

**Document** - Draft Public Health Goal for Hexavalent Chromium in Drinking Water , OEHHA, California Environmental Protection Agency, August 2009

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The following is a review of the Draft Public Health Goal document for hexavalent chromium in drinking water (OEHHA, August 2009). Overall, this draft report is a well documented compilation of information on the metabolism and toxicity of Cr(VI) and on the evidence of the carcinogenic potential of Cr(VI) via the oral route. Specific comments/clarifications on the list of topics to be reviewed (from Attachment 2 of the Peer review request) are discussed below.

***I. Accuracy of the information presented on metabolism, toxicity, mode of action and exposure, including the potential for carcinogenicity and reproductive toxicity***

As detailed in the report, Hexavalent chromium is already recognized as a potent lung carcinogen (IARC and ATSDR reviews). Although older oral exposure studies such as Anwar et al, did not show any carcinogenic response in dogs, these studies were plagued with deficiencies (only 2 animals per dose etc). The Borneff study in mice also had several limitations. However, OEHHA's re-analysis of the data reveals an increase in forestomach tumors associated with exposure to hexavalent chromium.

Relatively few studies in the literature address the oral toxicity of Cr(VI). The Zhang and Li (1987) human study reported on health effects in 155 Chinese villagers who consumed drinking water contaminated with hexavalent chromium at 20 ppm. However, this study has its limitations as well, short latency period, there is only one exposure level in the study, remediation efforts had reduced the concentrations in the ground water by 1967 (as reported in the article by Smith and Steinmaus, 2009) so the actual exposure and level is unclear, no information on other possible contaminants in the water and no clear data if the villagers were also exposed to inhalable levels of Cr(VI). However, the study of Zhang and Li and recent re-analysis by Beaumont et al. 2008, suggests that gastrointestinal effects in humans may occur at an exposure level of 20 ppm of hexavalent chromium in drinking water. It is unfortunate that there is no other available epidemiological data in humans for low levels of exposure to Cr(VI) such as the total chromium study in Nebraska.

In addition, the facts compiled in this report demonstrate that the capacity of the saliva and gastric fluids to reduce hexavalent chromium in water will not be exhausted at levels that are likely to be ingested by humans. It has been previously suggested that the absorption of hexavalent chromium would occur only when the reduction capacity of the saliva and gastric

fluids is overwhelmed at high doses. The data in humans and rodents indicate that absorption occurs at all doses. This indicates that there is no threshold likely and further justifies the use of the linear extrapolation approach for the risk assessment.

Based on the evidence presented in this report, it is clear that Cr(VI) is genotoxic in vitro, in vivo in animals and in humans. Genotoxicity is seen in humans and animals when Cr(VI) was administered via multiple routes. Unfortunately the oral cavity or digestive system tissues of exposed animals have not been tested for genotoxic effects.

As discussed in the report, exposure via the presence of Cr(VI) in drinking water is likely to be via drinking the water, possible dermal exposure in the shower and potential inhalation in the shower. Of these, the maximum exposure will occur by ingestion of Cr(VI) in the drinking water.

In my opinion, except for the specific clarifications listed below, the topics of metabolism, mode of action, toxicity and carcinogenicity have been adequately addressed in this draft document.

Specific clarifications for this section -

1. Section Immunotoxicity (page 58) - Chromium is the one of the most common contact sensitizers. According to the ATSDR report on Chromium, "Estimates of the prevalence of chromium sensitivity in the general U.S. population range from 0.08 to 7%, depending upon the population evaluated..... **However, oral exposure to chromium(VI) has been shown to exacerbate dermatitis of sensitive individuals.**" As mentioned in this draft PHG document, it is estimated that there will be no response at concentrations below 4-5 ppm. I agree that although there is no definitive study or data that links oral exposure and bathing or swimming to increased incidences of Cr (VI) related Allergic Contact dermatitis, it is important to acknowledge that the 4 ppm cutoff level has several uncertainties. Although the Felter and Dourson study did show no responses are likely to be detected below 4 ppm of Cr(VI), there are several factors that affect the interpretation of the results – individual susceptibility, different compounds used in the testing and the fact that levels required to elicit a reaction in previously sensitized persons will be quite variable.
2. On page 40 under Section Summary about Genotoxicity, the authors comment that "It is unclear whether inhalation exposures among workers are also associated with cancers of the digestive system and other non-respiratory sites. Given what is known about the toxicokinetics of hexavalent chromium, the likelihood of detecting a carcinogenic response at non-respiratory sites in workers exposed via inhalation is uncertain, because a relatively small portion of the inhaled dose would be expected to reach non-respiratory sites." But later in section on Cancers of ingestion- and digestion-related organs reported in occupational studies (page 61), the authors' present data that is indicative of such an effect.

