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November 2, 2009

Mr. Michael Baes
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1515 Clay St. 16th Floor
Oakland, California 94612
Attn: PHG Project

Re: Comments on the Draft Public Health Goal of Hexavalent Chromium [Cr(VI)] of August 2009 by the California Manufacturers and Technology Association (CMTA)

Dear Mr. Baes:

Please include the attached comments on the Office of Environmental Health Hazard Assessment's (OEHHA) draft CrVI public health goal (PHG) released for public comment in August 2009. We believe that these comprehensive comments address the many weaknesses in the proposed PHG requiring further evaluation and appropriate change to the proposed PHG at this time. We further believe that the now ongoing research at The Hamner Institutes will result in the provision of critical scientific findings which may have significant impacts on the level and scientific credibility of the PHG for CrVI proposed by OEHHA. Since the Hamner Institutes research will be completed within the coming year we ask that OEHHA consider waiting to finalize this PHG until OEHHA has considered the findings of that research.

Thank you for the opportunity to comment.

Sincerely,

Michael J. Rogge
Policy Director, Environmental Quality

1115 Eleventh Street, Sacramento CA 95814-3819

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Comments on the Draft Public Health Goal (PHG) for Hexavalent Chromium [Cr(VI)] of August 2009

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November 2, 2009

Comments on the Draft Public Health Goal (PHG) for Hexavalent Chromium [Cr(VI)] of August 2009

The California Manufacturers & Technology Association (CMTA) has conducted a detailed review of OEHHA's draft Public Health Goal (PHG) document for hexavalent chromium [Cr(VI)] and submits these general and specific comments. Our specific comments expand on points raised in the general comments and provide additional information, with references and supporting examples.

General Comments

Our review indicates that substantial revision to the current document is needed to more thoroughly and accurately summarize and present the current state of knowledge regarding oral and inhalation exposures to Cr(VI). We have noted:

- There are many errors in the document, including instances where the scientific literature has been misquoted or misrepresented. Of particular concern is the review of epidemiological evidence for cancer of the gastrointestinal (GI) tract, which is not only incomplete and inaccurate, but also misleading.
- The literature review is also incomplete and dated throughout, and valuable new publications are not included.
- OEHHA's approach to the critical evaluation of data for Cr(VI) does not follow the latest U.S. EPA (2005) guidelines for human cancer risk assessment, nor does it follow the Human Relevance Framework recommendations made by regulatory agencies in the US and Canada and by an international team of experts.
- OEHHA has failed to integrate and interpret findings in one type of study given the information presented in another type of study into a weight-of-evidence analysis and narrative. For example, the discussion of kinetics describes the detoxification of Cr(VI) by reduction following ingestion. However, the conclusion that Cr(VI) is genotoxic in various *in vivo* studies fails to consider that these studies administered Cr(VI) by routes of exposure that by-passed the detoxification mechanisms that normally operate in biological systems when exposed to Cr(VI) in drinking water. Genotoxicity data for Cr(VI) administer by drinking water are almost entirely negative. This is an example of the lack of integration of genotoxicity data with pharmacokinetic data.
- It is also clear that OEHHA has not adequately addressed the University of California peer reviewers' comments, and has completely disregarded the important and highly critical comments of the Department of Toxic Substances Control (DTSC).
- Correction of these errors and omissions would show that the proposed PHG is extremely uncertain, and that the scientific evidence and best risk assessment practices support a PHG that is orders of magnitude higher.

OEHHA failed to systematically evaluate the Mode of Action (MOA) for small-intestine tumors in mice reported in the National Toxicology Program (NTP) study. Federal and international guidance for risk assessment clearly requires evaluation of the MOA and human relevance (termed the Human Relevance Framework [HRF]) through a structured analysis, identifying key events, the temporal occurrence and dose-response for key events, and whether they are qualitatively and quantitatively relevant for human exposures (U.S. EPA 2005; ILSI Risk Science Institute 2005; Sonich-Mullin et al. 2001; Cohen et al. 2004). Although OEHHA suggests that the MOA is mutagenicity, in the target tissue (small intestine), genotoxicity data are negative (DeFlora et al. 2008). This undermines the credibility of mutagenicity as the MOA for small-intestine tumors in mice, and further, indicates that mutagenicity is not operative in the low dose range. Full consideration of the genotoxicity data could lead to the conclusion that a non-genotoxic mode of action is operative, which would result in a PHG that is two orders of magnitude higher. The lack of an MOA/HRF evaluation is a fundamental flaw for evaluating risk in the low dose range and must be addressed in the PHG document. The California Health and Safety Code (Cal H&SC) specifically requires that OEHHA employ the most current practices and methods used by health science experts when proposing a new PHG [Cal H&SC Sec.116365(c)(1)]. The current draft PHG document does not meet this requirement.

OEHHA's analysis relies solely on those studies in which the kinetics, genotoxicity, toxicology, and epidemiology of Cr(VI) was evaluated at high doses, and it uses those studies to assert positions that are not supported by available data for exposures to Cr(VI) that are environmentally relevant. For example, OEHHA's analysis of a threshold for carcinogenicity is based on tissue accumulation data for rodents exposed at drinking-water concentrations greater than 5 mg/L, but tissue accumulation data published by Sutherland et al. (2000) showed no accumulation of chromium in tissue at exposures an order of magnitude less (i.e., 0.5 mg/L). At 5 mg/L and higher, it is evident that Cr(VI) was not entirely reduced in the stomach, but observations at more relevant exposures do not support OEHHA's position that there is no threshold for carcinogenicity. Further, genotoxicity data from drinking-water exposures in humans and animals are overwhelmingly negative and consistent with studies of Cr(III), because Cr(VI) is reduced to Cr(III) before systemic absorption of Cr(VI) can occur. Rather than using the most relevant *in vivo* genotoxicity data, OEHHA focuses on older studies, where Cr(VI) is administered by non-drinking-water routes at extraordinarily high doses that do not reflect human exposures. OEHHA's reliance on high-dose data permeates the document, and many additional examples are provided in the specific comments.

OEHHA should use physiologically based pharmacokinetic (PBPK) modeling to quantify the extremely important interspecies differences in kinetics between rodents and humans, and to extrapolate from the high exposures of the NTP study to environmentally relevant exposures. The default approaches in the current draft do not account for interspecies differences in GI anatomy and physiology, which specifically affect target tissue dose, nor do they account for potential differences at low-concentration exposures. Addressing these factors is highly critical to setting a credible Cr(VI) PHG. Without the use of PBPK modeling, the resultant PHG is established without using the best available

science. Further, PBPK modeling can be used for evaluation of sensitive subgroups with reduced gastric acid production and/or conditions that result in a more neutral pH level in the stomach. We recognize that the currently available PBPK models for Cr(VI) (O'Flaherty et al. 1996, 2001) are limited in their ability to quantitatively address target tissues, but ongoing research at The Hamner Institutes will result in refined PBPK models for mice, rats, and humans within a year. Further, it is expected that U.S. EPA will include PBPK modeling in its update of the Cr(VI) IRIS file, currently planned for completion in 2010. PBPK modeling is essential for accurate extrapolation across species to arrive at a scientifically defensible risk assessment. Full consideration of the kinetic data leads to the conclusion that the dose response is sublinear in the low dose range, which would which could significantly affect the assumptions used to develop the PHG.

The non-cancer PHG was developed using methods that are inconsistent with current OEHHA guidance. Current OEHHA guidance for development of chronic reference criteria recommends using benchmark dose (BMD) methods to quantify the dose-response and lessen the need for large uncertainty factors. Using BMD analysis of the same NTP data set (chronic inflammation of the liver in female rats of the NTP study), the Agency for Toxic Substances Disease Control (ATSDR 2008) calculated a Health-Protective Dose (HPD)-equivalent for Cr(VI) that is seven times higher than that developed by OEHHA for the non-cancer PHG. Further, the derivation of the non-cancer PHG also did not adequately consider questions, highlighted by the NTP, about the biological significance of nonneoplastic liver effects at low doses, particularly in light of the high background levels of these effects in control animals, and potential gender and species differences in Cr(VI) pharmacokinetics and pharmacodynamics suggested by the NTP (2008) study results. Finally, it should be recognized that the non-cancer risk assessment could similarly benefit from PBPK modeling, to characterize interspecies differences in kinetics, and a HRF for non-cancer effects (Boobis et al. 2008; Seed et al. 2005).

We recommend that OEHHA make substantial revisions to the current draft PHG document. For development of a PHG that meets the requirements of the California Public Health Code, OEHHA must:

1. Update the literature review, addressing the many errors and omissions identified herein and by others during public and peer review, and also correct the scientific deficiencies and substantially revise the current draft.

2. Revise the PHG document to address the spirit and specific content of the UC peer reviewers and comments of DTSC.

3. Include a MOA/HRF evaluation for cancers of the mouse small intestine. There are recognized uncertainties in the currently available MOA data, so we recommend that OEHHA utilize the research that is currently under development at The Hamner Institute for Health Sciences to fill data gaps in the MOA and provide additional information to quantify the differences in reducing capacity across doses and species. With these data, it is possible to develop a PHG that

utilizes the best available science and is protective of public health for Californians exposed to low levels of Cr(VI) in drinking water; however, without the MOA/HRF evaluation, the analysis is fatally flawed.

4. Focus the literature review and analysis in all sections on data that are most relevant to current human exposures to Cr(VI) in California drinking water. Specifically, concentrate on data collected using *ad libitum* drinking-water administration and at concentrations that most closely represent reasonable drinking-water exposures in California.

5. Provide a balanced review of the epidemiologic literature, using accepted methods, specifically addressing the human relevance of cancers consistent with the findings of the NTP study by focusing on oral cavity and small-intestine cancers, and evaluating epidemiologic findings for exposures to Cr(VI) at levels that are relevant for the California drinking-water supply.

6. Use benchmark dose (BMD) modeling for the non-cancer PHG, and a weight-of-evidence analysis to determine appropriate uncertainty factors, which is consistent with OEHHA guidance.

7. Use PBPK modeling tools under development at The Hamner Institutes or U.S. EPA to evaluate tissue dose, extrapolate between species, and evaluate sensitive subgroups.

8. Include a quantitative and expanded qualitative uncertainty analysis. This should include an evaluation of the uncertainties in each significant science policy choice that is made in the derivation of the PHG and the quantitative impact of science policy choices and the scientific support for alternatives.

These revisions and refinements are essential for reliable cancer and non-cancer risk assessments of Cr(VI) in California drinking water, and for determination of a health-protective, yet reasonable, PHG for Cr(VI). To meet its responsibilities to the public, OEHHA must objectively describe the inherent uncertainties in the data available to describe the MOA. and quantify the impact of the uncertainty on the proposed PHG. For example, OEHHA's assumption of a mutagenic MOA for small intestine tumors, an assumption made without scientific support and specifically contrary to the only available GI genotoxicity data, results in a PHG that is at least two orders of magnitude lower than that which would be calculated if the MOA was not mutagenicity and non-linear. To increase credibility in the PHG and reduce uncertainty, we strongly recommend that OEHHA complete the PHG document after the results of the ongoing research efforts at The Hamner Institute are available.

Specific Comments

Specific comments are provided regarding OEHHA's revisions based on the UC peer-review comments (Comment 1), and those prepared by DTSC (Comment 2). Thereafter,

comments are presented in the order of the text citation in the draft PHG document. The page number in the PHG document to which the comment refers is provided, as well as the text of the PHG document cited. The text of the PHG document is italicized. Our comment follows the quoted (italicized) text.

Specific Comment 1: The PHG document does not adequately address the comments of the UC peer reviewers.

Review of the UC peer-reviewer's comments and OEHHA's responses indicates that OEHHA did not adequately address the review comments. Specifically:

1. The peer reviewers repeatedly emphasized that the approach used to extrapolate from high-dose animal data to set a PHG was crude and overestimated risk in the low dose range. We strongly agree with this general observation, and with the specific points identified in the peer reviews with regard to this issue.

2. Dr. Gwiazda, of UC, pointed out that all the studies presented in the documents that were specifically cited to support the PHG, administered Cr(VI) at doses that are several orders of magnitude higher than drinking-water exposures in California and the proposed PHG. OEHHA's response and arguments provided in the PHG document do not respond to Dr. Gwiazda's comments, because: 1) systemic absorption is not necessary for tumors of the GI tract to occur, because these tumors resulted from direct contact of high concentrations of Cr(VI) in lumen with epithelial tissues of the small intestine, and 2) OEHHA's kinetic arguments rely entirely on high-dose and gavage studies, ignoring the important findings in the lower dose range in a number of studies. Specifically, OEHHA relied on studies of chromium administered at >5 mg Cr(VI)/L, but Sutherland et al. (2000) found **no** increase in chromium tissue levels following drinking-water exposures of 0.5 mg Cr(VI)/L for 44 weeks in rats. This finding specifically refutes OEHHA's arguments regarding the lack of a threshold, more appropriately described as sublinearity in the low dose range, but this issue has not been addressed.

3. OEHHA's responses to some of the peer reviewers' comments were not technically correct. For example, in response to Dr. Gwiazda's comment number 6, regarding OEHHA's argument against the existence of a threshold based on kinetics and genotoxicity data associated with the "peculiarities of a gavage study," OEHHA states, "Given that CrIII is not associated with genotoxicity, this finding indicates that not all the administered CrVI was reduced to CrIII. Otherwise, no genotoxicity would have been observed." However, this statement is incorrect. Bagchi et al. (1995), a study cited by

OEHHA in the PHG document, shows that Cr(III), a cationic metal, is nearly as genotoxic as Cr(VI) when administered by gavage.[1]

4. Further, in response to Dr. Bjeldanes, OEHHA states (Response 2), "No marked increase in oral absorption of hexavalent Cr was observed with dose, which would be expected if the reducing capacity of the GI tract had been overwhelmed." However, as noted above, OEHHA overlooked the findings of Sutherland et al. (2000)—another paper cited in the PHG but not carefully considered—of no chromium absorption at exposures of 0.5 mg/L, administered *ad libitum*, which is still far higher than exposures to Cr(VI) in drinking water in California and the proposed PHG. At higher exposures of >3 mg/L, Sutherland et al. (2000) observed chromium accumulation in tissues consistent with the observations of other researchers for high-dose exposures. OEHHA used only high-dose exposure data to justify its position of linear extrapolation from high to low doses, which is a critical flaw in the evaluation.

5. OEHHA did not make the simple corrections to the document that were pointed out by Dr. Gwiazda, for issues that were factually incorrect or unclear. This is evident, because the statements corrected by Dr. Gwiazda appear uncorrected in the current draft.

6. Dr. Gwiazda stated that the uncertainty in the PHG should quantitatively addressed. Although OEHHA's response to Dr. Gwiazda was that such an analysis is infeasible, we disagree. As discussed herein, it is possible to quantify the uncertainty associated with the assumptions used to derive the PHG. OEHHA should provide a thorough qualitative and quantitative uncertainty analysis.

7. Most of the substantial uncertainties identified by the three peer reviewers will be addressed through additional ongoing research, designed to quantify tissue dose in animals and humans via PBPK models, and to evaluate biological response to Cr(VI) at environmentally relevant exposures. Importantly, research specifically addressing each is being conducted at The Hamner Institutes and will be completed in less than one year.

Specific Comment 2: The PHG document does not adequately address the comments offered by the Department of Toxic Substances Control (DTSC).

In October of 2008, The California EPA DTSC offered comments that were highly critical of the pre-released draft PHG document (Attachment 2). These comments were

[1] Bagchi et al. 1995 reported an increase in DNA single strand breaks of 1.7 and 1.5, respectively, following admistraiton of Cr(VI) and Cr(III), 48 hours after administreation, at equitoxic doses.

not addressed. DTSC offered many excellent comments that should be considered by OEHHA in a revised PHG document. Most notably, we specifically agree with the following points, both for the reasons identified by DTSC and based on our own findings from reviewing the scientific literature:

1. PBPK modeling should be used to quantify the effective dose at the target organ. Use of a PBPK model refines both the cancer and the non-cancer risk assessments, because it can address the interspecies scaling uncertainty factor. Simple allometric scaling is inadequate for a site-of-contact-based carcinogenic MOA, because target tissue dose cannot be quantified adequately for the purpose of scaling to humans.

2. Risk assessment should be based on an MOA evaluation that considers the key events necessary for carcinogenicity and whether those key events, such as inflammation and hyperplasia, can occur at environmentally relevant exposures to Cr(VI) in California's drinking water.

3. OEHHA's highly conservative approaches substantially overestimate the carcinogenic potency of ingested Cr(VI).

4. Historical occupational exposure to Cr(VI) resulted in exposure of oral cavity tissues to Cr(VI), yet no study has reported a significant excess of oral-cavity tumors among workers, an observation consistent with OEHHA's review of the epidemiology literature presented in the PHG document. This lack of concordance in tumor sites between humans and rats should be discussed. The oral-cavity tumors in rats, which did not occur in mice, appear to be a species-specific observation.

5. The MOA for small-intestine tumors in mice has not been adequately addressed. The NTP data suggest that an MOA associated with chronic local inflammation, induced by chronic tissue damage, resulting from direct contact with high-dose Cr(VI), is a promotional mechanism that is likely not relevant at environmental exposure levels.

6. Tumors in the small intestine appear to be related to direct contact of the small-intestine epithelial tissues with high doses of Cr(VI); therefore, species-specific variability in GI anatomy and physiology are critical to understanding the relationship between observations in mice and relevance to low-concentration exposure in humans.

7. The inhalation cancer slope factor is based on dated information and an inadequate review of the published literature. Published risk estimates, developed from the original data sets, are available for estimating the lung cancer risk associated with inhalation exposure, and these estimates should be used in developing the PHG.

8. OEHHA's analysis of the mouse stomach's reductive capacity and tissue accumulation (Appendix A) does not provide a clear scientific basis to discount a threshold-based dose-response. The NTP studies clearly demonstrate that over-burdening the GI tract's ability to reduce Cr(VI) to Cr(III) results in overt tissue damage at the site of contact, as well as chronic inflammation and regenerative hyperplasia.

9. The analysis of the Borneff et al. (1968) et al. study and the Helicobacter hypothesis is highly speculative, lacks relevance, and should be deleted.

10. The Hamner Institute's ongoing studies, which have progressed significantly since the DTSC's comments of last year, are definitely "prerequisites" to any revisions to the OEHHA PHG for Cr(VI).

Specific Comments on Summary and Introduction

Comment 3 Page 2, "*It has been suggested that hexavalent chromium is completely converted to trivalent chromium in the acidic environment of the stomach, and therefore poses a negligible risk of toxicity (carcinogenic or non-carcinogenic) by the oral route (De Flora et al. 1997; Proctor et al., 2002b).*"

This statement, and several others like it in the text of the PHG document, misrepresent the papers cited, and importantly, do not discriminate between observations at very high doses and at lower doses. Neither Proctor et al. or DeFlora et al. indicate that all Cr(VI) is completely reduced at any dose. OEHHA has misunderstood and misrepresented this research. For example, Proctor et al. states, "In short, at concentrations at least as high as the current U.S. maximum contaminant level (100 ppb), and probably at least an order of magnitude higher, Cr(VI) is reduced to Cr(III) prior to or upon systemic absorption. The weight of evidence supports that Cr(VI) is not carcinogenic in humans via the oral route of exposure at permissible drinking-water concentrations" (Abstract, page 701). Clearly, these authors are specifying that reduction of Cr(VI) to Cr(III) is does-dependent.

Additional comments regarding information in the summary are provided herein where they appear in the text. They also apply to similar text in the summary.

Specific Comments on Environmental Occurrence and Human Exposure

Comment 4 (page 5, Water) *"As of February 2002, 483 systems that collectively serve approximately 19.6 million of the state's 34 million people had sampled 32 percent of their sources (CDHS, 2002). Hexavalent chromium was detected in 59 percent of the sources (detection limit of 1 ppb)..."*

This information is out of date. CDPH data for Cr(VI) monitoring is current through February of 2009 and is available on the CDPH website at

http://www.cdph.ca.gov/certlic/drinkingwater/Pages/Chromium6sampling.aspx. OEHHA cites data from 2002 that are not consistent with currently available information. Specifically, Cr(VI) has been detected in approximately one-third of more than 7,000 sources. Levels of 1–5 ppb have been measured in 65% of those sources, levels of 6–10 ppb have been measured in 20.7%, and levels of 11-20 ppb have been measured in 10.5%.

In addition, this discussion should include updated information regarding the widespread nature of Cr(VI) occurrence in drinking water from natural sources, as documented in recent publications (Gonzales et al. 2005; Ball and Izbicki 2004; Kulongoski and Belitz 2005; Oze et al. 2007; Boufounos et al. 2009).

