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Memorandum

February 7, 2020

To:	Sheila Holman Assistant Secretary N.C. Department of Environmental Quality
From:	Chad Thompson, PhD, MBA ToxStrategies, Inc.
Subject:	Comments on the North Carolina Secretaries' Science Advisory Board (SSAB) Meetings on Hexavalent Chromium
Cc:	Tom Augspurger, Ph.D. Chairman Secretaries' Science Advisory Board

ToxStrategies has followed with interest the North Carolina Secretaries' Science Advisory Board (SSAB) meetings discussing hexavalent chromium (Cr(VI)). We would like to take the opportunity to address some scientific issues raised during the Board's discussions on Cr(VI) at the October 2019 and December 2019 meetings before the SSAB finalizes their report and recommendations to DEQ.

December 2, 2019 SSAB Meeting

At the latest meeting on December 2, 2019, a slide titled "*Draft summary statements for the SSAB's Cr(VI) charge from the 10/7 meeting*" was shown with the following text:

> Data from drinking water studies with rats and mice have been the subject of robust mechanistic toxicity assessments of cancers in the oral cavity and stomach between 2011 and 2019. Available mutagenicity data are negative; there were not dose-related increases in K-Ras mutant frequency, micronuclei, or changes in mitotic or apoptotic indices. Toxicant localization and histological examinations have helped elucidate the mode of action in the rodent drinking water papers. If considering the mouse and rat drinking water exposure papers only, there is strong support for a non-mutagenic mode of action involving chronic wounding of intestinal villi and crypt cell hyperplasia. This was the basis of the Health Canada conclusion which placed more emphasis on oral exposures and mode of action studies most relevant to the critical effect endpoint and less emphasis on other endpoints or routes of exposure. **Other organizations concluded these studies alone did not compel a determination that a mutagenic mode of action was not operative.** Further, rat oral tumors

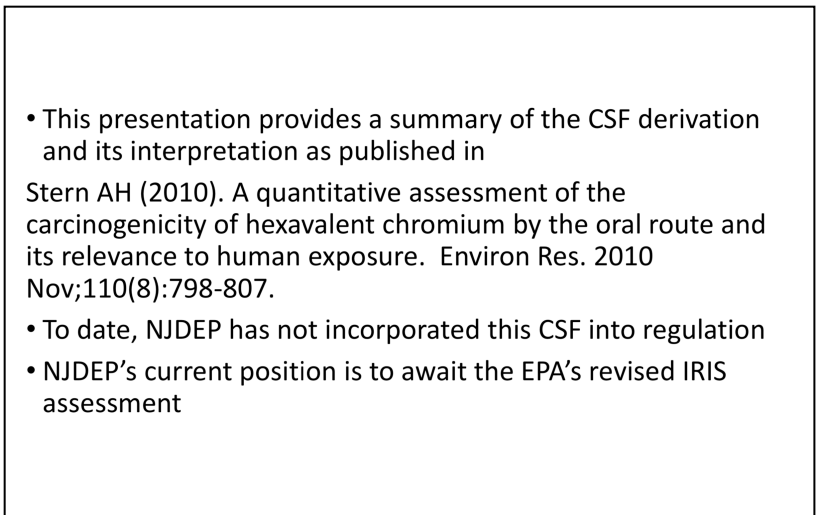
were not preceded by hyperplasia and results demonstrating wounding of intestinal villi and crypt cell hyperplasia do not account for these tumors. (**emphasis added**)

We would like to clarify/comment on some of the statements on this slide:

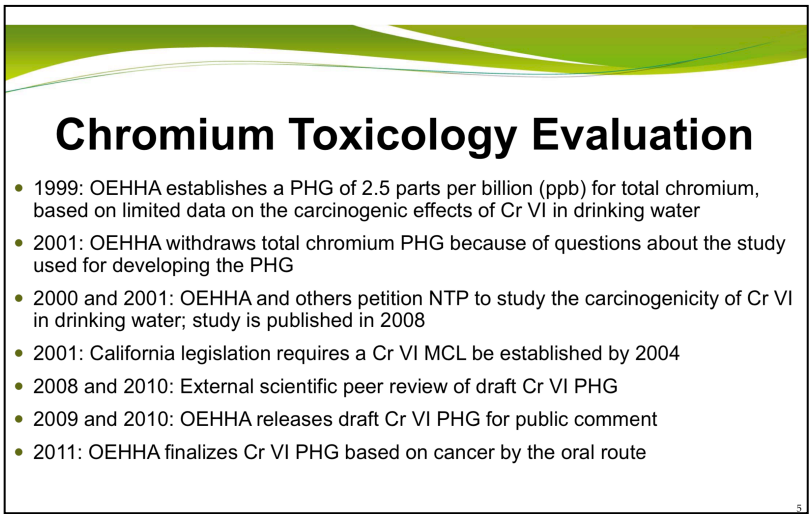
1. The mode of action (MOA) drinking water research has been on the oral cavity and duodenum, not the stomach.