3. On page 8, under the heading Dermal route, results from the Corbett et al., 1997 study are reported. The average value of Cr(VI) in the urine of the 4 volunteers is listed. What is the standard deviation of this value? I do not have ready access to this article. It is already a small sample size (N=4) and there is bound to be variability. I am sure any evidence of variability will still not dramatically change the contribution likely from the dermal route but it would be good to list the std. deviation for clarity purposes.
4. In the Summary section, page 2, last paragraph, it is mentioned that “Review of occupational studies in which humans were exposed to hexavalent chromium primarily by the inhalation route revealed an increase in stomach cancer, which suggests that cells in the stomach are being exposed to hexavalent chromium, although the primary exposure route was inhalation.” As detailed in the Results section (page 61) of Cancers of ingestion- and digestion-related organs reported in occupational studies, this data is indicative but not all-conclusive. Therefore the summary statement must be revised to reflect that.
5. As presented in Appendix II, it is believed that infection with *Helicobacter pylori* is likely to increase susceptibility to the occurrence of stomach cancers, this hypothesis should not be relegated to the Appendix section or to a small comment in the Sensitive subpopulation section but at least a summary/synopsis should be discussed within Sensitive subpopulations.
6. Comments by reviewer Dr. Robert Gwiazda, (Detailed review, point A) has raised an important point “It is assumed that the fraction of Cr(VI) that is reduced to Cr(III) is the same at high exposures, at the point of departure, at lower exposures and at the protective level.” What is the authors’ view on this? Currently it is not clear if low doses of Cr(VI) will also evade reduction and/or cause DNA damage in the oral cavity or GI tract.
7. In response to Dr. Leonard Bjeldanes comment about the rodents being more sensitive to Cr(VI) toxicity than humans – OEHHA’s authors have responded that the oral absorption appears to be quite similar in rodents and humans. The references depicted by the authors’ shows a range of 2-8 % (including the Donaldson and Barreras 1966 study in humans with pernicious anemia) in humans and 2% in rats (only one reference). I think it is not correct to argue that the absorption is similar. Looking at the data, one can argue that there is high variability in humans and this is likely in rats as well. There is not enough evidence to assume that the absorption is the same.

**II. *Selection of the NTP data set and supporting information extrapolation to humans, particularly regarding interpretations of carcinogenicity data and mechanism***

There are limited studies that address the carcinogenicity of Cr(VI) when administered via the oral route. As listed in the section above and as clearly elucidated in the Draft report (Page 33-34 and Table 1), all of the older studies have several limitations that make it difficult to use them for a quantitative risk assessment. The latest state of the art NTP cancer bioassay in 2007 provides additional evidence of carcinogenic activity via oral route and clearly demonstrates evidence of cancer in the oral cavity in rats and cancer of small intestine in mice when Cr(VI) was administered in drinking water. Therefore, it is logical to use this study for the derivation of the PHG. Amongst the various datasets in the NTP study, the most sensitive species and the most sensitive endpoint were chosen for the risk assessment thereby adding further conservativeness.

It is acceptable to use the NTP carcinogenicity bioassay to predict cancer in humans. As also discussed in the EPA Cancer guidelines 2005, tumors in animals are assumed to indicate the potential of the chemical to cause cancer in humans. Although it might seem impractical from a human exposure point of view, typical cancer bioassays are conducted with large doses of chemicals in order to demonstrate the potential for a chemical to cause cancer. Because small populations are used, it is necessary to use large doses of chemicals to demonstrate an effect.

It is interesting to note that the cancers in the various oral studies are all different – NTP 2007b rats – cancers of the upper alimentary tract, NTP 2007b mice – cancers of the lower alimentary tract, Borneff study – tumors in forestomach of the mice, and stomach cancer in the Chinese epidemiological study. It appears that there is no clear hypothesis to explain these differences.

**III. *Appropriateness of the risk assessment methodology used for extrapolation to human exposure to Cr6 in drinking water***

Based on the more sensitive species, dose response curves seen in the NTP study (2007b) were used to extrapolate to zero and a LED 10 was then determined. Based on the superior fit of the male mice data, the linearized multistage model, a model that is widely used in risk assessment, was then used to determine the Cancer slope factor. Inhalation cancer potency has also been calculated based on an occupational exposure study. This covers the possible inhalation exposure to Cr(VI) during showering.

The risk assessment methodology used in this review is conservative but it is largely consistent with current EPA guidelines (US EPA cancer guidelines 2005) and OEHHA's own recent guidelines (OEHHA 2009). These approaches have been used in the risk assessment of several other carcinogens.