Finally, and most importantly, Cr(VI) in California drinking water occurs widely in the low parts per billion range. OEHHA has relied on studies of animals and humans exposed in the high part per million (ppm) range to develop a PHG that is in the part per trillion range (60 ppt). This is an extrapolation of over five orders of magnitude and is simply not justifiable, given the underlying species differences, kinetics, epidemiologic evidence, and low environmental exposures compared with the animal toxicologic data. The resulting PHG is highly uncertain and overly conservative.

Specific Comments on Metabolism and Pharmacokinetics

Comment 5 (page 11) *"Given that the maximum plausible levels of hexavalent chromium in water that would likely be ingested by humans has been estimated to be less than 5 mg/L, exhaustion of the capacity of saliva and gastric fluids to reduce hexavalent chromium appears unlikely. Moreover, evidence of hexavalent chromium absorption and/or toxicity observed at 10 mg/L or less, and perhaps up to 50 mg/L, would not appear to be a consequence of the exhaustion of the capacity of saliva and stomach fluids to reduce the metal."*

First, it is not reasonable to assume that the maximum plausible level of Cr(VI) that would be ingested by humans is 5 mg/L. This level is 100 times higher than the current MCL in California and far higher than the levels of Cr(VI) measured in drinking water, as discussed in the PHG document and shown by the most current monitoring data. Exposure to Cr(VI) at 5 mg/L is clearly not realistic for Californians.

Second, OEHHA did not correctly consider the kinetic processes that are crucial following ingestion. The critical kinetic process is the rate of reduction, not an estimated capacity for reduction, because reduction and absorption are competing processes, and capacity will be highly variable by species and over time. OEHHA needs to consider the half-life of Cr(VI) reduction in these biological media in order to understand the tissue dose of Cr(VI) at the target tissue. These kinetic processes can be quantified only by using a PBPK model.

Third, OEHHA should consider data that are available for lower levels of exposure that are more representative of human exposures. Finley et al. (1997) found no dose-related

increases in plasma and red-blood-cell (RBC) chromium at ingested concentrations of 0.1 mg/L, and Sutherland et al. (2000) found no increase in chromium concentrations of any tissue in rats exposed to 0.5 mg/L for 44 weeks. OEHHA's discussion of kinetics needs to be revised to address what has been observed in the low dose range.

Comment 6 (page 12) *"In the study of Finley et al. (1997), the percent of the administered dose of hexavalent chromium recovered in the urine did not increase with dose. Therefore, the results of these studies do not indicate that oral absorption of administered hexavalent chromium begins to occur when the reducing capacity of the stomach is exhausted."*

This statement is incorrect. Finley et al. (1997) reported average absorption of 1.7% at 0.1 mg/L and 3.5% at 10 mg/L, which is an increase, and they suggest increased absorption with increased exposure. Also, it is clear that one of the three participants absorbed considerably more when given chromium at 10 mg/L, with 8% absorption. These data demonstrate variability in absorption and are not useful for evaluating reduction capacity. Further, Kerger et al. (1996) found temporarily increased levels of chromium in RBCs and plasma following Cr(III) administration; thus, it is questionable whether these data can be used, as OEHHA has done, to surmise whether Cr(VI) or Cr(III) is being absorbed in these studies. Absorption and reduction are competing kinetic processes that, for the purposes of risk assessment, can best be addressed using a PBPK model.

Comment 7 (page 12) *"Kerger and associates administered hexavalent chromium to humans mixed with orange juice to determine to what degree the acidic-organic environment (somewhat analogous to the stomach) reduces oral absorption of the metal (Kerger et al., 1996a). The addition of hexavalent chromium to orange juice prior to its ingestion was a de facto reductive pretreatment of hexavalent chromium. In spite of this, the fraction of the administered dose of chromium recovered in the urine appeared to be greater for hexavalent chromium than when trivalent chromium was administered (0.6 percent versus 0.13 percent). However, the absorbed fraction was considerably less than when hexavalent chromium was administered in water (6.9 percent)."*

In this statement, OEHHA argues that Cr(VI) was reduced to Cr(III) in orange juice, but on page 16, OEHHA argues that, in the same study, Cr(VI) was not completely reduced to Cr(III) in orange juice.

> *"In the experiment of Kerger and associates involving administration of hexavalent chromium mixed with orange juice (Kerger et al., 1996a), presumably reducing much of the hexavalent chromium, the urinary half-life of the absorbed chromium was still prolonged (15 hours versus 10 hours for trivalent chromium controls). This finding provides additional evidence that mixing chromate with food in an acidic environment somewhat analogous to the stomach does not completely reduce hexavalent chromium to trivalent chromium."*

OEHHA should be consistent in its interpretations of the literature. Certainly, Cr(VI) can be reduced to Cr(III) in orange juice; therefore, the discussion on page 16 is tenuous at best and should be deleted.

The Kerger et al. (1996a) study demonstrates different pharmacokinetic patterns with different forms of ingested chromium, which finding is consistent with other research related to chromium-containing vitamins. Further, all exposures in the Kerger et al. study were to 10 mg Cr/L, which is far more than would be expected in California drinking water, and as such, the findings are of questionable relevance to drinking-water exposures.

Also, there is a grammatical error in the first line—Cr(VI) was mixed with orange juice; humans were not mixed with orange juice.

Comment 8 (page 12) *"Finley and associates observed marked increases in plasma chromium levels in some individuals (but not in others) that ingested three daily doses of hexavalent chromium, at total doses as low as 0.1 mg/day (Finley et al., 1997)."*

However, Finley et al. (1997) states that "dose-related increases in plasma and RBC chromium concentrations were not apparent following ingestion of USEPA's MCL of 0.1 mg/L." OEHHA is not correctly citing this study. If OEHHA is attempting to reinterpret the data, this should be stated explicitly and explained. However, it is apparent from our review of the Finley et al. study data that OEHHA's statement (if it is a reinterpretation rather than a misquote) is not supportable.

Comment 9 (page 15) *"The widespread distribution of chromium into tissues following hexavalent chromium administration by inhalation, intratracheal installation, subcutaneous injection, intraperitoneal injection and ingestion indicates that although reduction is likely to be occurring in the blood, it does not occur at a fast enough rate to prevent hexavalent chromium from reaching and being taken up by tissues. While chromium was detected in high levels in the kidney, spleen, RBCs, and liver when hexavalent chromium was administered, little chromium was detected in these tissues following the administration of trivalent chromium except at the site of its excretion, the kidney (and at much lower levels than when hexavalent chromium was administered) (Weber, 1983; Costa, 1997; Yamaguchi et al., 1983; Yamamoto et al., 1981; Suzuki et al., 1984)."*

First, the kinetics of Cr(VI) following inhalation, intratracheal instillation, subcutaneous injection, and intraperitoneal injection is substantially different from that associated with exposure to Cr(VI) in drinking water at environmentally relevant concentrations, and therefore, is of no relevance to the development of a PHG for Cr(VI) in drinking water. It is not appropriate to summarize these findings as if there is no difference.

The important study of Sutherland et al. (2000) found no increase in chromium in tissues following drinking-water exposures of 0.5 mg/L of Cr(VI) for 44 weeks in rats. However, at drinking-water exposures of 3 and 10 mg/L, tissue chromium levels were

increased (Sutherland et al. 2000). The most critical data are those observed at low exposures in drinking water, not at high doses and by irrelevant routes of exposure. The entire discussion of toxicokinetics should be refocused and rewritten.

Second, the discussion of Cr(III) binding on page 14, reproduced below, indicates that there is considerable uncertainty in concluding whether Cr(VI) or Cr(III) is systemically absorbed.

> *"An apparently non-specific binding of chromium to proteins on the outside of RBCs can also be significant, particularly at higher concentrations. Edel and Sabbioni (1985) observed that 15 percent of trivalent chromium in the blood was associated with RBCs 24 hours post-administration. Up to 35 percent of the trivalent chromium in the blood was associated with RBCs in the study of Gao et al., 1993. Increased blood levels of chromium following oral administration of trivalent chromium to humans were associated with the plasma fraction (Kerger et al., 1996a). Increased levels of chromium also occurred in the RBCs in one of four individuals in the study."*

In light of this discussion, OEHHA should reconsider whether the profile of total chromium in RBCs and plasma can be used as a measure of systemic absorption of Cr(VI).

Comment 10 (page 15) *"Oral administration of hexavalent chromium revealed a slightly different pattern of distribution compared to other exposure routes, with high levels of chromium in the liver, spleen, and kidney but much lower levels in the RBC (Sutherland et al., 2000; Thomann et al., 1994; Witmer et al., 1989; NTP 2007b). Higher levels of chromium in the liver are consistent with the immediate passage of blood from the gut to the liver. The reduced levels in the RBC relative to other routes of exposure may be due to uptake in the liver. Little chromium was detected in these tissues following oral administration of trivalent chromium. If hexavalent chromium were rapidly and completely reduced to trivalent chromium it should have been distributed in a manner that is virtually identical to that observed following trivalent chromium administration. This is not apparent in any study regardless of the route of administration."*

First, if OEHHA carefully examines the tissue accumulation data of the NTP study, they would recognize that there are notable differences between rodent species, the basis for which has not been explained, nor has its relevance to humans been described. The data suggest that far more Cr(VI) was absorbed in the mouse than the rat, and that the rat had increased capacity to reduce Cr(VI) to Cr(III) in the stomach. Humans, with greater gastric acid production capacity than a rat, and a greater volume of gastric acid in the stomach, are expected to be able to reduce more Cr(VI) to Cr(III) in the stomach, and thus to have a increased ability to detoxify Cr(VI).

Second, in this paragraph, OEHHA sites Sutherland et al. (2000) but ignores the findings at the lowest dose by the relevant route of exposure. Instead, OEHHA focuses only on the high-dose data and the data collected by non-relevant routes of exposure; however, it

should focus the discussion to provide an understanding of kinetics of ingested Cr(VI) in the low exposure range.

The last statement in this quote again illustrates OEHHA's lack of understanding of the reductive capacity of biological tissues, in particular those in the GI tract, at doses in the low dose range. To continue to draw broad conclusions based on high-dose data in the assessment of low doses in drinking water borders on scientific irresponsibility.

Comment 11 (page 15-16) *"The prolonged urinary half-life following hexavalent chromium administration suggests that there is a pool(s) of chromium that is slowly being released. This release or elution is reminiscent of the slow release of chromium from RBCs that occurs when labeled RBCs are introduced into humans in nuclear medicine (ICSH, 1980)."*

OEHHA's PHG document should provide an accurate, concise summary of the available literature. The profile of chromium in the blood and urine in the Kerger et al. (1996) study is, as the author notes, more consistent with absorption of Cr(III) than Cr(VI); however, we recognize that this conclusion includes uncertainty. The study includes only a few participants, and those individuals had significantly variable patterns of absorption. The fact that OEHHA finds it necessary to speculate at length about the kinetics of Cr(VI) following ingestion demonstrates the uncertainty associated with the current state of the science, and the importance of understanding and being able to correctly quantify the kinetics of Cr(VI) following exposure at low concentrations. Rather than devoting the considerable amount of time spent to reinterpret this and several other studies, OEHHA's time and resource would be better invested in improving the science through the use of PBPK modeling.

Comment 12 (page 16) *"This finding provides additional evidence that mixing chromate with food in an acidic environment somewhat analogous to the stomach does not completely reduce hexavalent chromium to trivalent chromium."*

Consistent with the authors' report, the observation of a prolonged half-life is also evidence that there is a difference in the toxicokinetics of Cr(III) bound to an organic matrix. It is misleading to reinterpret the authors' reported methods and findings without a solid basis, and OEHHA presents no data to support that there was Cr(VI) in the orange juice administered in the Kerger et al. (1996a) study. Again, the repeated speculation in this document is not appropriate and does not serve the public. The most appropriate tool to address this uncertainty is a PBPK model.

Comment 13 (Page 17) *"Kerger et al. (1996b), De Flora et al. (1997), De Flora (2000), O'Flaherty et al. (2001), Proctor et al. (2002b) and others have suggested that at plausible maximum levels of hexavalent chromium in drinking water, the saliva, stomach and blood have abundant and essentially inexhaustible ability to rapidly convert hexavalent chromium to trivalent chromium. Based on this belief that orally administered hexavalent chromium is completely converted to trivalent chromium in the stomach and saliva, no differences in absorption, distribution, or elimination should be apparent for*

hexavalent versus trivalent chromium. However, the results of the toxicokinetic studies in humans (Donaldson and Barreras, 1966; Kerger et al., 1996a; Finley et al., 1997; Paustenbach et al., 1996) or animals (MacKenzie et al., 1958; Costa, 1997) do not support the conviction that hexavalent chromium is completely converted to trivalent chromium."

This paragraph mischaracterizes this research. It has been well recognized for decades that Cr(VI) is reduced to Cr(III) in the stomach and other tissues, which reduces the toxicity of Cr(VI). To our knowledge, no researcher has claimed that the capacity of these tissues to reduce Cr(VI) to Cr(III) is "inexhaustible" at any dose. In fact, O'Flaherty et al. (2001) clearly states that absorption and reduction are competing kinetic processes. Further, all of the papers quoted by OEHHA that provide actual kinetics data state that administered doses that far exceed levels that are "*plausible maximum levels of hexavalent chromium in drinking water*," with the single exception of the lowest dose in the Finley et al. study (0.1 mg/L), at which there was no evidence of chromium absorption. Finally, Costa (1997) is a review paper, and does not represent primary literature to support the statement.

Comment 14 (Page 17) *"Proctor and coworkers investigated the reducing capacity of stomach secretions using human gastric fluid and a simulated stomach fluid (Proctor et al., 2002a). The findings of these investigators appear to be consistent with estimates of De Flora and others that gastric fluids are capable of rapidly reducing large quantities of hexavalent chromium. Both human stomach fluid and simulated stomach fluid reduced from 300 to 1,000 µg/L (gastric fluid) to 10,000 µg/L (simulated fluid) of hexavalent chromium within minutes. Neither dilution nor the addition of an antacid markedly altered the reducing properties of the simulated stomach fluid."*

This statement misquotes the paper cited. The abstract actually states that real human gastric fluid reduced 0.3 to 1 mg Cr(VI) per liter of gastric fluid within 2 minutes. Increasing the pH from 1.5 to 4.5 reduced both the rate and capacity of Cr(VI) reduction by approximately one-third. However, further increasing the pH to 8.2 by adding Rolaids did not affect the reduction rate or capacity, as compared to that at a pH of 4.5. Thus, between a pH of 4.5 and 8.2 there was no affect of pH on reduction rate or capacity, but between a pH of 1.5 and 4.5, there clearly was.

In the presence of food within simulated gastric fluid, 10 mg of Cr(VI) per liter of simulated stomach fluid is reduced in 4 minutes, and Proctor et al. concludes that, under fasting conditions, Cr(VI) at 1 ppb would exist in the stomach for less than 1 minute before being reduced to Cr(VI). This study found that dilution does make a significant difference in reduction capacity. The mass reduced is proportional to the level of dilution. The study reported half-lives of 0.7 to 10 minutes. Dilution did have a significant impact on reduction capacity, as did pH. OEHHA should cite the study correctly, and advance its discussion of kinetics to focus on rates of reduction and rates of absorption, rather than speculation regarding absolute quantities.

Comment 15 (page 18) *"The differences in the distribution of hexavalent and trivalent chromium in tissues and the difference in the urinary half-life of the two forms of the metal are indicative of the reason for concern about hexavalent chromium exposure. If the absorbed hexavalent chromium was rapidly reduced to trivalent chromium in the plasma, then the pattern of tissue distribution and rate of urinary elimination should be essentially identical to what is observed for the trivalent form of the metal. Following hexavalent chromium administration, the findings of a prolonged plasma and urinary half-life and its distribution to the liver and other tissues (relative to trivalent chromium) indicate that the hexavalent chromium form of the metal is moving into cells prior to its reduction to trivalent chromium."*

Although OEHHA speculates at length about the findings of the Kerger et al. paper—most of which are contrary to the author's conclusions—this dialog is entirely unnecessary, because the observations of cancer in the NTP study, and other studies that OEHHA deems of value (Borneff et al. 1968; Zhang and Li 1987), occur only at the site of exposure in the GI tract, not in distant tissues. Systemic absorption is not necessary for these tumors to occur. Further, the Kerger et al. study involved only four people, exposed at 10 mg/L of Cr(VI). The doses are not relevant to environmental exposures, and the findings demonstrate considerable variability among study participants.

Comment 16 (pages 19 and 20)

Figures 1 and 2 are overly simplistic. We concur with DTSC that these figures do not add to the understanding of the toxicokinetics of Cr(III) or Cr(VI).

Comment 17 (page 21) *"Quantitative differences in the propensity of hexavalent and trivalent chromium to associate with RBCs and differences in other characteristics such as the rate of decline of chromium in RBC following uptake of trivalent chromium (rapid) and hexavalent chromium (delayed) allow one to identify which form of chromium occurred in tissues."*

Given the binding of Cr(III) to proteins on the outside of RBCs (as noted in comment 7 from OEHHA's own text), OEHHA's speculation regarding differences in half-life and elimination does not "allow one to identify which form of chromium occurred in tissues and in which tissues." OEHHA should specifically report the half-life of Cr(VI) and Cr(III) from oral drinking-water exposure, and provide a quantitative analysis of why Cr(VI) was absorbed, because our review of the literature would indicate that the half-life in RBCs would be much longer than that reported by Kerger et al., if Cr(VI) was systemically absorbed. The most meaningful data by Sutherland et al., which find no increase in chromium in any tissues following prolonged exposure to Cr(VI) at 0.5 mg/L, are very important for understanding the kinetics of Cr(VI) from lower-level Cr(VI) exposure and should be highlighted in the OEHHA document.

Specific Comments on Toxicology

Comment 18 (page 26) *"At very high oral doses of hexavalent chromium, embryotoxic and fetotoxic effects have been observed in rodents. At lower doses the picture is less clear. Zahid and associates (Zahid et al., 1990) and Li and coworkers (Li et al., 2001) observed reduced sperm counts and/or increased abnormalities in mice or rats. In the National Toxicology Program studies, no effects were observed on spermatogenesis or reproductive outcome in mice and rats exposed under similar conditions (NTP 1996, 1997a,b)."*

It should be noted that Finley et al. (2003) published a comment that critically examined the methods and results of the Zahid et al. (1990) study. Finley et al. (2003) commented on the inconsistencies between the methods and reported results, insufficient statistical power and inappropriate statistical methods for data analysis, and questionable tissue sample preparation methods. These authors concluded that the Zahid et al. study is inadequate to evaluate the effects of ingested chromium.

Clearly, the methods and results of the NTP reproductive and developmental toxicity studies are far superior to those of Li et al. and Zahid et al., such that, at relevant exposure levels, OEHHA should conclude that Cr(VI) does not cause reproductive and developmental toxicity. Stating that potential for effects at low doses is "less clear" is not an accurate reflection of the available science.

Subchronic Toxicity

Comment 19 (page 27; re: NTP 1996, 1997a); *"No treatment-related mortality was observed in these studies. Cytoplasmic vacuolization of hepatocytes was observed in both male and female mice at concentrations of 50, 100 and 400 ppm. In the male mice, 1 of 6 animals exhibited mild cytoplasmic vacuolization in hepatocytes at a concentration of 50 ppm, 2 of 5 mice exhibited minimal or mild vacuolization at 100 ppm, and 2 of 6 exhibited mild or moderate vacuolization at 400 ppm."*

OEHHA provides a reasonable summary of the results for these two studies (NTP 1996, 1997a) that are intended to evaluate reproductive effects of oral Cr(VI) exposure. However, the apparent differences in interspecies sensitivity to liver effects from these exposures should be discussed. Although mice seemed to be sensitive to cytoplasmic vacuolization in hepatocytes at doses as low as 50 ppm in diet, this effect was not seen in rats under the same conditions at doses as high as 400 ppm in diet. Further, these effects were not observed in mice in the 2008 NTP study. These findings are not reproducible and, as such, should not be used for risk assessment.

Comment 20 (page 28) *"Chopra et al., 1996...Histopathological examination of the liver of animals receiving hexavalent chromium revealed "degeneration with reticular arrangement of hepatocytes, widened sinusoidal spaces, vacuolation and necrosis, which was more pronounced in the periportal region."*

This text actually refers to results reported for ethanol. Regarding chromium-treated rats, the authors state briefly, "Similar changes were observed in the histology of liver in chromium

treated rats, except the injury was more pronounced in the periportal area," but provide no specific descriptive or quantitative data on the nature of the liver injury due to hexavalent chromium. Indeed, they state that "five or six" animals were treated, without precise indication of the numbers of animals treated. The weaknesses in the study design and results description should be better characterized as such in the PHG document.