2. The bolded text is misleading. To our knowledge, no "other organizations" that have considered the "robust mechanistic toxicity assessments of cancers in the oral cavity and stomach [sic] between 2011 and 2019" have concluded that these studies "did not compel a determination that a mutagenic mode of action was not operative." To our knowledge, all of the organizations that have formally reviewed and stated conclusions on the MOA resulting from oral exposure to Cr(VI) have concluded that the MOA is a threshold non-mutagenic MOA:
    a. Texas Commission on Environmental Quality (2016) Hexavalent Chromium Oral Reference Dose: Development Support Document (Final).
    b. Health Canada (2016) Guidelines for Canadian Drinking Water Quality: Guideline Technical Document — Chromium. Water and Air Quality Bureau Health Canada: Ottawa, Ontario.
    c. Food Safety Commission of Japan (2019) Risk Assessment Report Hexavalent Chromium (Beverages). *Food Safety Commission of Japan*, 7, 56-57. DOI: doi: 10.14252/foodsafetyfscj.D-1900002.
    d. World Health Organization (2019) Chromium in Drinking Water: Draft Background Document for Development of WHO Guidelines for Drinking-water quality.

3. When Alan Stern of the New Jersey DEP and Elaine Khan of California OEHHA presented to the SSAB, each explicitly stated that their presentation focused on documents their respective organizations wrote ***prior*** to the MOA studies being completed.
    a. Stern (June 18, 2018) – Slide 2 (untitled) indicates that his evaluation ended in 2010 (see below). This is further supported by the audio recording of the meeting (file name 'SAB mtg June 18 Part 3') where Dr. Stern states at the 48:20 mark that "*This presentation that I am going to be giving you is a summary of the cancer slope factor derivation and its interpretation that it contained in the 2010 publication, of which I am the sole author. There is really going to be no new information other than what was presented in the paper.*"



b. Khan (August 20, 2018) – Slide 5 titled "Chromium Toxicology Evaluation" indicates that the OEHHA evaluation was finalized in 2011 (below). This is also evident in the audio recording of the meeting available on the NC DEQ website, where Dr. Khan states at the 4:23:00 mark that "*I did specify that I will be speaking about the PHG that was established in 2011 because we have announced we are updating, we are reviewing and updating the PHG so I can't comment on ongoing work, but I can speak what was done leading up to our current public health goal*."



4. None of "robust mechanistic toxicity assessments of cancers in the oral cavity and stomach [sic] between 2011 and 2019" claimed that the MOA for rat oral cavity tumors involved hyperplasia. Critically, a top tier transgenic rodent mutation assay in the oral cavity of Big Blue® F344 rats was negative for mutation at the highest Cr(VI) concentrations employed in the 2-year NTP cancer bioassay:
   a. Thompson, C. M., Young R. R., Suh M., Dinesdurage H. R., Elbekai R. H., Harris M. A., . . . Proctor D. M. (2015). Assessment of the mutagenic

potential of Cr(VI) in the oral mucosa of Big Blue® transgenic F344 rats. *Environ Mol Mutagen*, 56, 621-628. DOI: 10.1002/em.21952.

5. Targeted MOA research is intended to inform risk assessment of specific tumor locations. As noted above (see #2), several organizations have used the MOA research on Cr(VI) to support recent risk assessments. Therefore, we do not understand the use of the word 'if' in the first sentence:

   "If considering the mouse and rat drinking water exposure papers only, there is strong support for a non-mutagenic mode of action involving chronic wounding of intestinal villi and crypt cell hyperplasia. This was the basis of the Health Canada conclusion which placed more emphasis on oral exposures and mode of action studies most relevant to the critical effect endpoint and less emphasis on other endpoints or routes of exposure."

October 7, 2019 SSAB Meeting

We would also like to clarify some of the statements made at the October 7, 2019 SSAB meeting. Below are excerpts from the recordings available on the DEQ website:

1. Dr. Dorman stated: "So what I'm asking is for us, it's more procedural, is there a guideline that we have to follow or should follow with respect to being able to go from a threshold to a non-threshold to threshold response? Is there actually a set of rules that say, 'For compound X, it has to meet these assumptions in order for us to switch over to a threshold mechanism of [inaudible 00:20:29]'?"
   a. This statement implies that the SSAB is not being guided by the best available science, but rather by a set of rules or "guidelines" members may believe they have to follow. Please clarify whether the SSAB has received such guidelines, and if so, please provide the public with a copy of such guidelines.

