion of their work and preparing for publication of their own risk assessment.

Their risk assessment paper could be published as early as March, Proctor said, indicating they are awaiting additional modifications to their work before the paper can be published. "It is still in peer review, but we feel relatively confident in our results," Proctor said.

She said one of the potential delays to the paper's publication includes what Proctor described as ongoing discussion with IRIS staff over the model the researchers are developing to assess the metal's risks. Such physiologically-based pharmacokinetic (PBPK) models have become core to risk assessment practice over the last decade or so, because they provide assessors with information on how chemicals moves inside the body.

Proctor said the researchers have provided their model to EPA staff, who have been reviewing it and suggesting modifications. "We've given our code for the model to EPA," she said. "We're tweaking the model based on their comments."

She declined to indicate what reference dose (RfD), or maximum amount she and colleagues estimate can be ingested daily for a lifetime without anticipating adverse health effects. But Proctor indicated that the researchers have also calculated an equivalent to EPA's maximum contaminant level goal (MCLG), a health protective standard EPA's water office calculates for drinking water that serves as the basis for a regulatory drinking water standard.

While she declined to provide any numeric risk estimates until the studies are published in a peer-reviewed journal, Proctor indicated that the researchers' MCLG equivalent is "slightly above," or slightly weaker, than the existing federal standard for total chromium of 100 parts per billion (ppb).

"Risk Assessment using new MOA study data supports that the current MCL is protective for sensitive human subpopulations," according to slides that Proctor presented at the briefing.

Risk Assessment

While EPA, in its draft assessment, calculated an oral slope factor, or estimate of cancer potency, of 0.5 (milligrams per kilogram bodyweight per day)^-1, the researchers calculated a RfD using the risk assessment procedures that EPA usually uses in analyses of effects other than cancer.

For these non-cancer assessments, EPA generally assumes there is a threshold exposure below which ingestion is safe. Since the researchers concluded that Cr6 acts by a non-mutagenic non-linear MOA, they applied this non-cancer methodology and crafted an RfD rather than a slope factor for Cr6.

While the industry assessment is weaker than EPA's 2010 draft, Proctor argued it remains protective of the population, including children and those with susceptibilities to Cr6 exposure, such as those with certain gastrointestinal conditions. Proctor explained that with their PBPK model, the researchers were able to consider safe levels for infants, children and those with lower stomach acid pH.

Chromium in drinking water is a mixture of Cr6 and trivalent chromium (Cr3), a non-toxic and essential nutrient. Cr6 rapidly converts to Cr3 in the stomach, Proctor explained, but elevated pH can slow this process. Therefore, individuals with stomach conditions who take antacids or proton-pump inhibitors like Pepcid AC which elevate pH are less efficient at converting Cr6 to Cr3.

Similarly, children, infants and the elderly have higher stomach acid pH than adults. Proctor said the researchers were able to evaluate Cr6 ingestion in adults and children with varying stomach pH, also accounting whether they had full or empty stomachs while they were exposed to Cr6 in drinking water. Stomach contents also change pH.

As a result of these calculations, Proctor said the group did not include an age-dependent adjustment factor (ADAF) in their RfD. EPA applies this ADAF, a multiple of as much as 10, in cancer calculations of risk estimates of chemicals that children are particularly susceptible to. Since the researchers were able to account for children's susceptibilities with the model, Proctor argued that it was not necessary to include an ADAF in their risk estimate. Proctor did include uncertainty factors totaling 30 in the estimate, accounting for differences between people in their susceptibility and differences between people and lab animals used in the toxicology studies that are the basis for their assessment.

Proctor also pointed to their use of a precursor effect to calculate their RfD as another improvement that makes their assessment conservative and health protective. "We can model precursor response rather than tumors," Proctor said. They selected hyperplasia, which Proctor describes as "a proliferative response in the crypt [a gland in the small intestine that produces new cells to line the intestine] that precedes tumor formation in dose and time" as the basis for the assessment, rather than tumor formation itself. "If you prevent hyperplasia, you'll prevent tumor formation," Proctor said.

The researchers' studies stemmed from a study that the National Toxicology Program published in 2007 -- which indicated for the first time that Cr6 could cause cancer when ingested. Cr6 had long been identified as a carcinogen when inhaled, but its effects when ingested had previously been unknown. However, Proctor and colleagues argue that the high doses of 5,000-180,000 ppb that NTP scientists gave the lab animals "overwhelmed the mice and rats' ability to reduce Cr6 to Cr3 before it moved into the small intestine," Proctor said, resulting in tumors in the mice's stomachs.

That 2007 NTP formed the basis for EPA's 2010 draft assessment. Proctor says that California and New Jersey also referenced the NTP study in their efforts to set state water standards.

Proctor's colleagues repeated the NTP study, using the same contract lab and doses, and also added two much lower doses: the federal MCL of 100 ppb and dose of 1400 ppb. Proctor said that they saw no effects at the two lower doses. Additional studies of the animals' DNA provided additional evidence that Cr6 was causing the tumors at the higher doses through cytotoxicity rather than mutagenicity.

"We looked at different forms of DNA damage and we also looked for a specific change to the micronucleus, and we didn't see any damage," Proctor said. "We also looked for k-ras mutation, which is usually associated with cancer. We couldn't find any k-ras . . . No effects in the low dose range is also typical of a cytotoxic MOA."