Note that the Chopra et al. (1996) and Acharya et al. (2001) studies were conducted by the same laboratory using nearly identical study protocols, with the exception that Chopra et al. (1996) evaluated female Wistar rats while Acharya et al. (2001) evaluated male Wistar rats, and the same weaknesses that are apparent in the Chopra et al. study (e.g., lack of detail about study-group size, lack of detail about histopathological findings) are apparent in the Acharya et al. (2001) study.

Comment 21 (page 30; re: Vyskocil et al., 1993) *"Significant increases in urinary albumin at three and six months and β_2-microglobulin at three but not six months were observed in female rats... No statistically significant changes in any of these parameters were observed in male rats."*

Quantitative results for male rats are not tabulated or described, which makes it difficult to compare the relative sensitivity of female vs. male rats difficult and limits the utility of this study. β_2-microglobulin was increased at three months, but not six, in female rats, but the daily chromium intake per kg body weight was lower during the second three months because doses were not adjusted through the study. These findings add further evidence that lower chromium doses (e.g., <2 mg/kg-day), more closely approximating environmentally relevant levels, are more readily tolerated.

Comment 22 (page 30; re: NTP, 2007a) *"Mean body weights of both male and female rats were reduced in the high dose group. As with other studies, water consumption was reduced at higher concentrations, which may be responsible for the reduced body weight."*

These data suggest that at least the males in the highest dose group (1000 mg/L), and possibly the second-highest dose group, exceeded maximum tolerated doses (MTDs). Rats were administered water concentrations of 62.5, 125, 250, 500, or 1000 mg/L sodium dichromate. Water consumption rates were lower than controls in the three highest dose groups (250, 500, and 1000 mg/L) for both males and females, and the final mean body weights and body weight gains of males and females receiving 1000 mg/L and males receiving 500 mg/L were lower than controls (11%, 6%, and 5% lower, respectively). Varying definitions of the MTD have been proposed, but a frequently applied definition is "the dose that suppresses body weight gain slightly (i.e., 10 percent) in a 90-day sub-chronic study" (Eaton and Klaassen 2001). The use of doses in excess of the MTD in toxicity studies is undesirable for a variety of reasons, including lack of relevance to expected environmental exposure levels. Notably, chronic inflammation of the liver was reported in female rats in this study in only the highest (1000 mg/L) dose group, and in none of the male rat dose groups, and fatty liver was not reported for any dose group.

It is also important to recognize that health-effect findings above a dose level at which water consumption is decreased may or may not be due to the test substance (Campbell et

al. 2009). In the sodium dichromate studies, high concentrations in water are presumably unpalatable to rodents, such that comparisons to control animals may be confounded because controls consume standard volumes of drinking water. This issue can complicate interpretation of study results.

Comment 23 (page 30; re: NTP, 2007a) *"Water consumption and body weight were reduced in both males and females [mice] in a dose-dependent manner."*

Water concentrations of 62.5, 125, 250, 500, or 1000 mg/L sodium dichromate were administered to mice. Water consumption rates were lower than controls in all but the lowest dose group for males and females. Final mean body weights and body weight gains of all dose groups of males and all but the lowest dose group of females were less than controls (body weights for males for the five dose groups were 6%, 10%, 14%, 19%, and 20% less than controls, respectively, and body weights for females in the four highest dose groups were 8%, 8%, 11%, and 13% less than controls, respectively). These data suggest that at least the four highest dose groups (125, 250, 500, and 1000 mg/L) likely exceeded the MTD.

As discussed above, interpretation of study results associated with doses above the MTD and reduced water consumption is problematic.

Chronic Toxicity

Comment 24 (page 32; re: NTP, 2007b) *"Groups of 50 male and female rats ... and mice ... were administered sodium dichromate in drinking water (male and female rats and female mice: 14.3, 57.3, 172, or 516 mg/L; male mice: 14.3, 28.6, 85.7, or 257.4 mg/L) for two years (NTP, 2007b)... Significant reductions in mean weight gains were observed in the high dose group, in both male and female rats. Reduced water consumption due to poor palatability of high concentrations of chromium VI+ probably accounts, in part, for the decreases in weight gain in the high dose groups (NTP, 2007b).*

As evidenced by the water consumption and body weight data from this and the 3-month study (NTP 2007a), the highest dose administered to rats and mice likely exceeded the MTD. As discussed above, interpretation of study results associated with doses above the MTD and reduced water consumption is problematic, and may not reflect toxic effects of the chemical agent itself. If a BMD model is used with these study results to calculate a non-cancer PHG in the future, the uncertainty regarding the effects seen at the higher dose levels would need to be considered.

Comment 25 (page 33; re: NTP, 2007b) *"The animals appeared to recover from the anemia by 12 months."*

This statement is not supported by the data in the study and should be revised. While recovery appeared to be taking place over the course of the first 12 months, at the 12-month point, hemoglobin was still significantly decreased and erythrocyte counts significantly increased in the high-dose males (Appendix E, NTP 2008), indicating that

recovery was not complete at 12 months. Because data beyond 12 months were not collected, it is not possible to know whether the rats recovered completely. Nonetheless, regarding this endpoint, NTP (2008) states, "There was an amelioration of the effects by the 12-month time point, suggesting that the erythron effect was transient and resolved with time. The transient nature suggests an adaptive response by the exposed animals."

Comment 26 (page 33; re: NTP, 2007b) *"Administration of chromium VI+ to female rats resulted in a dose-related increase in liver toxicity as evidenced by increased fatty changes and chronic inflammation. Statistically significant increases in the number of animals exhibiting fatty change plus chronic inflammation were observed in female rats administered 57.3 mg/L or more of Cr VI+, and chronic inflammation alone in animals administered 14.3 mg/L.. No treatment related non-neoplasm toxicity was observed in the oral mucosa, forestomach, glandular stomach or duodenum. Hematology, considered a special study and not routinely performed in two-year NTP studies, was not done in the female rat. A LOAEL of 14.3 mg/L was identified in the female rat, based on chronic inflammation, which is below exposure levels associated with hematological effects in the male rat."*

This study is particularly important, because OEHHA selected it as the critical study for the derivation of the non-cancer PHG. As such, four main issues relevant to the endpoint of female rat liver chronic inflammation are discussed: 1) relevance of high doses to environmental exposures; 2) questions, highlighted by the NTP, about the biological significance of nonneoplastic liver effects at low doses, particularly in light of the high background levels of these effects in control animals; 3) potential gender and species differences in Cr(VI) pharmacokinetics and pharmacodynamics suggested by the NTP (2007b) study results; and 4) general human and rodent species differences in sensitivity to liver effects of toxicants.

First, given the relationship between the reducing capacity of the GI tract and Cr(VI) toxicity, the high dose levels used in the NTP study are of questionable relevance to much lower environmental exposure levels. The fact that responses may be qualitatively, as well as quantitatively, different at high vs. low dose levels is well recognized in toxicology. This issue was discussed in regard to interpretation of the carcinogenicity data, as well as by the UC peer reviewers and the DTSC. Specifically, the animal studies used doses that overwhelmed the test animals' capacity to reduce Cr(VI) to Cr(III) in the gastrointestinal tract, resulting in tissue damage in the small intestine (including chronic inflammation). Extrapolating from these doses to doses that are environmentally relevant overestimates the non-cancer hazard. OEHHA should consider data that exist for lower levels of exposure that are more representative of human exposures. For example, Finley et al. (1997) found no dose-related increases in plasma and RBC chromium at ingested concentrations of 0.1 mg/L, and Sutherland et al. (2000) found no increase in chromium concentrations of any tissue in rats exposed to 0.5 mg/L for 44 weeks. OEHHA's discussion of kinetics needs to be revised to address what has been observed in the low dose range.

Second, the NTP (2007b) expressed clear reservations concerning the biological significance of the chronic liver inflammation observed in the Cr(VI) study animals.

They state that liver inflammation "was generally of minimal to mild severity in most groups, including the controls, except 516 mg/L females in which there appeared to be a slight increase in the severity (mild to moderate)." NTP further states, "Chronic inflammation is consistent with changes that are considered to be background or spontaneous lesions commonly observed in aged rats and appears to be exacerbated by exposure." NTP's statements about the significance of these findings raise questions about the suitability of these data for use as the point of departure in derivation of the PHG. NTP's statements are supported by examination of historical control data from other NTP studies, which show that liver inflammation and fatty changes are common in these species of rat and mouse. All studies reported in NTP Long-Term Study Reports released in 2004 or after (http://ntp.niehs.nih.gov/?objectid=D16D6C59-F1F6-975E-7D23D1519B8CD7A5) in which F344 rats and/or B6C3F1 mice were fed rodent diet NTP-2000 were identified, and data regarding liver inflammation and fatty changes for each sex and species were compiled (Table 1 of Attachment 1). The NTP studies only summarize observed effects, so if an effect is not observed in any dose group, control data are not reported by NTP.

Examination of the historical control data for F344 rats shows that the incidence of nonneoplastic liver lesions, including chronic liver inflammation and fatty changes, is highly variable. As shown in Table 1, the incidence of chronic liver inflammation in NTP 2-year study historical controls ranged from 2% to 92% for female F344 rats and from 2% to 82% in male F344 rats. The rate of fatty liver in control animals ranged from 2% to 32% for female F344 rats and 6% to 44% in male F344 rats (fatty liver was reported infrequently; rates of vacuolization of the liver ranged from to 2% to 80% in female F344 control rats and from 2% to 74% in male F344 control rats). Rates of chronic liver inflammation and fatty liver tend to be higher in F344 rats than in B6C3F1 mice (Table 1), but rates in mice are also highly variable. Numerous factors can influence the relative rate of occurrence of neoplastic and nonneoplastic lesions in animal studies, including diet, housing, timing and rate of feeding, colony health, age, gender, genetics, and other factors (Blodgett 2002; Sharp et al. 2002; Haseman et al. 2003; Rao and Crocket 2003; Leakey et al. 2004). Consistent with the historical control data from NTP studies, the rates of chronic liver inflammation were high in the female and male rats of the NTP (2007b) study, including controls, with an incidence of 24% in female controls and 38% in male controls.

Third, examination of the data on distribution of Cr(VI) and dose-related nonneoplastic effects in rats and mice suggests gender and species differences in Cr(VI) pharmacokinetics and pharmacodynamics. However, data on tissue concentrations were not collected for female rats or male mice. Tissue concentration data collected for male rats and female mice show that, in the 14.3-mg/L dose group, the amount of chromium in the liver of female mice at the end of the study was 2.7 times higher than that in male rats (Appendix J, NTP 2007b). Because tissue data are not available for all relevant study groups, and particularly for the group determined to be most sensitive (female rats), use of the NTP data to support characterization of species and gender differences in ADME (absorption, distribution, metabolism, and excretion) and response is difficult. Further, higher tissue concentrations do not correlate with greater effect. For example, despite the

higher liver concentrations in mice, rates of chronic liver inflammation were not increased in either female or male mice at any dose. Dose-related increases in chronic liver inflammation were seen in female rats starting at the 14.3-mg/L dose, but no dose-related increase in nonneoplastic liver effects were seen in male rats. For this study, even though tissue concentration data are incomplete, these data suggest that rats are more sensitive than mice to chronic liver inflammation, and that females are more sensitive than males. Male mice were particularly insensitive to development of liver lesions, in both control and exposed animals. These data, and information on the relative sensitivity of the human liver, should be taken into consideration in determining an appropriate point of departure and uncertainty factors for derivation of the non-cancer PHG.

A fourth issue that we believe should be taken into consideration is data that suggest the human liver is less sensitive to toxicological effects from chemical exposure than the rat liver. In general, it is useful to have specific MOA information to perform a species-to-species comparison. Although this is not known definitively for Cr(VI), several studies have indicated that the non-carcinogenic hepatic effects of Cr(VI) are due to oxidative stress (Susa et al. 1996; Lalouni et al. 2007; Wang et al. 2006), which is consistent with other metals. However, even without that information, it is possible to generally discuss the sensitivity of the rat and human to liver injury.

Fentem and Fry (1993) discuss the well-known species differences in coumarin heptatoxicity (humans are much less susceptible than rats due to metabolism differences). Rat and mouse hepatocytes were both shown to be more sensitive than humans to acetaminophen-induced hepatic injury (Jemnitz et al. 2008). In fact, some investigators have stated that the rat liver is a poor model for human liver toxicity and is not relevant due to metabolic differences (Langsch et al. 2009). Data from the mode of action and PBPK studies being conducted by The Hamner Institute will provide important information for interpretation of animal data and selection of endpoints for toxicity assessment.

These points all lead to significant uncertainty in OEHHA's non-cancer PHG calculation. The administration of high doses that overwhelm the reductive capacity of the GI tract in animal studies likely overestimates risks at environmental exposure levels. The use of a different point of departure due to uncertainty regarding the validity of the liver effects would result in a corresponding increase in the PHG. Finally, the use of a different uncertainty factor (less than 10) to account for the apparent greater sensitivity of rats to oral Cr(VI) exposure would also result in an increase in the non-cancer PHG.

Comment 27 (page 33; re: NTP, 2007b) *"Much has been written on the elements of a good long-term animal bioassay to evaluate the safety of a chemical...Doses should be selected so that the low dose group shows no evidence of toxicity..."*

The majority of studies cited by OEHHA for the noncancer assessment do not meet this criterion. A NOAEL was reported for only two of the noncancer studies (NTP 1997a and Mackenzie et al. 1958), highlighting the fact that most of the studies examined excessively high doses that overwhelmed the test animals' capacity to reduce Cr(VI) to Cr(III) in the gastrointestinal tract, allowing mechanisms of toxicity to emerge that are

not relevant at lower, environmentally relevant doses.

Comment 30 (page 34) Table 1

Strengths and weaknesses of the Borneff et al. study are included in this table, but the study is not described in the preceding text. It is described only in the discussion of carcinogenicity, which occurs thereafter. We recommend deleting the considerations of Borneff et al., because it is an equivocal study and reached a conclusion that was not reproduced in the NTP study.

The "weaknesses" for NTP (2007a), the subchronic toxicity study, should note that the higher doses administered to rats (at least the 1000-mg/L dose group) and mice (at least the 125-, 250-, 500-, and 1000-mg/L dose groups) likely exceed the MTD.

The "weaknesses" for Acharya et al. (2001) should note that, while food and water intake were monitored, the results were not reported.

Comment 31 (page 34; re: Strengths and Weaknesses of studies) *"All of the bioassays contained important deficiencies, as summarized in Table 1. These deficiencies introduced substantial uncertainty in assessing the risks associated with human exposure to hexavalent chromium in drinking water."*

We concur with this statement and believe that the human health risk assessment could be improved substantially through additional research and use of PBPK modeling.

Genetic Toxicity

Comment 32 The majority of studies conducted by the drinking-water route were negative using a variety of tests and in a variety of tissues. In the NTP study, Cr(VI) was not genotoxic in two other strains of mice, including B6C3F1, the strain tested in the 2-year cancer bioassay. No effects were observed on DNA cross-linking in leukocytes from volunteers who ingested a bolus dose of 5 mg potassium dichromate in 0.5 L of water (10 mg/L) (Kuykendall et al. 1996). De Flora et al. (2006) evaluated the effect of Cr(VI) exposure on micronucleus frequency in adult mice exposed via drinking water, and offspring of dams exposed to sodium dichromate dehydrate at concentrations up to 500 mg/L for up to 210 days. No effects on micronucleus frequency were reported in bone marrow, liver, or peripheral blood, nor was Cr(VI) positive in a micronucleus test in bone marrow in mice administered Cr(VI) in drinking water at a concentration of 20 mg/L (Mirsalis et al. 1996). The weight of evidence strongly supports that Cr(VI) is not genotoxic from drinking-water exposures. OEHHA should revise this section to reflect this highly relevant observation.

Comment 32 (page 37) [Genotoxicity Summary for] *Oral Exposures*

This section is extremely dated. Many missing and important studies are not cited, including DeFlora et al. (2006 and 2008) and the genotoxicity data collected as part of the

recent NTP study. This section must be updated, because it provides valuable insights into the MOA, and methods for collecting genotoxicity data have improved considerably in recent years. The findings of the studies not included but referenced above are negative or equivocal in the micronucleus test among animals exposed to very high concentrations of Cr(VI) in drinking water.

Comment 33 (page 37) *"Surprisingly, no study to date has looked for DNA damage in the oral cavity or gastrointestinal tract following oral administration of hexavalent chromium."*

This is not correct. DeFlora et al. (2008) evaluated DNA damage in the stomach, forestomach, and small intestine of mice exposed to Cr(VI) at 5 and 20 mg/L administered in drinking water for 9 months. As noted above in the general comments, there was no evidence of DNA oxidative damage or DNA cross-linkage, two key indicators indicating that genotoxicity in mice, in the target tissues of the small intestines or other portions of the GI tract evaluated, is not part of the mode of action. OEHHA's lack of consideration of this study, which is very important for assessing the MOA, represents a serious flaw in OEHHA's evaluation and calls into question their conclusions regarding the MOA tumor development in mice, the extrapolation of those findings to low doses, and the relevance to human health in populations potentially exposed to Cr(VI) in drinking water at environmentally relevant concentrations. The results reported by DeFlora et al. (2008) should be considered, and the cancer risk assessment should not be based on a linear low-dose extrapolation method, for consistency with the EPA guidelines for cancer risk assessment (2005).

Comment 34 (page 40) *"Data summarized by De Flora (2000) suggest that the saliva and stomach have the capacity to completely reduce the dose that a human would receive from rapid ingestion of hexavalent chromium-containing drinking water at concentrations typically found in California water supplies. However, genotoxic effects in distant tissues (i.e., bone marrow, liver and brain) have been observed in rodents chronically administered hexavalent chromium by gavage at doses (1.0 mg/kg-d, Bigaliev et al., 1977; 2.5 mg/kg-d, Bagchi et al., 1997) not likely to overwhelm the reductive capacities of the stomach, intestines and blood."*

OEHHA provides no basis for concluding that genotoxic effects occur at doses that do not overwhelm the reductive capacity of the stomach. What is the basis for saying the gavage dose administered by Bigaliev et al. did not overwhelm the reductive capacity of the stomach, intestines, and blood? These very large doses were administered by a gastric tube, and the absorption and reduction are competing biological processes. Further, the data set from Bagchi et al. (1997) for DNA single strand breaks in the brain seems very unreliable. The study used only 4 to 6 animals, and there was no difference between DNA-SSB in control and treated mice at three of the six time points investigated. In addition, the Bagchi et al. findings of genotoxicity in the brain are either limited to extreme high-dose exposures of the Bagchi et al. study or are of questionable reliability, because Sutherland et al. (2000) did not observe increased levels of chromium in brain tissue of rats exposed to Cr(VI) at 10 ppm for 44 weeks.

OEHHA should consider the totality of the genotoxicity data. Studies where Cr(VI) is administered in drinking water are generally negative (Mirsalis et al. 1996; Kuykendall et al. 1996; Coogan et al. 1991). Studies that administer Cr(VI) by gavage and other unnatural routes of exposure are not. OEHHA repeatedly cites the findings of Bagchi et al. (1997) of DNA strand breaks in brain tissue, without critically considering the reliability of those data.

The weight of evidence, especially considering the DeFlora et al. (2008) findings, does not indicate that Cr(VI) is genotoxic from environmentally relevant exposure levels via drinking water.

Carcinogenicity

Comment 35 (page 51) *"The effective number of mice in Tables 5 and 6 (the denominator) reflects animals whose duodenum (where most of the tumors occurred) was examined and excludes animals whose duodenum was not examined due to autolysis or where the tissue was missing. Animals were also excluded if they died more than 40 days prior to the appearance of the first tumor in the small intestine. Statistical analysis in which the effective number of animals was based on animals where the duodenum* ***or*** *jejunum were examined (slightly increasing the denominator) resulted in essentially the same findings (data not shown)."*

First, it is important to emphasize that most of the tumors did occur in the duodenum, the portion of the small intestine in closest proximity to the stomach, and with greater distance from the point where the stomach empties into the small intestine, fewer tumors were observed. This is an important observation for evaluation of the MOA. These data suggest that direct content of Cr(VI) in lumen contents with epithelial tissues of the duodenum is the "target tissue" dose that should be quantified for the purposes of risk assessment and extrapolation between rodents and humans.

Second, the denominator data in Tables 5 and 6 are not consistent with those presented by NTP for the 28.6-mg/L and 257.4-mg/L dose groups of the male mice, and for all the dose groups of the female mice. OEHHA should provide a more detailed description as to why the numbers are inconsistent, or use the results presented by NTP if the result is "essentially the same."