Specific clarifications or corrections about this topic are listed below -

1. The Health protective level of 2 ppb for non-carcinogenic effects derived in this document is based on the body weight of a child and the respective water consumption. However the current draft PHG for cancer effects does not account for effects in children. As stated in the Attachment 2 of the Peer review request documents, this PHG is intended to protect the ENTIRE population from a lifetime of exposure from cancer and non-cancer effects. The attachment 2, page 10 suggests that since this PHG assessment was completed prior to the release of the OEHHA's own guidelines for early life exposures, this important aspect was not included in the risk assessment. This is unacceptable since the USEPA Supplemental Guidance for assessing susceptibility from early life exposure to carcinogens (2005) was already available for reference. Evidence in literature suggests increased susceptibility to cancer from early-life exposure, particularly for chemicals acting through a mutagenic mode of action (Barton et al., 2005, USEPA Supplemental Guidance 2005 and OEHHA 2009). The EPA Supplemental Guidance recommends using appropriate modifications to the cancer potency slope. The PHG derivation should take into account an age dependent adjustment factor (ADAF) or age sensitivity factor (as also recommended by OEHHA's own guidelines).. **The PHG needs to be recalculated accordingly.**
2. There is no explanation in the draft document on why the multistage model and corresponding LED 10 value was picked for derivation of the cancer slope factor when there are other LED 10 values with higher potency (such as the Quantal linear model in male and female mice) that could have been more conservative and health protective. I did notice that in response to one of the reviewers' comment (Page 13 of Responses to comments), the authors have detailed that this is based on the California Code of Regulations. If this is the reason the multistage model was chosen, an explanation needs to be included in the Draft document so it is clear to all readers.
3. On page 43 under the NTP 2007b study, the body weight gains of the rat are discussed but there is no mention about the water consumption. Please add a few sentences to explain the water consumption, which presumably is just like the mice data which was reduced in the highest dose groups (this is mentioned in the Mice section, Page 47).
4. As detailed on Page 46 under the section Neoplasms, it is indicated that in the NTP 2007b study there were other tumors in male rats (benign pheochromocytomas) and female rats (adenomas in the clitoral gland). The authors have not indicated how many animals were affected and what is the historical rate of such tumors in male and female rats? Has NTP addressed these tumors? Is there an explanation on their occurrence and their significance? Can they be dismissed even though they were statistically significant?

5. First sentence on Page 54 mentions that “There was very little evidence of toxicity in rats treated with hexavalent chromium.” The occurrence of tumors and other effects definitely indicates toxicity. I think this should read “There was very little evidence of clinical toxicity in rats treated with hexavalent chromium.”
6. Similarly, the sentence under the MTD- Mice section Page 55 should be changed to include “clinical signs of toxicity”.

**IV. *Identification of the uncertainties in the risk assessment and proposed PHG calculation***

As expected with Risk assessments of this nature, there are bound to be uncertainties and conservative assumptions and these have been well characterized in this document

In addition, the uncertainty factors for the derivation of the HPD for the non-cancer have been clearly elucidated.

**V. *Other comments are listed below:***

1. The subheading Physiologic and Nutritional role (page 21) under the section on Metabolism and Pharmacokinetics seems unnecessary. The last sentence (about dietary intake of chromium) of this point on nutritional role has been discussed under Food (page 6). I think that there is no specific need to mention it again here. The first two sentences of this paragraph can also be mentioned under Food and this heading eliminated from this section.
2. The heading on Page 22 is Toxicological effect in Animals and Plants but there are no effects in plants discussed anywhere in the document. The index should also be changed accordingly.
3. On page 56, the last sentence in the first paragraph under the heading Non-oral routes reads “Although the data are rather sparse, it appears that rodents are relatively insensitive to hexavalent chromium when it is administered by inhalation.” Did the authors mean to write trivalent chromium since it is apparent that hexavalent chromium causes toxicity via inhalation in rodents?
4. Under the heading, Cancers of ingestion and digestion related organs reported in occupational studies (Page 60-65), the authors have detailed the Methods and Results of their analysis, for completeness, a small paragraph of Discussion/Conclusion/Summary should be included at the end of this section that indicates the conclusion of the authors based on the results i.e the presence of a “suggestive link between inhalation exposure in epidemiological studies and ingestion related cancer”.

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5. It appears as if undue time/space is devoted to the Helicobacter hypothesis and Borneff study, these could be remnants of an earlier hypothesis or arguments from the earlier draft proposal by OEHHA. Since this hypothesis is not provable given the current facts and it doesn't add any value to the current derivation of the PHG, Appendix II can be condensed considerably. I do agree that it adds to the argument that Cr(VI) is carcinogenic orally but this can be represented in a short summary in the main document itself .
6. In Appendix II, the Borneff study is described in multiple places. There is no need to elaborate on the study design again in Page 135; it could just refer to the details in the earlier paragraphs (Page 121).
7. Under the section Vagotomy (page 133), it would be clearer to add 1-2 sentences to describe what it is and why it is used.