2. Dr. Dorman stated: "So I'm sorry, I'm looking at the guidelines…Nonlinear approach should be selected when there is sufficient data to ascertain mode of action and conclude then it is not linear at low doses and…the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses. It's in their 2005 guideline. It's two pieces. So it does say, and, it's not mutagenic. So that's on page 3-22, paragraph one. That was when I went back and read that guidelines, it's not an 'or' it's an 'and' statement."

   a. The U.S. EPA guidance is not as black and white as Dr. Dorman's reading implies. The U.S. EPA (2005) Guidelines for Carcinogen Risk Assessment (page 3-22) state:

      A nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not

> demonstrate mutagenic or other activity consistent with linearity at low doses. **Special attention is important when the data support a nonlinear mode of action but there is also a suggestion of mutagenicity.** Depending on the strength of the suggestion of mutagenicity, the assessment may justify a conclusion that mutagenicity is not operative at low doses and focus on a nonlinear approach, or alternatively, the assessment may use both linear and nonlinear approaches.
>
> Both linear and nonlinear approaches may be used when there are multiple modes of action. **If there are multiple tumor sites, one with a linear and another with a nonlinear mode of action, then the corresponding approach is used at each site.** If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur. Modeling to a low response level can be useful for estimating the response at doses where the high-dose mode of action would be less important. (**emphasis added**)

b. The EPA guidance addressing the issue of multiple tumor sites, one with a linear and another with a nonlinear MOA, is directly relevant to the SSAB discussions where members appear to apply proposed MOAs in other tissues to the small intestine. For example, rather than considering different MOAs per the EPA guidance, Dr. Dorman later seems to imply that mutation data from the liver negates the negative mutation data in the intestine. Dr. Kenyon later posits that the MOA for Cr(VI)-induced lung tumors is known to be "mutagenic" when, in fact, several prominent research groups argue that MOA for lung tumors involves non-mutagenic mechanisms (e.g., epigenetics). Such mechanisms are not synonymous with a mutagenic MOA.

3. Dr. Dorman stated: "The other thing about the Canadian assessment is that they dismissed mutagenic effects seen with chrome 6 in tissues other than G.I. tract. because they were looking for that there would have to be close [inaudible] for mutagenic responses. So if it was a mutagenic response in liver, since there had not been any tumors identified by NTP in liver, they said that was less relevant. But, again, when you look at the total evidence across multiple organs, it shows mutagenic abilities. So, you come back and you have to ask is [inaudible 01:15:55] major driver for the mode of action data and that, again, that's the

challenge that we're faced with, that's what Canada was faced with. You know, it kind of comes back to my original question that what's our rules that we're playing under?"

a. As noted previously, this comment appears to reference "rules" instead of a transparent assessment of the best available science. We are aware of transgenic mutation studies conducted in the 1990s that reported mutations in the liver of mice exposed to 40 mg/kg chromium by i.p. injection. Notably, administration of this dose in a small i.p. injection volume implies a concentration of ~4000 ppm chromium, which is an extremely concentrated dose that is likely to cause local tissue damage and perhaps oxidative damage. Other shortcomings of this study are the small sample size and control animals that were not exposed to vehicle (i.e., completely unmolested controls). In short, these off-target mutation results by a non-physiological route of exposure provide little insight to the MOA for the tumors in the NTP bioassay. Moreover, no liver neoplasms were observed in the NTP bioassay.
b. Current OECD guidance on transgenic mutation studies state: "In general, the anticipated route of human exposure should be considered when designing an assay. Therefore, other routes of exposure (such as, drinking water, subcutaneous, intravenous, topical, inhalation, intratracheal, dietary, or implantation) may be acceptable where they can be justified. Intraperitoneal injection is not recommended since it is not a physiologically relevant route of human exposure." (OECD TG 488, 2013).

4. Dr. Dorman stated: "Is there a downside to our recommending to the state that they pursue calculation of both numbers to bring those back [inaudible] seem rare. I mean we're making some assumption that the non-linear and linear approaches would have very different numbers."

a. The SSAB should have investigated the quantitative implications of linear and non-linear extrapolation. The linear extrapolation proposed by NJDEP, EPA, and OEHHA (all based on Dr. Stern's analysis) suggest cancer risks at current background exposure levels and lower. Linear extrapolation leads to acceptable concentrations of Cr(VI) in drinking water at something less than 100 ppt depending the exposure assumptions used. Importantly, the USEPA UCMR monitoring data for Cr(VI) in North Carolina drinking water suggests an average concentration of 150 ppt and maximum detect of 11,000 ppt. A non-linear approach leads to acceptable drinking water concentrations for Cr(VI) much closer to the existing EPA MCL of 100 ppb for total chromium (that assumes 100% hexavalent chromium) with significant peer reviewed science to support this approach. Clearly, MOA and selection of a linear or nonlinear approach will have a dramatic impact on the perceived safety of North Carolina water supply.

We appreciate the opportunity to provide feedback on the scientific discussions at the recent SSAB meetings. Please do not hesitate to contact me with any questions or concerns.

Sincerely,

Chad Thompson, PhD
Director, Mechanistic & Computational Biology
ToxStrategies, Inc.
23501 Cinco Ranch Blvd.
Suite B226
Katy, TX 77494