In addition, the New Jersey Department of Environmental Protection (NJDEP 2009) also developed a cancer slope factor from the male mouse small-intestine tumor data. The denominator value that NJDEP used was different from (and higher than) that used by OEHHA. However, NJDEP specifically explained that the number of animals at risk was the population tested at each dose group (50) minus those that died prior to day 451, when the first tumor was detected. This was done following personal communication with Dr. David Malarkey of NTP, who recommended that the denominator should be 50 animals in each dose group, because all tissues were grossly inspected for tumors, and all tumors are detected by gross inspection. Thus, according to NTP, it is highly unlikely

that any tumors were missed because tissues were not available for microscopic examination. We recommend that OEHHA follow the direction of NTP and use the number of animals in each dose group as the denominator for calculation of the oral cancer slope factor, or at least subtract only the number of animals that died within the first year of the study.

Comment 36 (page 52) *"No statistically significant increases in tumors of the oral cavity were observed at any dose, unlike what was observed in the rat. No statistically significant increases in tumors were observed in the forestomach, unlike what was observed in mice in the Borneff et al. (1968) study. The statistically significant increase in stomach tumors observed in humans exposed to chromium VI+ in drinking water in China (Zhang and Li, 1987) may or may not be consistent with what was observed in the duodenum of mice as the precise site of the tumors in the human study is unclear."*

We concur with this statement. Because there is no tissue concordance between species, it is essential for risk assessment to understand the target tissue doses of Cr(VI) that caused tumors, and to use a PBPK model to evaluate the target tissue dose for the relevant tissue in humans. Because Cr(VI) appears to act at the site of exposure where direct contact with tissues occurs, simple allometric scaling is insufficient for scaling from animals to humans. For example, allometric scaling would result in a lower effective dose in rats, as compared to mice, but the NTP tissue data clearly indicate that the target tissue does in the mouse was higher than that in the rat. Hence, allometric scaling from mice to humans is expected to be unreliable.

Comment 37 (page 53) *"Statistically significant increases in chronic inflammation were observed in the liver of female rats administered 57.3 mg/L or greater of hexavalent chromium. Fatty changes were also observed. The inflammation was described as minimal to mild in severity except in the high dose females, where it was described as mild to moderate in severity. Chronic inflammation was also observed in male rats administered 172 mg/L of hexavalent chromium."*

This statement is incorrect. The LOAEL for the female rat for chronic liver inflammation was identified as 14.3 mg/L. In describing the observed pathology in the rodent studies, the NTP (2008) states that the chronic liver inflammation "was generally of minimal to mild severity in most groups, including the controls, except 516 mg/L females in which there appeared to be a slight increase in the severity (mild to moderate)." They further state, "Chronic inflammation is consistent with changes that are considered to be background or spontaneous lesions commonly observed in aged rats and appears to be exacerbated by exposure." Rates of chronic inflammation of the liver were also high in the control groups of females and males (24% and 38% respectively). Also, it should be noted that while the 172 mg/L dose group of male rats had a significant increase in chronic liver inflammation, the highest dose group, 516 mg/L did not. Regarding the overall study outcome, NTP (2008) states, "In the current 2-year studies, administration of sodium dichromate dihydrate in drinking water did not affect survival or produce clinical signs of toxicity in rats or mice of either sex."

Comment 38 (page 55) *"A statistically significant and dose related increase in diffuse hyperplasia in the duodenum was observed in mice. This finding was not unexpected given that hyperplasia may be a precursor to the observed tumors in the duodenum. While no injury was reported, NTP indicated that collectively, these lesions are considered consistent with regenerative hyperplasia secondary to previous epithelial cell injury."*

Regenerative hyperplasia, secondary to previous epithelial cell injury, is consistent with a non-mutagenic mode of action, especially when combined with the findings of no genotoxicity in these tissues (De Flora et al. 2008). For a non-mutagenic mode of action, a non-linear dose response in the low dose range is consistent with EPA guidance (U.S. EPA 2005). If the MOA is as NTP indicates, the resulting PHG would be at least 200-fold higher than that calculated with the assumption of a linear dose-response. Further, the observations of the NTP study are consistent with a direct-irritation effect of the small-intestinal epithelium, which occurred with the greatest severity where the stomach empties, indicating that, at the doses administered in the NTP study, Cr(VI) was not reduced in the stomach but passed the duodenum and was reduced as it passed through the intestines of the animals.

Comment 39 (page 56) *"In a short-term cancer study conducted by Davidson and associates, groups of 6-week old hairless SK1-hrBR mice (20 animals per group) were exposed to potassium chromate in their drinking water and/or UV light and observed for skin tumor formation (Davidson et al., 2004)... Since many humans are exposed to both UV radiation from sunlight and hexavalent chromium in drinking water, the authors concluded that the findings support concern over the potential carcinogenic hazards posed by hexavalent chromium in drinking water."*

The Davidson et al. (2004) paper has many limitations. Because OEHHA has found it appropriate to reanalyze the results of some studies (Kerger et al 1996; Finley et al. 1997) and discard others (Cole and Radu 2005), an objective consideration of the validity of the methods and results of other studies, including Davidson et al. (2004), is warranted.

The Davidson et al. (2004) study has several methodological flaws that render it inapplicable to human exposures. First, the UV radiation to which the mice were subjected was not consistent with natural sunlight and included UV-C radiation, which is a highly potent carcinogen. The authors never measured dose, but only reported the drinking-water concentration administered, not how much water the animals consumed. They reported the total number of tumors in each dose group and did not report the number of tumor-bearing mice nor the number of tumors per animal, both of which are the appropriate parameters for reporting results.

The results of this study were also highly subject to observational bias. Only 49 of 172 (28%) of the observed tumors greater than 2 mm were selected for histopathological examination to determine whether the tumors were malignant. Of that 28%, a highly disproportionate number of tumors was selected for evaluation from each treatment group. In animals treated with:

- UV only: 11/12 (92%) of the observed tumors were evaluated histopathologically
- UV + 0.5 ppm K_2CrO_4: 16/16 (100%) of the observed tumors were evaluated histopathologically
- UV + 2.5 ppm K_2CrO_4: 7/50 (14%) of the observed tumors were evaluated histopathologically
- UV + 5 ppm K_2CrO_4: 15/94 (16%) of the observed tumors were evaluated histopathologically.

Hence, the conclusion that a higher fraction of tumors were malignant among Cr(VI)-dosed animals is not supported by the data.

Finally, studies of Cr(VI)-exposed humans, including studies of Cr(VI)-exposed workers who presumably have also been exposed to sunlight, have never reported a statistically significant increase in skin cancer; thus, the relevance to humans is highly questionable. OEHHA should provide an analysis of the Davidson et al. paper to put the findings into the context of the significant limitations of the study.

Toxicological Effects in Humans

Comment 40 (page 58) *"Immunotoxicity Dermal exposure to hexavalent chromium has been linked to allergic contact dermatitis (ATSDR, 2000)."*

The discussion of allergic contact dermatitis is dated and incomplete. Dose-response data are available to assess dermal contact with Cr(VI), and the U.S. EPA Office of Pesticide Programs has recently used this data set to evaluate exposures to treated wood (Proctor et al. 2006a,b). The studies by Proctor et al. were conducted in human subjects who were known to be allergic to Cr(VI) based on their medical history and patch-testing conducted at the beginning of the study. The studies used repeated, open application of test solutions containing Cr(VI). They studied two different types of Cr(VI) compounds—potassium dichromate, commonly used for studying environmental exposures, and acid copper chromate (ACC), a wood pesticide. In their technical reports that were submitted to EPA's Office of Pesticide Programs, Proctor et al. reported a clear dose-response effect for the occurrence of allergic contact dermatitis with increasing dose of Cr(VI) (as mass of Cr(VI) per unit area of skin). Proctor et al. (2006a,b) also performed dose-response modeling of the data obtained in these studies using EPA's Benchmark Dose software and reported minimum elicitation thresholds for Cr(VI)-induced allergic contact dermatitis (i.e., the minimum dermal dose of Cr(VI) required daily to elicit allergic skin reactions in sensitized individuals on repeated exposure). It is noteworthy that the study methodology of repeated, open applications is representative of potential environmental exposures to Cr(VI). We recommend that OEHHA update the PHG to include these data.

Comment 41 (page 58). *"In 1998, the U.S. EPA reviewed the available human epidemiological evidence on hexavalent chromium and respiratory cancer risk (U.S. EPA, 1998) and concluded, as did IARC in 1990, that hexavalent chromium is a strong carcinogen for the respiratory system. The U.S. EPA report also contained a risk quantification (potency estimate) based upon the best data available at the time, from Mancuso (1975). The following discussion focuses on studies and reports published since the U.S. EPA review."*

Many pertinent papers are missing from this review. It is not clear how OEHHA selected only three papers for discussion of carcinogenicity by inhalation. Other studies that should be included are Boice et al. (1999), Birk et al. (2006), and Luippold et al. (2005). For a more complete discussion of carcinogenicity from inhalation, the OSHA hexavalent chromium rule (2006) provides a highly detailed review of the literature.

Comment 42 (page 59) *"Gibb et al., 2000 - Gibb et al. (2000) examined mortality rates from lung cancer, prostate cancer, and all cancers combined among 2,357 male chromate production workers first employed between 1950 and 1974."*

Gibb and colleagues studied cancer mortality at all sites, but reported only that for lung, prostate, and all cancer. Observed and expected cancers for all sites are available from the original authors. The SMR for stomach cancer in this cohort is 0.48 (CI: 0.13, 1.24), demonstrating that even among this highly exposed cohort of chromate production workers, stomach cancer rates were not elevated. This observation should be included in OEHHA's review of GI-tract cancers among occupationally exposed populations.

Comment 43 (page 60) *"OEHHA has concluded, however, that the Cole and Rodu paper is of limited usefulness because it included studies in which there was no exposure to hexavalent chromium (e.g., steel polishers in Jarvholm, 1982), did not include studies in which there was hexavalent chromium exposure (e.g., chromate spray painters in Boice, 1999), and included a study that has since been retracted by the journal that published it (Zhang, 1997; Brandt-Rauf, 2006)."*

A review of the papers that OEHHA did not include or decided to include in its review of the epidemiological literature on pages 60 through 69 indicates that the OEHHA review is more problem ridden than that of Cole and Radu (2005). Although there are limitations to the Cole and Radu (2005) study, those limitations identified by OEHHA are not meaningful. Specifically, of the 474 stomach cancers that were included in the Cole and Radu meta-analysis, 17 were derived from the Zhang and Li (1997) study [the retracted paper], 4 were from Jarvholm (1982), and Boice et al. (1999) did not report an increase in stomach cancer with 11 cases and an SMR of 1.03. Inspection of the studies included in the Cole and Radu study indicates that, while the authors did not limit the studies included to only those that had exposure to Cr(VI), the vast majority did, and there is considerable overlap in the studies included by Cole and Radu (2005) and those included by OEHHA. Cole and Radu did make a very important observation: specifically, that when looking at occupational studies of chromium-exposed workers, it is important to consider confounding by socioeconomic status (SES). The importance of

SES in evaluating stomach cancer among Cr(VI)-exposed workers has also been addressed by Sorahan et al. (1987) regarding chromium platers. OEHHA should include a review of SES and stomach cancer, or cite the findings of Cole and Radu (2005).

Comment 44 (pages 60-69) ***"Cancers of ingestion- and digestion-related organs reported in occupational studies"***

There is no compelling evidence that Cr(VI) causes GI-system cancers in humans based on a review of occupational studies where the primary route of exposure was by inhalation (the premise being that inhaled chromium particulates could be ingested following removal from the lung by the mucocilary transport). OEHHA's review of occupational epidemiology data is riddled with errors and does not reflect a thorough review of the epidemiologic literature on exposure to Cr(VI) and digestive-system cancers. Further, with regard to conclusions on stomach cancer, to focus on the relative risk estimates as evidence of an effect, without consideration of the lower bound on the confidence limits—which in the vast majority (22 out of 25 of these studies) was less than 1, indicating that the evaluated endpoint was not significantly increased—is inappropriate and generally not considered an acceptable scientific practice in the broader scientific community.

We have called OEHHA's attention to some of the errors we identified, but it is not possible to check all of the information presented for accurate extraction of data from the papers cited. Part of the difficulty in checking the references is that the majority of the articles cited in this section are not fully described in the reference section of the PHG document. This includes two of the three papers that OEHHA states showed a statistically significant increased stomach cancer risk. It is not possible for the public to conduct a thorough review of this section when virtually all of the papers identified in this section are not included in the reference section. Additionally, at least one (Raffnsson 1984, cited on page 65) does not exist in PubMed, so obviously, it is not quoted correctly in the tables presented in this section. This section should be deleted or subjected to a complete quality control review and re-released for public review.

There are several inconsistencies between the rules stated for data abstraction and what appears to have been used for the review. Other studies appear to have been overlooked among those considered for the PHG document. We thus do not believe that this section of the draft PHG reflects a thorough review of the epidemiologic literature of occupational studies reporting on exposure to Cr(VI) and digestive-system cancers. Differences in the studies chosen for review, and discrepancies in the relative risk estimates abstracted, could affect any conclusion regarding human health risk from ingestion of Cr(VI).

Further, in OEHHA's review, only three studies reported a statistically significant increase in stomach cancer; however, none showed a significant increase in oral-cavity or small-intestine cancer (which if found, would be consistent with NTP's findings).
A review of the three studies revealed that the evidence for an association is extremely weak, if such evidence even exists. OEHHA states that their evaluation concluded that

there is a "suggestive link between inhalation exposure to hexavalent chromium and cancer of the digestive organs"; however, such an evaluation is premature, at best, and suggests an attempt to support a pre-determined regulatory conclusion.

OEHHA should provide a complete, accurate, and balanced review of the epidemiology literature.

Comment 45 (page 60) *"The articles incorporated into the summary met the following inclusion criteria: 1) employment in an occupation or industry with potential Cr 6+ exposure was documented by employer, labor organization, or government records 2) the article stated that exposure to a Cr+6-containing substance occurred..."*

OEHHA should describe how they searched for Cr(VI) exposure by employer, labor organization, or government records, and what papers were identified by this means.

OEHHA missed many papers that have been published in the peer-reviewed literature and present epidemiology findings for cancers of the organs identified. These include Costantini (1989), Iaia (2006), Montanaro (1997), and Pippard (1985), which presented findings in tannery workers in Italy and the United Kingdom, and wherein the authors specifically identified that the workers were exposed to Cr(VI). Even though OEHHA criticized Cole and Radu (2005) for having missed a paper of workers exposed to Cr(VI) by painting, it missed the Guberan (1989) study of painters who used metal protective primers containing zinc chromate pigments. Also not included were a study of mild-steel and stainless-steel welders in France (Moulin et al. 1993); a study of deaths among die-casting and electroplating workers in the United States (Silverstein et al. 1981); a study of stainless-steel, mild-steel, and shipyard welders in nine European countries (Simonato et al. 1991); and a study of chrome platers in Japan (Takahashi et al. 1990). These studies should all be included in an updated review of relevant literature. Further, this may not be a complete list of all of the papers that OEHHA missed, and OEHHA should revisit efforts to search the literature. OEHHA should describe exactly how it "systematically searched" for studies and "screened" the results.

Comment 46 (page 60) *"at least half of the study population was likely exposed to Cr+6;"*

How did OEHHA determine that at least half of the population likely has been exposed to Cr(VI)? What papers/findings were included or excluded on this basis?

Comment 47 (page 60) *"These articles were screened to identify epidemiologic studies of occupational populations exposed to hexavalent chromium that reported any results for the buccal (oral) cavity, pharynx, or the digestive system."*

Although OEHHA investigated risk measures for specific GI sites, it also included a category of "all digestive system cancers" which should be removed for the summary. The main problem with examining digestive-system cancers as a group (ICD 150–159) is that this represents a broad category that includes cancers of several organs, and the

etiologies of cancers at these various sites are diverse. While there are several shared risk factors within the group, their epidemiology is not uniform, and there is no evidence to even consider an association between cancer of some digestive organs, such as gall bladder, liver, and pancreas, and Cr(VI) exposure. Therefore, in assessing digestive-system cancers as a group, it is unclear which cancer among the group is associated with an excess, if observed, and this obscures any more precise examination of the epidemiology of the individual cancers (e.g., risks in stomach cancer are mixed with risks in rectal cancer). OEHHA's review should consider only individual cancers, not the digestive system as a whole.

Comment 48 (page 60) *"4) the statistical analysis controlled for the potentially confounding variables age, calendar time, race, and gender"*

OEHHA has not explained their criteria for control of confounding variables. There are several approaches to control for potential confounding in a study, which include restricting to a certain subgroup of a population (e.g., women) to hold the effect of this potential confounder constant across; stratifying by the confounding factor to calculate risk estimates within strata of the population (e.g., for men and women separately), which also holds the effect of the variable constant within the stratum; and including the potential confounder as a covariate in models used to calculate the risk estimate, which mathematically accounts (i.e., adjusts) for the effect of this variable on the analysis of how the independent variable (i.e., exposure of interest) is associated with the dependent variable (i.e., health outcome). From the description provided in the draft PHG document, it is not clear what OEHHA's requirement that the "statistical analysis controlled for potentially confounding variables" refers to. At face value, it appears that OEHHA refers to the third option of accounting for potential confounders described above. Most studies calculated age-adjusted relative risks, by virtue of using reference (standard) populations and assuming that the occupational cohort shares a structure of age, gender, race, etc., similar to that of the reference population. Several studies were limited to a white male reference population, because the occupational cohort was largely white. Several studies calculated stratified effect estimates for men and women separately, or for black and white men/women separately. The assumption that underlies rate standardization methods is often questioned, because age, race, and gender distributions of occupational cohorts are unlikely to parallel those of the standard population.

Comment 49 (page 61) *"6) the article was the most recent update of cancer findings if more than one article was published regarding the study population."*

OEHHA twice included the same occupational cohort in the German chromate industry—Korallus et al. (1993) and Birk et al. (2006).[2] While Birk et al. represents the most recent follow-up of this occupational cohort, this more recent study includes only part (n=901 workers) of the original cohort (n=1,417 workers) last reported on by

[2] Birk et al. (2006), which focused on lung cancer by exposure level and could be considered for quantitative lung cancer risk assessment, was included in the GI-tract cancer summary but not in the lung cancer dose-response analysis.

Korallus et al. in 1993. In addition, OEHHA reported data from an unknown paper ("Raffnsson 1984") concerning concrete mixers in Iceland. As noted in an earlier comment, Raffnsson (1984) is not listed in the reference section and is not in PubMed. However, there is a more recent publication by Raffnsson et al. (1997) that could be the same cohort of Icelandic masons.[3] Data from the more recent study should be included in accordance with the review inclusion criteria.

There may be additional mistakes that we did not identify. A thorough quality control review of this entire section is needed.

Comment 50 (page 61) *"Data Abstraction. The following rules were followed in abstracting the rate ratios and numbers of cancers from the articles. If results were presented only for specific gender or race categories or factories, and no distinction was made in the exposure levels, we combined the observed and expected values for the races, genders, and factories to make a single rate ratio and confidence interval. If results were presented for categories of time since first exposure (TSFE) and for all TSFE, we used the results for all TSFE because few studies presented results for categories of TSFE. Similarly, if results were presented for categories of duration of employment (DOE) and for all DOE, we used the results for all DOE because few studies presented results for categories of DOE. For studies of chrome platers, if results were presented separately for "hard" and "bright" chrome electroplating processes, the results for "hard" chrome plating were abstracted because hexavalent chromium exposures are known to be higher in hard chrome plating (Guillemin, 1978; Franchini, 1983)."*

This is an incomplete description of data extraction. For several studies included in the PHG draft, OEHHA appears to have extracted relative risk estimates for more highly exposed subcohorts within the individual studies, but the approach taken appears random and is not adequately described. A justification is provided for studies of chrome platers, for which results were abstracted for "hard" chrome plating if presented separately for "hard" and "bright" chrome electroplating processes, citing Cr(VI) exposures being higher in hard chrome plating as a reason. Reasons were not given for abstracting risk estimates for other more highly exposed subcohorts. Specific examples are provided below.

1) Axelsson et al. (1980) tabulated estimated levels of Cr(VI) exposure by working site at the ferrochrome plant (Table 1 in paper), demonstrating that exposure to Cr(VI) occurred in three (arc-furnace; transport, metal grinder, sampling; maintenance) of the four work sites (office or storage area) at the plant where members included in the occupational cohort worked. Cr(VI) exposures at the three work sites ranged from 0.01 mg/m^3 to 0.25 mg/m^3, with arc-furnace welders incurring the highest Cr(VI) exposures at the plant. The relative risk in the arc-furnace workers was 0.78 (95% CI = 0.25, 1.89). Overall relative risk for the exposed cohort was 0.91 (95% CI = 0.45, 1.63).

[3] Risk estimates in the 1997 Raffnesson et al. study are not consistent with that presented by OEHHA for Raffnesson 1984, so it is unlikely to be the same study.

2) Horiguchi et al. (1990) reports relative risk estimates for the entire cohort of chrome plating workers in Japan and for subcohorts with varying years of employment. OEHHA abstracted the relative risk estimate for workers with >10 years of employment (i.e., those with the greatest duration of exposure), despite the rule specified that if results were presented for categories of duration of employment (DOE) and for all DOE, "results [were used] for all DOE because few studies presented results for categories of DOE."

3) Sorahan et al. (1987) reported results for bright chrome platers. The authors present results for all chrome plating exposures, and SMRs were significantly increased for both stomach and liver cancer. However, OEHHA instead chose to present the results for stomach cancer among workers whose first employment was as a "chrome bath work," a category with fewer stomach cancers and a lesser SMR that was not significantly increased.

These are three more examples of poor-quality work by OEHHA in this section of the PHG document. This section should be deleted or subjected to significant revision following a careful review of all the information presented.

Comment 51 (page 61) *"For stomach cancer, 18 of 25 (72 percent) estimated a rate ratio above 1, while in 7 out of 25 studies, the rate ratio was below 1 (suggesting a reduction in stomach cancer) (Table 7 and 8). The rate ratios were above 1 in 18 of 26 studies for cancer in all digestive organs, 8 out of 11 studies for cancer of the esophagus and 12 out of 16 studies for cancer of the rectum. Interestingly, for stomach cancer, only in 3 out of 25 studies did the lower confidence interval of the rate ratio exceed 1 (Table 7)."*

It should be recognized that OEHHA's literature review is incomplete, and its methods for abstracting data are inconsistent and/or not completely described; thus, a conclusion regarding the number of studies with risk ratios less than or greater than one is not reliable. Further, evaluating the totality of the literature by counting the number of studies with relative risks greater than or less than one, without considering the confidence intervals, is not a valid epidemiologic data analysis method.

Only three of the 25 studies had risk measures that were significantly increased for stomach cancer (McDowell et al. 1984; Knutsson et al. 2000; Rosenman and Stanbury 1996). OEHHA states that this finding is "suggestive" of an association between stomach cancer and Cr(VI) exposure, but that statement is not convincing considering that two of the three studies with significantly increased cancer risk were studies of workers presumably exposed to Cr(VI) in the cement industry. Exposures to Cr(VI) among cement workers are low compared to other industries, because Cr(VI) occurs only at low concentrations in cement. Frias and Rojas (1995) report that samples of cement in Europe contain levels of Cr(VI) from less than 1 ppm to 24 ppm, and only exposure to dry cement dust potentially offers the opportunity for exposure.

The authors of these studies (McDowell et al. 1984; Knutsson et al. 2000) do not attribute the increased risk to Cr(VI) exposure. McDowell et al. (1997) does not even mention chromium in the paper, and Knutsson et al. (2000) states of exposures in the cement industry, "Concrete is a mixture of cement, sand, rock, and water... Mixtures are often added to cement to change concrete setting time and to improve the concrete quality. These mixtures are sometimes carcinogenic—for example, asbestos. Concrete might also contain radioactive granite aggregates, and radon gas might diffuse through concrete. Silica and chromium are other carcinogenic components of concrete. Due to the risk of chromium eczema, addition of ferric chloride in concrete has been mandatory in Sweden since the beginning of the 1980s." Consistently, other cement studies cited by OEHHA discuss the possible carcinogenic exposures among these workers. Amandus et al. (1986) stated that airborne cement-plant dust consists of trace metals, coal, silica, and nuisance dusts. In addition, the authors speculate that quartz exposure in the cement and quarry workers could contribute to the observation of gastric carcinogenicity.

Clearly, it is not expected that, of all the industries with historically very high levels of Cr(VI) exposure, exposure to Cr(VI) in cement would be sufficient to cause an increase in stomach cancer risk. It is illogical to identify the increased stomach cancer risk observed in these studies of cement workers to Cr(VI) exposures, when far higher exposures in other industries are not associated with a significant increased risk. OEHHA's argument that there is suggestive evidence of an association between gastric cancer and Cr(VI) exposure based on cement worker studies is not reliable.

The third study that found a significant increase in stomach cancer with Cr(VI) exposure (Rosenman and Stanbury 1996) also does not provide convincing evidence. Although it was derived from an industry with significant Cr(VI) exposure (chromate production), this study is a proportionate mortality ratio (PMR) study. OEHHA reported the PMR for stomach cancer relative to all mortality. However, the PCMR (Proportionate Cancer Mortality Ratio) from this same study was not significantly increased for stomach cancer. Further inspection of the data reveals that the PCMR for stomach cancer is only elevated among men with <1 year of exposure duration, and there is no increase among workers with 1 to 10 years, 10 to 20 years, or greater than 20 years of exposure. Rosenman and Stanbury conclude regarding stomach cancer, "Although the PMR for stomach cancer was increased among white men (Table II), the risk did not increase with years worked (Table IV)" (page 497). Once again, the best evidence that OEHHA can offer is not convincing and cannot honestly be described even as "suggestive."

Comment 52 (page 68) Table 8

The stomach cancer rate ratio for Franchini 1983 is listed as 3.3 in Table 7 but as 5.00 on Table 8. Either this is an error, or OEHHA is randomly selecting data to abstract from the epidemiology literature. It is important for OEHHA to adopt specific data abstraction procedures and then follow these procedures in this review.

It is important to note the extremely wide confidence intervals associated with these stomach cancer rate ratios for most of the studies identified in Table 8 with relative risks

greater than 1. Four of the 18 studies have confidence intervals greater than 10-fold, and another four have confidence intervals of >5-fold. For the studies with risk ratios less than 1, three of the seven have confidence intervals that are greater than a 5-fold spread. Evaluating the risk by counting the number of studies with risk ratios greater or less than one is not a valid scientific method for developing conclusions from epidemiologic studies.

Comment 53 (page 69) *"Only one study was identified in which cancer risk was investigated in a population demonstrably exposed to hexavalent chromium in drinking water."*

OEHHA has ignored other studies that contribute more significantly to the weight of evidence as to whether Cr(VI) is carcinogenic via drinking-water ingestion among humans. Additional studies of environmental exposure to Cr(VI) via ingestion, which were not reviewed by OEHHA, included studies of populations exposed to Cr(VI) in drinking water in the Leon Valley of central Mexico (Armienta-Hernandez and Rodriguez-Castillo 1995), the town of Lecheria in southern Mexico (Neri et al. 1982), 453 Nebraska communities (Bednar and Kies 1991), and towns in California (Fryzek et al. 2001). Similar to Zhang and Li (1987), all of these studies are of ecologic design and have limitation as such, but some are more relevant to exposure to Cr(VI) in California drinking water.

Fryzek et al. (2001) is a study of considerable relevance, because it is a study of a California population well known to have had Cr(VI) in drinking water at concentrations that are representative of possible environmental exposures. Fryzek et al. (2001) is a mortality study comparing mortality rates of lung cancer, all cancer, and all causes among residents in surrounding areas in California, where it is well known that soluble Cr(VI) had contaminated the groundwater used as a drinking-water supply. The authors concluded that there was no evidence that persons living in postal codes near gas compressor plants, the source of the contamination, experienced higher death rates from lung cancer, all cancers, or all causes, nor were their rates higher than those of residents in the non-exposed postal code areas.

Additionally, the study by Bednar and Kies (1991), which was identified by one of the peer reviewers for inclusion in the PHG document but was dismissed by OEHHA on the basis of inadequate data characterizing the valence of chromium, should be included. The exposure data are arguably better than those for Zhang and Li (1987), considering that the data were collected using known analytical methods, quality control was likely superior to that in rural China in the 1960s and 1970s, the drinking water was derived from groundwater, and >70% of total chromium in California groundwater used as drinking water is known to be Cr(VI). OEHHA's basis for dismissing the findings of Bednar and Kies (1991) is arbitrary at best. This and the other studies noted above should all be discussed in the PHG document. It is misleading for OEHHA to present a detailed discussion of the one positive study and ignore the other studies with negative findings. This is particularly important, because the exposures and characteristics studied

by Fryzek et al. (2001) and Bednar and Kies (1991) are more consistent with those in California.

OEHHA's risk assessment guidance states, "Human data are preferred whenever possible..." As discussed above, ignoring or discounting the epidemiological studies that provide negative evidence of effects at low levels of chromium in drinking water (Bednar and Kies 1991; Fryzek et al. 2001)[4] is directly in contravention of these guidelines. While these data are likely not appropriate for deriving a PHG, they are very useful in assessing low levels of exposure to chromium that are the type likely to occur in California. In the "weight-of-evidence" approach specified under OEHHA guidance,[5] these negative studies would be valuable for determining whether cancer effects, or potentially non-cancer effects, are relevant from oral exposure to chromium.

Finally, the recent paper by Kerger et al. (2009) regarding the Zhang and Li (1987) and Beaumont et al. (2008) studies should be added to the discussion.

Comment 54 (pages 69–71) Ingestion studies

The Zhang and Li (1987) data and related studies are very important for this PHG; therefore, full consideration of the reliability of these findings is warranted. We think that limitations identified by Smith (2008) regarding the Beaumont et al. (2008) paper are important to understanding the weight of evidence that this study provides for assessing the potential for Cr(VI) be carcinogenic in humans. Points raised by Smith (2008) include:

- Beaumont et al. cannot reconcile how the place of residence at the time of death was determined.
- Beaumont et al. had to do a rough age adjustment based on the known impact of age adjustment on the combined all-cancer crude mortality of rats. The cancer rates were not available for all years, no sex-specific data were available, and in some cases, only crude stomach or lung cancer rates were available for some villages.

In addition, Kerger et al. (2009) conducted another analysis of this population, but this time used data for cancer rates during the same time period for the same five exposed villages to those of four nearby areas with no Cr(VI) in groundwater, rather than to data for the average cancer rate in the district and province. The authors stated, "The use of a local comparison group is considered superior to the use of district or province averages because of the expected improved similarity among unmeasured covariants in nearby areas." The study authors concluded, "The overall findings in the studied population do not indicate a dose-response relationship or a coherent pattern of association of lung-, stomach-, or all-cancer mortality with exposure to Cr(VI)-contaminated groundwater."

[4] Fryzek et al. (2001) is listed in the reference section but is not cited in the text.

[5] "A "weight-of-evidence" approach is generally used to describe the body of evidence on whether or not exposure to a chemical causes a particular effect. Under this approach, the number and quality of toxicology and epidemiological studies, as well as other sources of data on biological plausibility, are considered in making a scientific judgment."

Another very significant weakness of the Zhang and Li (1987) study design, which requires further discussion, is temporal ambiguity, or the lack of certainty that the exposure preceded development of the disease. Depending on the exposure, a number of studies have identified the latency period for stomach cancer as being 15–50 years. As such, it seems more likely than not that exposure to Cr(VI) from drinking contaminated water did not precede the onset of cancer in the Zhang and Li studies. The longest possible latency period from the years included in the study is 14 years (1965–1978), which is lower than the expected latency periods for stomach cancer mortality. Thus, it is highly likely that the cancer mortality observed during 1965–1978 began to develop before water contamination took place, thus greatly diminishing the role of the contaminated water as a causative factor in the etiology of the cancers studied. Beaumont et al. (2008) argues that Cr(VI) exposure hastened the mortality of villagers with cancers initiated by other causes, which is a possibility given the timeline, but it is not reasonable to assume that Cr(VI) exposure caused the cancers reported in these studies. It should be recognized that, at best, these studies posit a hypothesis that very high exposures to Cr(VI) might be a promoter of GI-tract cancers.

An ecological measurement of exposure (i.e., community-level measurements of the exposure [Cr(VI) concentrations in well water]) was used to assign a level of Cr(VI) exposure to the individuals included in the study. This approach to assigning exposure assumes that the subjects in the study consumed contaminated water, and it can lead to misclassification of exposure if the assumption is not consistent with the actual circumstances. There is reason to question the assignment of exposure status because of discoloration and poor taste. It is questionable whether residents continued to consume the affected water and, thus, whether the assignment of level of exposure to Cr(VI) is accurate. Concentrations of Cr(VI) in drinking-water wells varied greatly within any village (Beaumont et al. 2008), such that a sizeable proportion of wells had minimal contamination, and a significant proportion of wells had *no* contamination detected at all. Furthermore, contamination was restricted to certain geographic regions of the particular village, and it was suggested that villagers may have been able to obtain drinking water from alternative sources (i.e,, tap water) and did not have to rely on well water. Thus, assignment of community-level exposure to Cr(VI) may have not accurately captured the true exposure of individuals in the study. Furthermore, no data were collected from individuals to determine their actual exposure (no questionnaire data were used to verify that individuals drank the water; no specimens were collected to analyze biomarkers).

Purported excesses in cancer were based on mortality rates—not incidence rates—for the regions studied. Mortality is a measure that is inherently dependent on prevention, detection, and treatment. Comparing populations from two different areas based on mortality rates relies on the assumption that the two populations are comparable with respect to risk factors, access to health care, and treatment. Villagers in rural regions may not have had the same access to medical facilities and treatment options as city dwellers, the population to whom they were compared. Furthermore, differences in gender, smoking, alcohol consumption, dietary factors, SES, and occupation, which are all relevant to stomach cancer risk, could have existed between the study and comparison populations, but they were not considered by the authors in their analyses as potential confounding factors. Thus, risk estimates of stomach cancer from consumption of Cr(VI)

in drinking water reported by the authors may be biased by the lack of adjustment for these confounding factors.

Surveillance bias and reporting bias are possibilities in this study. Death reporting was handled by the police department (Beaumont et al. 2008), and there is no mention of how complete or accurate the reporting was. Given the fact that residents and government officials in the villages were aware of the Cr(VI) contamination in their water, it is possible that this knowledge influenced their motivation to ensure that cancer and other deaths were recorded.

Stomach cancer is, and was at the time of the study, the most common form of cancer in China. As reported by the authors, average rates of stomach cancer mortality in all of China for the years 1970–1978 ranged from 5.2 to 40.2 per 100,000. Beaumont et al. (2008) reported estimated age-adjusted rates of stomach cancer in the unexposed villagers of 14 to 32 per 100,000 per year, and that in the exposed villagers of 26 to 52 per 100,000 per year. These are extremely high rates relative to age-adjusted stomach cancer incidence rate in California, which is only 8.1 per 100,000 per year based on 2001–2006 data. The epidemiology of stomach cancer in the Zhang and Li study population is expected to be notably different than that for the California population. OEHHA should consider the full weight of evidence and focus on those studies most representative of California drinking water exposures (Fryzek et al. 2001; Bednar and Kies 1991).

Comment 55 (page 69) *"In 1971, a survey of subjects in the second farthest village from the plant revealed 92 percent developed oral ulcers, 48 percent had diarrhea, and 36 percent had abdominal pains. These symptoms were observed in 1974 in the most remote of the five villages near the alloy factory."*

It is assumed that OEHHA is attributing these effects to Cr(VI) exposure, which clearly begs the question of how high the exposures could have been among these villagers. In rats and mice exposed to 180 mg/L for a lifetime, these lesions were not reported. Although information regarding exposure is difficult to discern from this study, it can be surmised that the exposures of these villagers are not representative of Cr(VI) exposures in California, and it is equally unlikely that the stomach cancer risk observed in this study could provide a reliable reference to health risks among Cr(VI)-exposed Californians.

Comment 56 (page 71) *"Another limitation was the study's relatively short observation time (14 years) after residents first noticed the yellow color of the water, which would limit the study's ability to detect increases in cancer. However, increases in stomach and lung cancers were detected in spite of this limitation."*

OEHHA should acknowledge that the observation of increased lung and stomach cancer might well be independent of the occurrence of Cr(VI) in drinking water. Further, what evidence exists that Cr(VI) in water causes an increase in lung cancer? OEHHA did not present findings for lung cancer, although such findings are presented in Beaumont et al. (2008). Lung cancer did not occur in the NTP study, and OEHHA did not consider that

the increased risk from both stomach and lung cancer could be due to increased prevalence of smoking, which is a risk factor for both diseases.

Comment 57 (page 71) *"Additional information resulting from a thorough groundwater hydrological investigation, information whether certain villages were provided alternative sources of drinking water, and information on the effectiveness of remedial measures could be employed to yield a more complete exposure analysis."*

We concur that more information is clearly needed to provide an adequate exposure assessment for Cr(VI), and without such, the study is of questionable reliability. However, it is unclear how this could ever be resolved. Is OEHHA going to conduct more research to better assess exposure? How would that be done? The discussion of Beaumont et al. (2008) clearly indicates that the exposure data are very limited, and for that reason, differences in exposure between villages are unreliable. OEHHA should recognize the uncertainty in the exposure data available for this study.

Comment 58 (page 71) *"Toxicokinetic studies suggest that absorption of hexavalent chromium following oral exposure is substantially reduced by acidic stomach juices that facilitate the conversion of hexavalent chromium to trivalent chromium. Little trivalent chromium is absorbed from the gut (Donaldson and Barreras, 1966). Therefore, human populations that are characterized by elevated pH in the stomach are likely to experience increased absorption of hexavalent chromium, and this factor is likely to be responsible for much of the observed variability in gastrointestinal absorption of hexavalent chromium."*

Petrilli et al. (1986) reported, "The circadian monitoring in several subjects of Cr(VI) reduction by gastric juice collected at 1-hour intervals for 24 consecutive hours showed that, irrespective of pH profiles—which were affected in some individuals by treatment with antisecretory drugs—there was basal activity during interdigestive periods and especially during the night, when each ml of juice was capable of reducing a few micrograms of Cr(VI)." Hence, stomach pH may not be a significant factor affecting human variability of Cr(VI) absorption.

OEHHA failed to cite the study that shows human variability of Cr(VI) absorption due to differences in stomach pH; we are not aware of any such data. The only data on human variability of chromium absorption is from Finley et al. (1997) and Kerger et al. (1996), and the participants in those studies were not reported to be on any medication or to have had conditions that would influence the pH of their stomachs. Hence, this statement appears to be speculative and should be supported or struck.

Examination of Evidence of Chromium Carcinogenicity

Comment 59 (page 72) *"In summary, there is substantial evidence that a sizable portion of the population is consuming medications that are aimed at increasing the pH of the stomach. The targeted pH of 4 or higher is in the range of pH of the forestomach in rodents (Browning et al., 1983; Browning et al., 1984; Kunstyr et al., 1976; Ward et al.,*

1986) where hexavalent chromium administration resulted in a statistically significant increase in tumors in female mice (Borneff et al., 1968). For this population, oral intake of hexavalent chromium would be expected to result in a higher effective dose in the stomach compared to individuals with a more acidic stomach environment."

Neither the rats nor mice of the NTP study developed forestomach tumors, but the epithelial tissue of the forestomach was exposed to Cr(VI) under conditions of naturally higher pH. Hence, OEHHA's hypothesis that higher stomach pH is associated with an increased risk is not supported by the findings of the NTP study. Further, the Borneff et al. study does not provide adequate evidence that tumors of the forestomach occurred due to higher pH, because two of the three generations in the Borneff et al. study did not have an increased risk of forestomach tumors, despite the naturally high pH of the forestomach.

Sensitive subpopulations, based on stomach pH, can be addressed quantitatively in risk assessment using a PBPK model, with parameters for differences in reduction rates based on stomach pH. This refinement should be available once The Hamner Institutes research on Cr(VI) is complete.

Comment 60 (page 72) *"Human studies - Human occupational exposure to hexavalent chromium has been linked to increased rates of cancer."*

For accuracy and clarity, OEHHA should insert the word "lung" before "cancer" in this statement.

Comment 61 (page 72) *"A summary of the findings of multiple studies where workers were exposed to hexavalent chromium by the inhalation route (conducted by OEHHA) was suggestive of a link between inhalation exposure to hexavalent chromium and cancer of the digestive organs."*

As described above in detail, this conclusion is based on a flawed analysis and is not correct.

Comment 62 (page 73) *"In the single study of human exposure to hexavalent chromium in drinking water identified, a statistically significant increase in stomach cancer mortality (statistical analysis conducted by OEHHA) was detected in the exposed population (Zhang and Li, 1987)."*

This statement is incorrect. OEHHA ignored the more relevant studies by Fryzek et al. (2001) and Bednar and Kies (1991). These studies are more relevant, because they evaluated populations and exposures more consistent with Cr(VI) exposures of Californians. The OEHHA analysis of Zhang and Li (1987) is very uncertain and limited and should be considered, as Beaumont et al. (2008) described, as the basis for "hypothesis-generating," because it does not provide strong evidence that Cr(VI) exposures in drinking water are associated with cancer, and although it may be true for

that population of rural Chinese villagers, it is not relevant for assessing the risk of cancer due to Cr(VI) in California drinking water.

Comment 63 (page 73) *"The findings in the Borneff et al (1968) study were diminished for several reasons: the occurrence of viral infection that caused substantial intercurrent mortality; the use of only one dose group; differences in the length of survival and total dose received in different generations in this study; and animals within each treatment group were related to one another. However, the statistically significant increase in stomach tumors was found despite these study limitations, none of which should have led to such results in the absence of a true effect."*

Borneff et al. is an equivocal study. Dr. McConnell, an expert pathologist and former director of NTP, reviewed the study findings and concluded that the observations were not associated with Cr(VI) exposure (McConnell 2006). Finally, the results of Borneff et al. were not reproducible in the NTP study. OEHHA should heed the advice of the expert peer reviewers of this draft and the previous draft, and discontinue its relentless and unjustified position that the Borneff et al. study constitutes evidence that Cr(VI) causes forestomach (not stomach) tumors.

Comment 64 (page 73) *"Oral administration of hexavalent chromium resulted in chromosomal aberrations, DNA single strand breaks or DNA-protein crosslinks in the liver, brain, or bone marrow (Bigaliev et al., 1977; Coogan et al., 1991a; Sarkar et al., 1993; Bagchi et al., 1995a,b, 1977)."*

OEHHA should focus its conclusions regarding genotoxicity on findings from drinking-water exposures that are more representative of environmental exposures. The findings of genotoxicity in these studies do not correspond to tumors in these tissues and are of questionable relevance for understanding the MOA. It is critical that OEHHA include the negative genotoxicity data of DeFlora et al. (2008), because this data set is specific to the target tissue (small intestine) where tumors were observed in the NTP mice, which is the basis of the cancer PHG.

Further, OEHHA cites the genotoxicity study of Bigaliev et al. (1977), conducted by gavage dosing, <u>seven</u> times in the PHG document, and not in a manner questioning the findings. Yet Footnote 2 of Table 2 (page 39) indicates that OEHHA does not understand what the authors were originally reporting in the study, presumably in part because the paper is in Russian. Yet a far superior study, Mirsalis et al. (1996), of mice and rats exposed by drinking water, and conducted using well-recognized and accepted scientific methods, is cited only three times. Another example of this biased reporting of the literature is the genotoxicity study of Kuykendallet al. (1996), which is a study in humans exposed by drinking water and is also cited only three times in the PHG document. Clearly, the data produced by Kuykendall et al. and Mirsalis et al. are far more meaningful for understanding risk assessment than the data on which OEHHA relies. OEHHA must revise the analysis to remove the bias and provide a balanced review of the literature, focusing on those studies that provide the most meaningful information for Californians exposed to Cr(VI) in drinking water.

Comment 65 (page 73) *The oral absorption of hexavalent chromium does not appear to be a consequence of exhaustion of the reducing capacity of gastric fluids and saliva, because the doses administered in toxicokinetic studies did not exceed the ability of the stomach to reduce hexavalent chromium to trivalent chromium."*

As noted above, the NTP study authors (Stout et al. 2009) recognized that the administered dose in the NTP study exceeded the reductive capacity of the stomach. They stated, "Under the conditions of this study, at least a portion of the administered Cr(VI) was not reduced in the stomach." OEHHA should accept the NTP authors' conclusions, rather than repeatedly asserting the opposite based on an obviously flawed attempt to calculate reductive capacity in a mouse based on a crude scaling of human data.

Comment 66 (page 74) "*Mechanism* . . ."

OEHHA has not addressed the MOA for small-intestine tumors in the NTP mice.

As noted by DTSC, the NTP study provides ample evidence for inflammation, chronic tissue damage, and regenerative hyperplasia, as key promotional events that are *necessary* for tumor development. Further, DeFlora et al. (2008) examined the potential for genotoxicity in the mouse small intestine (the target tissue) and found that at drinking-water exposures of 5 and 20 mg/L, oxidative DNA damage and DNA-protein crosslinks did not occur. While target tissue data in the small intestine at the doses that caused tumors in the NTP study do not exist, the only available target tissue genotoxicity data demonstrate that, at exposures far higher than current drinking-water exposures in California, a mutagenic MOA is not operative because necessary key events were not observed. Consistent with the current state of the science, these and other questions in the mechanism of carcinogenicity should be addressed with an MOA/HRF analysis.

OEHHA cites no data that would indicate that Cr(VI) is genotoxic in target tissues, but rather, relies on genotoxicity data developed from animals exposed to extremely high concentrations of Cr(VI) and doses delivered by non-drinking-water routes. The tissues evaluated in these studies included the liver and circulating blood lymphocytes, but evidence of tumors or the potential for a carcinogenic response in these tissues were not seen in the NTP study. Thus, these observations are of questionable usefulness, because they are not "anchored" in observations of tumors in these tissues. Further, studies that had negative findings for genotoxicity in humans following drinking-water exposures at 10 mg/L (Kuykendall et al. 1996), and in mice and rats at drinking-water exposures of 1, 5, and 10 mg/L (Mirsalis et al. 1996), were not given adequate consideration.

The OEHHA assessment has not followed the USEPA (2005) guidelines to assess the MOA of tumors, nor has it developed a convincing weight-of-evidence argument for their conclusions. Neither has OEHHA evaluated the potential for carcinogenicity in the HRF, through which key events, species differences, dose-response and temporal relationships, and other possible MOAs are adequately considered.

As noted above, The Hamner Institute's research is specifically designed to generate the critical missing data on the dose response for key events in the MOA. The Hamner MOA data are necessary to assess the cancer risk for humans exposed to low levels of Cr(VI) in drinking water. The draft PHG is based on default approaches to risk assessment, and OEHHA should revise the draft using the results of The Hamner Institutes' MOA research.

Comment 67 (page 74) *"Conclusion - Exposure to hexavalent chromium has been linked to increased incidences of tumors in humans and experimental animals. Increased tumor incidences were observed not only following occupational inhalation exposures but also were observed in humans and animals in the only available oral studies. Hexavalent chromium displayed genotoxic activity in vitro and in vivo in animals and humans following oral or inhalation exposure."*

This conclusion is highly debatable, as has been discussed in the above comments. This analysis seems to have been written in the chapter-by-chapter approach, in which a group of studies (e.g., genotoxcity studies) were reviewed and conclusions drawn in isolation without consideration of the data presented in other sections (e.g., the pharmacokinetic discussion). The weight of evidence for the production of GI tumors in humans is overwhelming negative, and the one study of Cr(VI) exposure by way of drinking water has serious limitations and can be used only to raise the qualitative possibility of an association; however, it provides no causal evidence. The animal data provide evidence of portal-of-entry effects, but no evidence of systemic effects and, therefore, raise valid arguments when considered with the negative genotoxicity data in these target tissues (DeFlora et al. 2008). The response in mice is likely due to non-genotoxic processes related to regenerative hyperplasia, which is secondary to epithelial injury and not operative at low doses. The toxicokinetics provides support for non-linearities at low doses, rather than providing any supporting evidence that Cr(VI) is a "possible human carcinogen." Until OEHHA conducts a complete weight-of-evidence analysis using the MOA/HRF, the relevance of these data for human health outcomes is questionable.

Comment 68 (page 74) *"The findings of available human, animal, genotoxic, and toxicokinetic studies all indicate that hexavalent chromium is a possible human carcinogen by the oral route."*

The question is really not whether the data indicate that Cr(VI) could cause cancer from ingestion exposures; there is clear evidence that Cr(VI) caused tumors in the NTP study. The current method for evaluating whether the collection of available data is relevant for humans is by using the MOA/HRF. This must be included in the PHG document.

Specific Comments on Dose-Response Assessment

Comment 69 (page 75) *Chopra et al. 1996 and Acharya et al. 2001*

The descriptions for these studies should indicate that the reported LOAEL was the only dose tested. Further, as discussed above (Comment 20), histological findings in the liver and kidney are not quantified or otherwise clearly reported.

Comment 70 (page 75); *"NTP 1997a - Doses of hexavalent chromium arranging from 1.1 to 29.3 mg/kg-day were administered orally to mice as potassium chromate in their diet for nine weeks in this subchronic study in mice. The NOAEL for chromium VI of 1.1 mg/kg-day was identified by the NTP. At doses of 3.6 mg/kg-day and above, vacuoles were detected in hepatocytes."*

As discussed previously, this is a reasonable summary of the study in question, which administered Cr(VI) in diet at concentrations of 15, 50, 100, or 400 ppm. However, this summary omits the results of a similar study in rats and mice that did not show similar liver effects. Rats in an NTP study of the same design (NTP 1996) did not show any liver effects from exposure at doses up to 400 ppm in diet. In a multiple-generation reproductive toxicity study in mice (NTP 1997b), the only liver effect found was an increase in absolute liver weight at 400 ppm in diet, a dose that may be at or above the MTD. Further, the finding of liver vacuoles was not reproduced in the 2008 NTP study. As such, use of this study in a dose-response assessment may not be appropriate given these conflicting results.

Comment 71 (page 76; re: NTP 2007b) *"Indications of mild hepatoxicity (chronic inflammation, fatty changes) were detected in female rats at the lowest doses administered (0.2, 0.9 mg/kg-day). A LOAEL of 0.2 mg/kg-day was identified."*

This statement is not clear. In the two-year NTP study of sodium dichromate, the only nonneoplastic lesion observed in the liver at the lowest dose was mild chronic inflammation in female rats.

Comment 72 (page 76; re: NTP 2007b) *"The critical noncarcinogenic endpoint for risk assessment of hexavalent chromium by the oral route is considered to be liver damage (mild chronic inflammation, fatty changes). A LOAEL of 0.2 mg/kg-day is the lowest dose where toxicity was detected. No NOAEL below the aforementioned LOAELs can be identified from these studies."*

Only mild chronic liver inflammation was observed at the lowest dose (0.2 mg/kg-day) in female rats. NTP (2008) describes these changes as of "minimal severity" and cites a "lack of corroborating evidence in other markers of liver injury."

Comment 73 (pages 76) *"Dose-response relationships were derived using U.S. EPA (1995b, 2000a) BMDS (Version 1.4.1)."*

All of the modeling conducted to derive a cancer slope factor was done with an outdated version of EPA's BMD model. The current version is 2.1 and is available at http://www.epa.gov/ncea/bmds/new.html. OEHHA should use the current version of the BMD model for their PHG slope factor derivation.

Comment 74 (page 77-78) *"Table 10. Cancer Potency Calculations for Combined Incidence of Adenomas and Carcinomas in the Small Intestine of Male B6C3F1 Mice (NTP, 2007b)"*

OEHHA should provide additional information regarding how the BMD modeling was conducted. Comparison of the results from Table 10 to those generated by the New Jersey Department of Environmental Protection, for the same data set, yields a different LED_{10} and p-value for most models (see Table 4a of NJDEP 2009). OEHHA should check the calculations and results to ensure their correctness, and should provide the detailed output information from the BMD modeling work. Further, as recommended by a UC peer reviewer, the dose-response curves generated by the BMD model should be presented in the text. Also, it is unnecessarily confusing to present the results for just the duodenum in Table 9, when the results for total cancers of the small intestine are the basis for the PHG.

It is important to recognize that the uncertainty in the assumption of a linear dose-response is readily quantified here. The LED_{01} can be used with a 30-fold uncertainty factor (3-fold factor for toxicdynamics and 10-fold for intraspecies variability) to derive a HPD that is 200-times higher than the value developed from the linear dose-response.

Comment 75 (page 78) Calculation of the human equivalent dose

The tumors observed in the small intestine of the mouse were probably associated with direct contact with Cr(VI) in the lumen by epithelial cells of the small intestine. Systemic absorption, metabolism, and circulation are not kinetic processes necessary to arrive at a target tissue dose sufficient to cause tumors. Hence, simple allometric scaling is not likely to be the correct approach for scaling from animals to humans. We believe that the use of a PBPK model is the only way that target tissue dose in the small intestine of mice can be scaled to target tissue in humans.

It is well recognized that Cr(VI) is detoxified on ingestion, through reduction to the trivalent state. There is certainly a dose at which the rate of reduction is insufficient to convert all of an ingested dose of Cr(VI) to Cr(III) in the stomach, and as a result, Cr(VI) is passed to the small intestine. In the NTP study mice, although tumors occurred only at the highest two doses, other effects, including hyperplasia, occurred in the small intestine at all doses, suggesting that all the doses administered were greater than the reductive capacity of the stomach, and that Cr(VI) moved to the small intestine unreduced.

Thus, scaling between species should consider anatomical and physiological differences in the GI tracts of rodents and humans. The rate of and capacity for reduction directly affect target tissue dose and the potential for Cr(VI) to pose a cancer hazard.

The findings of the NTP study suggest that interspecies variability between the reductive capacity of the GI compartments in the two different rodent species tested might be significant, and extrapolations to humans are not likely to be simplistic. For example, tissue damage in the small intestine of the mouse, but not the rat, suggests that more

Cr(VI) passed from the mouse stomach to the small intestine. NTP kinetics data support this position, because more chromium was measured in the mouse stomach, forestomach, blood, and liver—reflecting increased absorption of Cr(VI)—relative to the rat, and more chromium was in the feces of the rat than the mouse (on a body-weight-adjusted basis), indicating greater reduction of Cr(VI) to Cr(III) in the rat GI tract. Further, on a body-weight basis, mice drink more water than rats, which resulted in higher doses in mice administered the same concentrations as rats in the NTP study. All of these facts indicate that less Cr(VI) was reduced in the stomach of the mouse and passed to the small intestine.

As carnivorous omnivores, humans have more acidic saliva and gastric acid than rodents and have a higher body-weight-adjusted gastric acid production rate than rodents, which are herbivores. Thus, as compared to rodents, humans should more rapidly detoxify Cr(VI) by reduction. It is interesting to note that the findings of the NTP study for the mouse were not consistent with those for the rat, yet these two species have very similar GI anatomy and physiology, both of which are substantially different from that in humans. Hence, it is not reasonable to assume that findings in one rodent species (tumors in the small intestine) could be extrapolated to humans, when the same outcome did not occur, at the same and higher dose, in another rodent species (the rat).

Interspecies differences in GI reductive capacity and rate are critical to predicting cancer risk in humans. The PHG uses a customary approach to scale between species, but this approach does not adequately account for differences in Cr(VI) reduction in the human GI as compared to rodents.

Comment 76 (page 78) *"1.1 mg/kg-daymouse * (0.035 kg/70 kg)1/4 = 0.16 mg/kg-dayhuman"*

OEHHA used the body weight of the control male mice at the end of the study (0.035 kg) to conduct the human equivalent scaling. We suggest that, if this allometric scaling is to be used, it is more appropriate to scale the dose in each animal dose group to the human equivalent and conduct the BMD modeling using human-equivalent doses. The body weight of the male mice in each treatment group was approximately 0.05 kg at the end of the study. Interestingly, the male mice controls had a lower body weight at the end of the study than the treatment groups. New Jersey DEP (2009) used yet a different approach and applied the time-weighted average body weight at zero dose, which coincidently equals 0.05 kg. OEHHA should provide justification for the approach used to scale to humans.

Comment 77 (page 78) *"Using all dose levels, none of the models in the BMDS yielded an acceptable fit (p>0.1) for combined incidence of adenomas and carcinomas of the intestine in female mice. There was no evidence of saturation, given the incidences of intestinal tumors in the two highest dose groups were well below 100 percent. When the high dose group was excluded, all but one of the models yielded acceptable fits (Table 11)."*

If there is no evidence for saturation, OEHHA provides no basis for excluding the high dose group. More information regarding this analysis is needed. What is the basis for dropping the high-dose group? We could not reproduce the stated results for female mice without dropping the highest dose group. OEHHA should provide greater detail on how the BMD model parameters were set, so that the modeling analysis can be reproduced.

Comment 78 (page 79) *"The results from male mice will be employed in the derivation of the PHG as the data used in the modeling was more robust (based on more data points)."*

It is interesting to note that preference is given here for robustness of modeling results, but in the inhalation cancer risk assessment, models based on only two data points were given weight equal to those based on four.

Comment 79 (page 79-89) *"Cancer Potency for the Inhalation Route"*

The inhalation cancer risk assessment should be based on published risk assessments using the best available exposure-response data (Crump et al. 2003 and Park et al. 2004).

OEHHA attempted to use the findings reported by Gibb et al. (2000), which included results by quartile of exposure, to perform its own dose-response and quantitative risk assessment of the Baltimore chromate production workers. To improve model fit, OEHHA dropped the results of one of four dose groups in one alternative approach, and two of the four dose groups in a different alterative approach (i.e., one of the modeling approaches fit a curve through TWO points!). Although the basis for their decision is unclear, ultimately, OEHHA decided to use its OLD inhalation cancer risk assessment, developed in 1985 based on the 1975 Mancuso study data set, which is extremely limited. For example, in Mancuso (1975), the airborne exposures are described only for total chromium [not Cr(VI)], and the mortality rates are not adjusted.

It seems that OEHHA did not even consider using the published risk assessments of Crump et al. (2003) and Park et al. (2004), both of which were based on the original data—not a published summary based on a limited number of exposure groups—and had worker cohorts with extensive Cr(VI) monitoring data. The data sets used by Crump et al. and Park et al. are both far superior to the data in Mancuso (1975), and were selected by OSHA (2006) as the focus studies for quantitative risk assessments for the Cr(VI) Rule. The environmental unit risk from the Crump et al. (2003) study is 0.00978 $(\mu g/m^3)^{-1}$ (95% CI: 0.00640, 0.0138). Hence, the upper confidence interval on the more refined dose-response assessment by Crump et al. is more than an order of magnitude lower than the value used by OEHHA of 0.15 $(\mu g/m^3)^{-1}$. Park et al. (2004) also evaluated the Baltimore chromate production cohort data, but utilized the original data and incorporated a quantitative analysis to evaluate lung cancer risk due to smoking. Although Park et al. (2004) does not provide an environmental unit risk, we estimate from the occupational unit risk that the environmental unit risk and upper confidence

interval would be approximately five times lower than that developed by OEHHA more than two decades ago but reused yet again, in this PHG document.

OEHHA should delete its evaluation of an inhalation cancer slope factor using the Gibb et al. (2000) published data, and use the published risk assessments of Crump et al. (2003) and Park et al. (2004), because these risk assessments used far superior data sets, as compared to that used by CalDHS in 1985; they were not forced to rely on only the published findings in the mortality studies, but had access to all the original data from which to do their assessment.

Comment 80 (page 85) *"Because the low dose range represents exposure to the general population, an analysis of the lowest two levels of exposure was conducted. In this situation, the observed data conform to a linear dose-response. A perfect fit is achieved in this instance (Figure 20) since the model consists of two parameters and two data points are being fit, i.e., saturated model. The potency estimate from this fit is approximately two orders of magnitude greater than the potency estimate from fitting the entire data set."*

When there are only four data points to model, dropping the highest two is not advisable. Not surprisingly, OEHHA achieved a perfect fit with only two data points. However, this certainly does not mean that the result is correct. The most robust modeling analyses rely on larger numbers of data points. Park et al. modeled five, and Crump et al. modeled seven. OEHHA should use the published risk assessments, because they are far superior to the analysis presented.

Comment 81 (page 89) *"The uncertainties in the Mancuso (1975) exposure data were much less than in other studies analyzed as alternatives in the earlier reports (U.S. EPA, 1984b; CDHS, 1985; Crump, 1995). The measured values of hexavalent chromium in Mancuso (1997) apparently reduce some of the uncertainty about the Mancuso (1975) exposure to hexavalent chromium, but especially because it does not have a referent population, Mancuso (1997) is subject to too much bias to be useful by the present approaches. The earlier CDHS (1985) discussion of uncertainty in the Mancuso (1975) study applies to Mancuso (1997), especially reliance on sampling after the major exposures occurred. OEHHA concentrated on the Gibb et al. (2000) data because it provided superior exposure measurements, which were generally much lower."*

Mancuso (1997) does not provide new exposure data, and Cr(VI) was not measured in that plant by Mancuso. The only Cr(VI) exposure data from that plant have been analyzed extensively by Proctor et al. (2003, 2004). Both Gibb et al. (2000) and Proctor et al. (2003) provide a strong basis for using these newer data sets for risk assessment, as compared to the Mancuso studies, yet in this PHG document, OEHHA continues to rely on the cancer slope factor calculated in 1985 from the Mancuso (1975) study. We urge OEHHA to review the OSHA 2006 rule and utilize the published risk assessments as the basis for a new Cr(VI) inhalation cancer risk assessment in this document. OEHHA is mandated to use the best science available for development of the PHG, and clearly, that has not occurred.

Specific Comments on Calculation of the PHG

Comment 82 (page 90) *"For this purpose, health-protective doses (HPD) will first be calculated from the NOAELs and LOAELs of these studies to illustrate the range of potential choices based on the study limitations and the application of appropriate uncertainty factors."*

For consistency with OEHHA's most current guidelines for development of chronic toxicity criteria for noncancer effects, *Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (June 2008), OEHHA should use BMD modeling, rather than LOAELs and NOAELs, as the basis for determining an HPD. Use of this guidance, developed for the Air Toxics Hot Spots Risk Assessment program, is appropriate given that OEHHA later cites (p. 93-94) earlier Hot Spots Risk Assessment Guidance (OEHHA 2000, *Air Toxics Hot Spots Risk Assessment Guidelines, Part IV*) as the basis of its values for adult and child drinking-water intake used to calculate the PHG. The Technical Support Document is clear that use of benchmark dose modeling is the preferred approach for calculating reference concentrations. For example, OEHHA (2008) states,

> *"Two major strategies are used for dose-response assessment methods to estimate "thresholds" of responses from study data. These are the benchmark dose (BMD) or benchmark concentration (BMC) approach and the no-observed-adverse-effect-level (NOAEL) approach. Of the methods presented, the BMC approach is preferred."*
>
> and
>
> *"Based on recent experience with the benchmark method, new REL* [Reference Exposure Level] *values will be developed using the BMC approach whenever data of sufficient quality to support this methodology are available."*
>
> and
>
> *"The alternative NOAEL method may give the appearance of providing a result more easily with poor data, but in fact the uncertainty in such a result can be extremely large, and the situation is not improved by the inability to quantify this uncertainty."*
>
> and
>
> *"Use of a LOAEL should be a last resort; use of BMC methodology is preferable whenever possible."*

The limitations in the NOAEL/LOAEL approach have been described extensively and should be reflected in OEHHA's consideration of the appropriate approach for developing a noncancer PHG. They include: (1) The NOAEL/LOAEL is highly dependent on dose selection, because the NOAEL/LOAEL can only be one of the doses

included in a study; (2) the NOAEL/LOAEL is highly dependent on sample size—the ability of a bioassay to distinguish a treatment response from a control response decreases as sample size decreases, so that the NOAEL for a compound (and thus the point of departure) will tend to be higher in studies with smaller numbers of animals per dose group; (3) NOAELs/LOAELs do not correspond to consistent response levels for comparisons across studies/chemicals/endpoints and for use as points of departure for the derivation of reference concentrations; and (4) the slope of the dose-response curve is not taken into account in the selection of a NOAEL or LOAEL, and is not usually considered unless the slope is very steep or very shallow (U.S. EPA 2000).

The uncertainties in the NOAEL/ LOAEL approach further support the preference for using the BMD approach. Use of this approach, as in ATSDR (2000), would reduce uncertainty and likely increase the non-cancer PHG; e.g., the ATSDR Health Protective Dose (HPD)-equivalent is seven times higher than the current PHG.

Comment 83 (page 90) *"Concern that humans may develop toxic effects at levels below those in experimental animals (interspecies sensitivity) is typically addressed by using an uncertainty factor of ten in deriving a health-based criterion. Heightened sensitivity could be due to differences in absorption, metabolism, or tissue responses to the chemical."*

Noncancer studies using sodium dichromate suggest that rats are more sensitive than mice for development of nonneoplastic lesions in the liver. Further, it is possible that humans could be less sensitive than rodents, due to species differences in digestive fluid acidity and, hence, reducing capacity. OEHHA should use PBPK modeling to accurately quantify interspecies differences between rodents and humans. Use of these models would decrease uncertainty and likely result in an increased PHG. The magnitude of this increase cannot be calculated until the models are available.

Comment 84 (page 90-91) Description of uncertainty factors applied to specific studies

While use of the benchmark dose, rather than the LOAEL/NOAEL approach, is recommended in deriving the PHG, if a LOAEL/NOAEL is used, this discussion should reflect recommendations for selection of uncertainty factors (UFs) provided in OEHHA's recent guidance, *Technical Support Document For the Derivation of Noncancer Reference Exposure Levels* (OEHHA 2008). For example, OEHHA (2008) recommends a UF of 6 to extrapolate from a LOAEL for a mild effect to a NOAEL, and an uncertainty factor of 1 if the study duration is greater than 12% of lifetime, or $\sqrt{10}$ if the study is 8%–12% of estimated lifetime.

Comment 85 (page 91). *"NTP 1997a - In a limited study with small number of animals aimed at investigating the reproductive toxicity of hexavalent chromium, doses of 1.1 to 29.3 mg/kg-day of hexavalent chromium were administered to mice for nine weeks."*

As discussed previously, the inclusion of this study in the dose-response assessment or calculation of a PHG is problematic due to conflicting information from at least two other

studies. The liver effects seen in this mouse study at relatively low concentrations (50 ppm in diet) were not seen in another mouse study or another rat study at doses up to 400 ppm in diet, and were not seen in mice in the 2007b NTP study.

Comment 87 (page 91) *"An aggregate uncertainty factor of 3,000 is generally considered the maximum, based on recommendations of California's Risk Assessment Advisory Committee (1996) and the U.S. EPA (2002b).*

Per OEHHA's current guidance for derivation of RELs (OEHHA, 2008), if a cumulative UF of 3,000 is exceeded, this is "generally taken to indicate that the source data are insufficient to support derivation." In other words, such a study is of insufficient quality to use in the derivation of a reference concentration, and a study of higher quality should be sought.

Comment 88 (page 93) *"A LOAEL of 0.2 mg/kg-day was identified based on effects in the female rat liver (mild chronic inflammation, fatty changes)."*

For clarity, the <u>only</u> effect seen at the 0.2-mg/kg-day dose was mild chronic inflammation of the liver. Fatty changes were seen in the female rat liver at the next-higher dose (0.9 mg/kg-day).

Further, as discussed previously, per OEHHA's current guidance for development of chronic reference criteria (OEHHA 2008) and consistent with the analysis of the NTP (2008) study by the ATSDR (2008), benchmark dose modeling should be used, rather than a LOAEL, to develop the PHG. OEHHA (2008) states, "Use of a LOAEL should be a last resort; use of the BMC methodology is preferable whenever possible."

ATSDR (2008) evaluated the same endpoint (liver inflammation in female rats), as well as several others, and using a benchmark dose analysis, derived the HPD-equivalent of 0.0014 mg/kg-day, which is seven times higher than that used to derive the PHG. The ATSDR value is more consistent with the current EPA RfD of 0.003 mg/kg-day. OEHHA should use the benchmark dose modeling approach for consistency with its own guidance and that of ATSDR.

The endpoint of liver inflammation may not be biologically relevant to humans, because the NTP study rats had high rates of liver inflammation among control animals (24% of control female rats and 38% of male controls had liver inflammation), suggesting that these rodents are more prone to liver inflammation than humans. Clearly, the rats were also more sensitive than the mice, and while male rats had a slightly significant increased rate of liver inflammation at the second to highest dose (172 mg/L of sodium dichromate dihydrate [SDD]), liver inflammation was not significantly increased at the highest dose in male rats (516 mg/L of SDD). Other effects, including a dose-dependent increase in fatty changes and in histiocytic infiltration, in female rat liver occurred at the next-highest dose, 0.9 mg/kg-day (or 57.3 mg/L of SDD), and this value was noted in the NTP study as the effect level for hepatotoxicity in the female rat. For these reasons, chronic liver inflammation in the female rat may not be a representative endpoint for humans.

Although we recommend that benchmark dose modeling be used instead of the NOAEL/LOAEL approach, if the latter is used, OEHHA should correct the UFs in the calculation in accordance with their own guidance. OEHHA (2008) states that a variety of LOAEL-to-NOAEL UF values can be used depending on the severity of the effect found at the LOAEL. NTP (2008) described the rat liver histology data as providing "an indication of a chronic inflammatory process of minimal severity in the liver." Thus, inflammation would likely be considered a "mild" effect (as identified in OEHHA 2008), and a UF of 6, as opposed to 10, is appropriate.

The various uncertainties described above (critical-effect relevance, uncertainty-factor selection) decrease the reliability of the non-cancer PHG. Reduction of these uncertainties (for example, if a more definitive endpoint or more appropriate UF was selected) would likely result in a several-fold higher PHG.

Comment 90 (page 96) *"For the oral and inhalation route, the risk can be calculated as follows, using the human cancer potency value of 0.6 (mg/kg-day)-1 for the oral route and 510 (mg/kg-day)-1 for inhalation as derived above in the dose response assessment section"*

The inhalation cancer risk assessment section does not conclude that OEHHA is using its inhalation slope factor from 1985 for this PHG until it is presented here. We note our earlier comments that this is not the most scientifically advanced position, nor is it based on the best scientific data.

Comment 90 (Page 96-98) Risk Characterization

The PHG document would benefit considerably from inclusion of a quantitative, and expanded qualitative, uncertainty analysis. This was also specifically requested by Dr. Roberto Gwiazda in his peer-review comments, but OEHHA responded, "While there are many sources of uncertainty, the ability to quantify various sources of uncertainty (e.g., the uncertainty associated with using the findings in animals to predict effects in humans, extrapolating risk associated with high doses to low doses, etc.) is problematic given the lack of data. The PHG discusses uncertainty in the Risk Characterization portion of the document, but the PHG document does not attempt to quantify the uncertainty because there is no accepted method for carrying out such a calculation." This response is not accurate, and a quantitative assessment is feasible.

Numerous methods are available for quantitatively assessing uncertainty in risk assessments. Further, uncertainty regarding extrapolating from animals to humans and high to low doses in the Cr(VI) risk assessment can be addressed using data that are generated by PBPK modeling. Although we strongly recommend that OEHHA complete the PHG document using the refined PBPK models currently under development at The Hamner Institutes, the currently available models developed by O'Flaherty could be used for a quantitative evaluation of toxicokinetics between species. Other assumptions, such as linear extrapolation from cancer risk at high doses to that at low doses, can be quantified. Using OEHHA's current analysis, it is possible to quantify the PHG using

standard U.S. EPA (2005) methods, with the assumption of a threshold dose-response, and the resulting cancer PHG is at least 200 times higher. Also, a non-cancer PHG using BMD modeling similar to that conducted by ATSDR results in a cancer PHG that is seven times higher than the current value.

Further, OEHHA guidance indicates that a qualitative discussion of the sources and potential impact of uncertainty is important to include in risk assessments (OEHHA 2003). While the draft PHG document includes a brief discussion of uncertainty in the development of the PHG (p. 98), the document does not discuss the impact of OEHHA's compounded conservative assumptions on the resulting calculated PHG. Guidance on how to perform and interpret uncertainty analyses for risk assessment is found in numerous publications and regulatory documents (Hammonds et al. 1994; U.S. EPA 1997). OEHHA should perform a more extensive qualitative and quantitative uncertainty analyses and include these in the next draft document.

Comment 91 (page 98) *"The U.S. EPA stated: "There was inadequate data to demonstrate that Cr VI+ has oncogenic potential via ingestion" (U.S. EPA, 1989)."*

U.S. EPA set the MCL at 0.1 mg/L (total Cr) in a 1991 *Federal Register* notice (U.S. EPA 1991). OEHHA should reference this guidance and text from it, rather than quoting the EPA 1989 document. In this guidance, EPA specifically recognizes that (VI) is detoxified by reduction to Cr(III) following ingestion.

Specific Comments on Appendix A—Carcinogenic Threshold?

Comment 92 OEHHA's analysis of the lack of a carcinogenic threshold is flawed and should be removed from the document.

OEHHA has developed the position that a threshold reduction capacity in the mouse stomach can be estimated. Then OEHHA compared the administered doses of the NTP study to the OEHHA estimated threshold and concluded that the NTP doses did not exceed the estimated capacity. Because the doses that resulted in cancer in the NTP study were below OEHHA's estimated reduction capacity threshold, OEHHA incorrectly concluded that there is no threshold for carcinogenicity. These assumptions are flawed for a number of reasons. Most importantly, the findings of the NTP study demonstrate that at all does in the mouse, ingested Cr(VI) escaped reduction in the stomach and entered the small intestine where it caused damage. Stout et al. (2009) states,

> "However, the observed increases in neoplasms of the small intestine of mice and the systemic toxicity in the liver and blood suggests that under the conditions of this study, at least a portion of the administered Cr(VI) was not reduced in the stomach."

Even the lowest of the NTP doses exceeded the ability of the mouse stomach to reduce Cr(VI) to Cr(III) completely, as evidenced by hyperplasia in the small intestine.

OEHHA's estimates of reductive capacity in the mouse are obviously incorrect and its conclusions flawed.

Only through the use of a PBPK model could one quantify a threshold dose, because it is necessary to consider the rate of reduction and the rate of absorption, not absolute quantities, and quantify the differences in rates and volumes between species. The O'Flaherty et al. (2001) PBPK model makes this point quite clearly. However, the published O'Flaherty et al. (2001) model is not sufficiently sophisticated to accommodate the requirements of the current risk assessment, because it does not have a small-intestine compartment and is limited to humans and rats. The Hamner Institutes is currently expanding and refining the PBPK model for humans and rats and developing a model for mice using the NTP data and the preliminary results of ongoing studies. This work will allow for interspecies extrapolations and evaluation of tissue dose in the low dose range, which is relevant to environmental exposures.

Comment 93 (page 115) *"Because hexavalent chromium is rapidly converted to the trivalent form in the GI tract, several investigators have asserted that negligible amounts of hexavalent chromium are orally absorbed (because it would all be rapidly and completely reduced to trivalent chromium (De Flora and Wetterhahn, 1989; De Flora et al. 1997; De Flora, 2000, Proctor et al., 2002b)."*

As noted in earlier comments, this statement misrepresents the information in the papers cited. It is well recognized that there are exposures that exceed the capacity of the stomach to reduce Cr(VI) to Cr(III).

Further, OEHHA must consider that, because tumors occurred only in the alimentary tract of the rodents, whether the observed tumors occurred at exposures that exceed the reductive capacity of the rodent GI is actually not relevant (i.e., systemic absorption was not necessary for the observed effects to occur).

Comment 94 (page 115) *"Consistent with the estimates of DeFlora and associates, studies by Proctor and coworkers also showed that stomach fluids rapidly reduced hexavalent chromium to trivalent chromium at levels that ranged from 3 to 10 mg/L (Proctor et al., 2002a)."*

Proctor et al. (2002a) measured the rate of reduction of Cr(VI) in gastric acid; hence, the mg/L is of stomach acid, not mg/L of water. Further, the study tested Cr(VI) concentrations primarily in the ppb range. It is not clear where the 3 to 10 mg/L comes from. However, OEHHA uses this inaccurate statement to assume that the 10 mg/L of Cr(VI) administered in the Kerger et al. (1996) study is below a reductive threshold of the stomach. That clearly misrepresents the work quoted.

The quality of the review offered in this PHG document is far below regulatory and scientific standards. A complete and thorough quality control review is needed to correct the document before it is re-released.

Comment 95 (page 115) *"The findings of both of these studies are not consistent with the assertion that hexavalent chromium absorption occurs only when the reducing capacity of the GI tract is exhausted."*

OEHHA should recognize that this argument holds only at the exposure levels tested (>5 mg/L) and in the species tested (rodents). There is no basis to assume that the reductive rate and capacity of humans are the same as rodents, and further, the exposure levels tested clearly do exceed the capacity of the rodent stomach to reduce Cr(VI) to Cr(III). This is stated clearly in the NTP study paper (Stout et al. 2009), as noted earlier. If OEHHA actually believes that looking at tissue accumulation will identify a threshold, it should further consider the findings of Sutherland et al. (2000), wherein chromium accumulated in tissues among rats exposed at 3 mg/L and 10 mg/L but not at 0.5 mg/L.

This entire appendix should be deleted. Thresholds are not characterized correctly here, or in some of the papers cited, for that matter. The only means of identifying a threshold is through MOA research that will support an understanding of the temporal nature and dose response of key events, combined with PBPK modeling to quantify target tissue dose and allow for interspecies extrapolations.

Specific Comments on Appendix B

Comment 96 OEHHA's discussions of the Borneff et al. (1968) study and the Helicobacter Hypothesis should be removed.

It is not necessary to provide the detailed justification for considering the Borneff et al. study results, because the NTP study is used for risk assessment in the PHG document. Borneff et al. is an equivocal study, and its findings could not be replicated by NTP. OEHHA's assertion that the reason the Borneff et al. study observed forestomach tumors and the NTP study did not is because the Borneff et al. animals were infected with Helicobacter is pure speculation and does not belong in a PHG document. OEHHA should follow the direction of the expert peer reviewer, Dr. Gwiazda, when he recommended deleting this section. OEHHA did not, on the basis that, "Understanding/ explaining the findings of Borneff *et al.* (1968) can help us better understand why Cr VI is an oral carcinogen." In reality, what OEHHA has provided is a series of guesses to support their previous work. The study does NOT contribute to our understanding of why Cr(VI) is an oral carcinogen. The NTP study provides the only valid basis for a finding of GI-tract cancers in animals. In order to understand or explain why Cr(VI) is an oral carcinogen, OEHHA should follow EPA (2005) cancer risk assessment guidance and seek to understand the MOA for NTP study cancers. The body of data currently available to understand the MOA has several uncertainties and data gaps, but as noted above, they are currently being addressed by an ongoing research program. OEHHA should wait to finalize the PHG until the scientific data needed to understand the MOA—or as stated by OEHHA, "why Cr(VI) is an oral carcinogen"—and whether the MOA is relevant in humans exposed at environmental levels, are available for a refined cancer risk assessment.

Even though OEHHA refuses to believe what even Borneff et al. concluded about the study, that it is equivocal, one could accept the inconsistency between the Borneff et al. study and the NTP findings on the basis of dose administered. OEHHA has not considered in this entire dialog that Borneff et al. (1968) tested Cr(VI) at a dose more than two times higher than any of the NTP doses, so it is entirely possible that the effect, if it is real (which we don't think it is) is due to the higher dose. Clearly, Cr(VI) is an irritant, and tissue irritation is a cause of forestomach tumors, especially when administered with a surfactant. In this more likely case, the finding could have nothing to do with a hypothesized Helicobacter infection, for which there is no evidence.

OEHHA's analysis in this section is highly speculative and not based on any facts about the study. OEHHA has not only hypothesized that the mice of the Borneff et al. study were infected, but that the infection was eradicated in the second and third generations of mice by Cr(VI) exposure. If that is the case, why didn't the controls sustain forestomach tumors? This theory is so far reaching as to approach the absurd, and it clearly does not belong in a PHG document.

OEHHA has further made the leap of faith that Cr(VI) acts as a co-carcinogen with Heliobacter infection. However, in the Borneff et al. study, coexposure with the forestomach carcinogen benzo(a)pyrene demonstrated no synergy. Further, given the latency period between exposure and stomach cancer mortality in the Zhang and Li (1987) study, Cr(VI) could be, at best, a promoter of stomach cancer, which is not consistent with a mutagenic mode of action.

Finally, OEHHA has also not addressed the points raised by Dr. McConnell, a world-renowned pathologist and former director of NTP, that the tumors in the forestomach are not due to Cr(VI) exposure and were likely misclassified by the pathologist.

Additional Referencing Comments

1. The NTP study was finalized in 2007. The PHG document should cite the final report, rather than the draft, throughout.

2. Bigaliev et al. (1977), a genotoxicity study published in Russian, is frequently confused with Bagchi et al. (1997). The Bidaliev et al. study is likely of questionable quality. OEHHA should search the PHG and clarify these citations.

3. ATSDR 2002 is cited in the text but not provided in the reference section. OEHHA should be aware that ATSDR prepared a revised Toxicological Profile in 2008, which is available on the ATSDR web site and contains a substantially updated analysis of many of the issues covered in the PHG draft, including an exhaustive analysis of non-cancer endpoints using BMD modeling.

4. In many places in the document, it is stated that Borneff et al. (1968) observed stomach tumors. For accuracy, it should be clarified throughout that Borneff et al. (1968) only reported forestomach tumors.

5. Hexavalent chromium is abbreviated in many different ways in this document.

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Attachment 1 Table 1

Attachment 1. Table 1. Incidence of Nonneoplastic Lesions in the Liver of Fischer 344 Rat and B6C3F1 Mouse Controls in Two-Year Studies Conducted by the NTP Using the NTP-2000 Diet [a]

Chemical Investigated	Chronic Liver Inflammation; Female F344 rat	Chronic Liver Inflammation; Male F344 rat	Fatty Liver; Female F344 rat	Fatty Liver, Male F344 rat	Chronic Liver Inflammation; Female B6C3F1 mice	Chronic Liver Inflammation; Male B6C3F1 mice	Fatty Liver; Female B6C3F1 mice	Fatty Liver, Male B6C3F1 mice
1,2-Dibromo-2,4-dicyanobutane	43 (86%)	32 (64%)	1 (2%)	6 (12%)	35 (70%)	31 (62%)	1 (2%)	11 (22%)
1-Bromopropane	Not reported	Not reported	40 (80%) vacuolization	31 (62%) vacuolization	Not reported	Not reported	1 (2%)	1 (2%)
2-Methylimidazole	18 (36%)	12 (24%)	Not reported	23 (46%) focal vacuolization	13 (26%) mixed cell infiltration	5 (10%) mixed cell infiltration	Not reported	Not reported
4-Methylimidazole	17 (34%)	18 (36%)	16 (32%)	11 (22%) vacuolization	1 (2%) mixed cell infiltration	Not reported	1 (2%) vacuolization	4 (8%) vacuolization
5-(Hydroxymethyl)-2-furfural	43 (86%)	25 (50%)	6 (12%)	14 (28%)	40 (80%)	37 (74%)	34 (68%) vacuolization	31 (62% vacuolization
Androstenedione	21 (42 %) mixed cell infiltration	1 (2%)	6 (12%) vacuolization	25 (50%) vacuolization	2 (4%) mixed cell infiltration	1 (2%) mixed cell infiltration	6 (12%) vacuolization	17 (34%) vacuolization
Benzophenone	46 (92%)	1 (2%)	11 (22%)	22 (44%)	44 (88%)	33 (66%)	41 (82%) vacuolization	Not reported
Bis(2-chloroethoxy)methane	40 (80%)	32 (64%)	9 (18%)	19 (38%)	8 (16%)	5 (10%)	3 (6%) vacuolization	14 (28%) vacuolization
Bromochloroacetic Acid [c]	14 (28%)	10 (20%)	6 (12%) vacuolization	3 (6%) vacuolization	4 (8%) mixed cell infiltration	4 (8%) mixed cell infiltration	3 (6%) vacuolization	3 (6%) vacuolization
Bromodichloromethane c	Not reported	23 (46%)	Not reported	11 (22%) vacuolization	6 (12%) mixed cell infiltration	Not reported	6 (12%) vacuolization	Not reported
Chronium Picolinate Monohydrate	3 (6%)	1 (2%)	6 (12%) vacuolization	8 (16%) vacuolization	1 (2%)	Not reported	Not reported	3 (6%) vacuolization
Cresols [c]	Not tested	35 (70%)	Not tested	17 (34%)	43 (86%)	Not tested	3 (6%) vacuolization	Not tested
Cumene	1 (2%)	Not reported	11 (22%) vacuolization	Not reported	1 (2%)	1 (2%)	1 (2%)	Not reported
Dibromoacetic acid	2 (4%)	6 (12%)	3 (6%) vacuolization	14 (28%) vacuolization	Not reported	2 (4%) mixed cell infiltration	2 (4%) vacuolilzation	8 (16%) vacuolization
Dibromoacetylnitrile	35 (70%)	28 (56%)	22 (44%) vacuolization	37 (74%) vacuolization	7 (14%) mixed cell infilatration	Not reported	6 (12%) vacuolization	12 (24%) vacuolization
Diethylamine	Not reported	1 (2%) periportal inflammation	3 (6%) vacuolization	5 (10%) vacuolization	1 (2%)	Not reported	1 (2%)	2(4%)

Chemical Investigated	Chronic Liver Inflammation; Female F344 rat	Chronic Liver Inflammation; Male F344 rat	Fatty Liver; Female F344 rat	Fatty Liver, Male F344 rat	Chronic Liver Inflammation; Female B6C3F1 mice	Chronic Liver Inflammation; Male B6C3F1 mice	Fatty Liver; Female B6C3F1 mice	Fatty Liver, Male B6C3F1 mice
Divinylbenzene-HP	3 (6%) periportal inflammation	Not reported	4 (8%) vacuolization	1 (2%) vacuolization	1 (2%)	1 (2%)	2 (4%)	Not reported
Elmiron	36 (72%)	30 (60%)	Not reported	Not reported	40 (80%)	11 (22%)	4 (8%)	9 (18%)
Formamide	39 (78%)	38 (76%)	7 (14%)	14 (28%)	29 (58%)	16 (32%)	6 (12%)	31 (62%)
Ginseng	43 (86%)	35 (70%)	5 (10%)	4 (8%)	14 (28%)	8 (16%)	8 (16%) vacuolization	12 (24%) vacuolization
Goldenseal root powder	7 (14%) mixed cell infiltration	4 (8%) mixed cell infiltration	4 (8%) vaculolization	2 (4%) vacuolization	7 (14%) mixed cell infiltration	3 (6%) mixed cell infiltration	1 (2%) vacuolization	6 (12%) vacuolization
Isoeugenol	Not reported	Not reported	2 (4%)	2 (4%)	Not reported	Not reported	3 (6%)	Not reported
Methyl Isobutyl Ketone	Not reported	Not reported	3 (6%) vacuolization	4 (8%) vacuolization	Not reported	Not reported	Not reported	1 (2%) vacuolization
Milk thistle extract	37 (74%) mixed cell infiltration	31 (62%) mixed cell infiltration	8 (16%) vacuolization	8 (16%) vacuolization	Not reported	1 (2%) mixed cell infiltration	1 (2%) vacuolization	7 (14%) vacuolization
Propargyl Alcohol	1 (2%)	1 (2%)	8 (16%) vacuolization	7 (14%) vacuolization	Not reported	1 (2%)	Not reported	Not reported
Propylene Glycol Mono-*t*-butyl Ether	1 (2%)	Not reported	Not reported	3 (6%)	23 (47%)	9 (18%)	2 (4%)	Not reported
Pulegone	35 (70%)	41 (82%)	7 (14%)	1 (2%)	40 (82%)	24 (48%)	36 (73%)	38 (76%)
Sodium chlorate	39 (78%) mixed cell infiltration	36 (72%) mixed cell infiltration	17 (34%) focal vacuolization	26 (52%) focal vacuolization	7 (14%) mixed cell infiltration	2 (4%) mixed cell infiltration	4 (8%) vacuolization	2 (4%) vacuolization
Stoddard Solvent IIC [c]	Not reported	1 (2%)	2 (4%) vacuolization	3 (6%) vacuolization	Not reported	Not reported	Not reported	1 (2%)
Tetralin	Not reported	3 (6%) periportal inflammation	6 (12%) vacuolization	4 (8%) vacuolization	Not reported	Not reported	Not reported	Not reported
Triethanoloamine [c]	Not tested	Not tested	Not tested	Not tested	14 (28%)	9 (18%)	8 (16%) vacuolization	2 (4%) vacuolization
α-Methylstyrene	Not reported	Not reported	1 (2%) vacuolization	3 (6%) vacuolization	Not reported	Not reported	Not reported	Not reported
β-Myrcene	41 (82%)	34 (68%)	3 (6%)	4 (8%)	43 (86%)	26 (52%)	29 (58%)	25 (50%)

a In general, dose groups consisted of 50 animals. The percentage of animals with the indicated condition is given in parentheses. The NTP studies only summarize observed effects; thus, if the effect is not observed at any dose group, control data are not reported by NTP. If data for liver inflammation or fatty changes were not specifically identified, other related observations, such as cytoplasmic vacuolization and mixed cell infiltration were reported, because these effects may occur prior to fatty changes and inflammation, respectively, and are noted as such.
b Incidence of vacuolization and incidence of mixed cell infiltration are reported if fatty liver or inflammation, respectively, were not reported as observations in the NTP report pathology summary tables.
c Diet was irradiated.

Attachment 2

DTSC Comments

Linda S. Adams
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Environmental Protection

Department of Toxic Substances Control

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Arnold Schwarzenegger
Governor

MEMORANDUM

TO: Jeff Wong, Ph.D.
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FROM: David L. Berry, Ph.D. David L. Berry
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DATE: October 23, 2008

SUBJECT: Hexavalent Chromium Public Health Goal

The HERD was asked to provide review and comment on the "Confidential Pre-Release Draft, Public Heath Goal for Hexavalent Chromium in Drinking Water", prepared by the Pesticide and Environmental Toxicology Branch of the Office of Environmental Health Hazard Assessment (OEHHA) dated September 2008.

General Comments

The toxicity of hexavalent chromium [Cr^{+6}] has been known for at least 180 years and the carcinogenicity in humans of inhaled Cr^{+6} was first reported in the United States in 1948. The inhalation carcinogenicity of hexavalent chromium has been well documented in numerous human epidemiological investigations. The carcinogenicity of hexavalent chromium via the oral route has been a subject of speculation since the late-1960s and a lifetime bioassay in rodents conducted by the National Toxicology Program (2007) with Cr^{+6} in drinking water found an increased incidence of tumors in treated animals.

Human health risk assessments are based on the understanding of two basic components: toxicokinetics and toxicodynamics. Beginning in the late 1980s, the

physiologically-based pharmacokinetic models [PBPK] developed in the pharmaceutical industry for interspecies scaling in drug development began to be applied to other aspects of pharmacology and toxicology including human health risk assessment. These models address the first component (toxicokinetics) and allow consideration of the applied dose and the effective dose at the target organ after taking into account the absorption, distribution, metabolism, and excretion of a compound. These methods depend upon understanding of the route of exposure, partitioning of the compound across biological barriers and compartmentalization in various organs/tissues to scale effective dose across species. The PBPK models mathematically scale dose from a laboratory animal to humans with more precision than the traditional allometric (body surface area) methods promulgated at 22 CCR 12703; PBPK scaling is currently used by the World Health Organization, National Academies of Science, U.S. Environmental Protection Agency [2005], Health Canada, the U.S. Air Force, and the European Union.

The methods used by OEHHA to draft the Public Health Goal for Hexavalent Chromium in Drinking Water are consistent with the methods used in the development of all other Public Health Goals that have been issued by OEHHA. The OEHHA methods are the default protocols that were outlined in the 1985 California Department of Health Services *Guidelines for Carcinogen Risk Assessments and Their Scientific Rationale*. The 1985 methods were to be updated every 5 years, but as of today's date there have been no subsequent revisions or edition of those guidelines. The 1985 default methods ignore recent advances in interspecies scaling and evaluation of the mode of action (MOA or toxicodynamics) of various carcinogens (e.g., formaldehyde) that are utilized routinely by other regulatory agencies in derivation of toxicity factors for a wide range of materials. In the present case, the default methods employed by OEHHA are highly conservative and over-estimate substantially the carcinogenic potency of ingested hexavalent chromium. The reader may appreciate the fact that there are serious consequences associated with overly conservative analyses that fail to account for a carcinogenic MOA.

Most regulatory guidance is based on 'scientific principles' that provide the foundation for that guidance. Situations can occur where strict adherence to default regulatory guidance may violate (or significantly depart from) the basic principle(s) that the guidance was supposed to support. In this regard, it is standard OEHHA practice to assume the animal data can be described by a linear dose-response relationship [LMS], but no data (other than reference to the results of standard short-term tests for genotoxicity) to support that assumption were provided. As written, there is no *a priori* reason to accept the OEHHA assumption that Cr^{+6} –induced tumors of the gastrointestinal tract in rodents can be described most accurately with a statistical model that is linear at low-dose. It is important to remember the difference between the basic principles versus the default assumptions made in the 1985 guidance and to realize that the guidance should be modified in order to be consistent with current scientific principles (and not vice-versa).

Specific Comments

1. The proposed PHG of 0.06 part per billion [ppb] or 60 nanograms/L is well below any method detection limit for Cr^{+6} in drinking water to be found in any commercial or academic analytical laboratory. This has significant implications for warnings required under Proposition 65. Assuming Title 22 is revised at Section 12707(b)(4), and the OEHHA default risk assessment is applied, all potable water supplies with analytically-detectable levels of Cr^{+6} will be required to warn, if not implement mitigation measures. The DPH web site provides the number of domestic water supplies with detectable levels of Cr^{+6}; there are over 2,300 such cases in the State of California and the vast majority of the Cr^{+6} detections in water is associated with naturally occurring sources – including the State Rock (serpentinite) that contains upwards of 1,700 ppm total Cr.

2. The PHG for Cr^{+6} was based on an oral cancer "slope factor" of 0.6 mg/kg-day^{-1}, which OEHHA derived from the data for small intestinal tumors in male mice seen after lifetime ingestion of Cr^{+6} in drinking water [NTP, 2008]. OEHHA then used an occupational study with an inhalation slope factor [510 mg/kg-day^{-1}] derived for industrial conditions [chromium ore refinery] and modeled an exposure assessment for Cr^{+6} exposure during showering. Using a inhalation slope factor based on metal fumes from ore refining with temperatures (1275-1400° C) sufficient to generate chromium fume [Othmer, 2001] extrapolated to a 38°C domestic shower cannot be justified in that the OEHHA-calculated shower Cr^{+6} exposure far exceeds the empirical exposure to Cr^{+6} in shower water droplets [Paustenbach et. al., 2003]. Chromium ore processing conditions and the generation of metal fumes are simply not relevant to domestic showering conditions.

3. The accuracy of the OEHHA discussion of Cr distribution in tissues and organs can be improved by incorporating the PBPK model of chromium in the rat [O'Flaherty, 1996] and its extension to human beings [O'Flaherty et. al., 2001]. Discussion of *in vitro* chromium partitioning in erythrocytes may not be relevant to *in vivo* studies of chromium administered p.o., regardless of the form of chromium. Based on human epidemiological investigations, tumors of the lymphatohematopoietic [blood and lymph] system have not been reported. Use of PBPK modeling for risk assessment is encouraged in EPA's 2005 guidance and is especially important in understanding interspecies extrapolations given the divergent findings in rats and mice and the recognized differences in the human GI including a more acidic stomach.

4. The discussion of Cr kinetics, both trivalent and hexavalent, is incomplete. O'Flaherty [1996] cites relevant papers that are not included in the PHG document that provide an in-depth discussion of the differences in uptake between Cr^{+3} and

Cr^{+6} and that the rapid uptake of chromium in the erythrocyte [as Cr^{+6}] is followed by reduction [to Cr^{+3}]. The kinetics indicate that Cr^{+6} is eliminated differently than Cr^{+3} but that the half-life of Cr^{+6} is greater than a day which is remarkable given the rapid reduction of Cr^{+6} to Cr^{+3}. The loss of Cr^{+6} from the erythrocyte and subsequent uptake into liver and bone marrow suggests that not all Cr^{+6} is reduced to Cr^{+3} as it is distributed into various tissue compartments and eliminated in the urine and feces. The simplistic models proposed in PHG Figures 1 & 2 add nothing to understanding of the toxicokinetics of either Cr^{+6} or Cr^{+3} [see Figure 1, O'Flaherty, 1996].

5. The document places significant weight on the Borneff et al. [1968] study where a single dose level of 500 mg/L of potassium chromate was administered to male and female mice in a three generation study. The fact that only a single dose level was examined precludes any identification of a dose-response relationship, a key piece of evidence required in any assessment of causality. During the course of the investigation, an ectromelia epidemic affected both control and treated groups with significant loss of animals. The reduced numbers of animals severely limits the power of this investigation for both potential adverse reproductive outcomes and potential carcinogenic response. While the Borneff study may be historically interesting, the study is qualitative at best. Only the more recent, audited chronic drinking water study with Cr^{+6} that was conducted by the NTP [2008] can be relied upon for any potential rule making.

6. Inspection of the data generated in the subchronic toxicity study by the NTP [2007a] yields a NOAEL of 15 ppm for mice [1.6 mg/kg-day combined sexes, see pg 27]. In the OEHHA summary, a LOAEL of 1.6 mg/kg-day is reported for the NTP [2007a] study [see pg 76]. The identified LOAEL is actually a NOAEL.

7. The subchronic NTP study [NTP, 2007a] using F344 rats and B6C3F1 mice with sodium dichromate provided the range finding data for the subsequent 2 year chronic bioassay of. Based on these studies, doses of 14.3, 57.3, 172 or 516 mg/L [male and female rats and female mice] and 14.3, 28.6, 85.6, and 257.6 mg/L [male mice] were administered to animals for two years. Non-neoplasic, treatment-related lesions were not observed in male rats. Treatment-related liver toxicity was observed in female rats [fatty involution and chronic inflammation] that increased with increasing dose. Mice [male and female] survived the treatment and the only non-neoplastic lesions observed were diffuse hyperplasia in the duodenum. The NTP study reported no non-neoplastic lesions in the oral cavity of the rat, but no data from the subchronic study were collected for the oral cavity. The NTP reported the results of an additional review of the oral cavity tissues specifically to look for non-neoplastic lesions following observation of the tumors. As the mice failed to develop lesions of the oral cavity and rats are known to be more sensitive to oral cavity tumors than mice (according to NTP's historical data for all chemicals tested),

oral cavity tumors are apparently species-specific and/or a consequence of repeated exposure and associated with the potent chemical oxidizing properties of dichromates and repeat local tissue damage. It is noteworthy that there has not been any increase in oral cavity tumors among workers exposed to Cr^{+6} in any of the numerous epidemiology and clinical studies (e.g., Bloomfield and Blum, 1928; Baetjer, 1950; Gross and Kosch, 1943; Langard and Norseth, 1975; Mancuso and Hueper, 1951). The human data are relevant as chromium workers in historical conditions had ample opportunity for significant oral cavity exposures to inhaled Cr^{+6} in fume, concentrated particulate or aerosol forms [see #14].

8. The NTP two year chronic bioassay of sodium dichromate in F-344 rats and B6C3F1 mice found that rats developed increased incidence of papilloma and carcinoma formation in the oral mucosa and tongue. In mice, the tumors were adenomas and carcinomas found in the ileum, jejunum, and duodenum. These effects were dose-related with the highest dose yielding the greatest tumors per number of animals, only the highest dose yielded increased tumors - except in the case of the male mice. The HERD did not review the actual NTP data and restricted the present review to only the findings presented in the PHG document. The OEHHA combined the respective mouse and rat papillomas, adenomas, and carcinomas to yield a greater tumor response per animal, a statistical method that results in an increased "slope factor" or carcinogenic potency. The high dose tumor effect was also associated with the highest animal mortality and these doses were associated with development of hyperplasia in these tissues in the subchronic studies [NTP, 2007a].

9. The spectrum of tumors indicates that only those tissues with initial Cr^{+6} contact were affected by the treatment. For the rat, the initial tissues contacted by the dichromate in drinking water were the tongue and the oral mucosa. No tumors were observed in the rat forestomach or small intestine. Unlike the rat, the tumors in the mouse were found in the small intestine, an organ with greater residence time and increased opportunity for Cr^{+6} direct tissue contact. Tumors in other organs (including the forestomach) were not detected in the mice, a unique finding for such a chronic study. Although the study was not designed to allow for investigation of the Cr^{+6} MOA, it is clear that tumor development is related to local inflammation and hyperplasia in the target tissue. One candidate MOA concerns the chronic local inflammation induced by the chronic tissue damage inflicted by high-dose chromate and the role of reactive oxygen species. Since the NTP concluded that the lesions in the duodenum in mice were seen in concert with local regenerative hyperplasia, it appears that the highest dose induced overt tissue damage (in addition to the presence of chronic inflammation) and that the tumors arose as a result of that damage. Given that the subchronic investigations revealed hyperplasia in the rat oral mucosa and in the mouse small intestine, the tumor response is very similar to

the promotional response in epithelial cells induced by phorbol diesters. All of these features point to the conclusion that ingested doses of Cr+6 that are insufficient to produce local irritation, tissue damage, inflammation and regenerative hyperplasia are also without additional carcinogenic risk.

10. In the discussion of the results on page 52 of the PHG document the authors mix a human study with the rodent studies. The comparing and contrasting of rodent and human data occurs later in the text.

11. In all of the high dose groups, decreased water consumption and body weight were noted. This observation is consistent with the high dose being unpalatable or due to the effects of systemic poisoning by high-dose sodium dichromate. Thus, only at exposures where either the water would be refused by consumers due to foul taste or at doses sufficiently high to induce gastric or other distress could a practical or measurable increase in carcinogenic risk be measured.

12. The OEHHA weight of evidence discussions are based on human epidemiologic studies of hexavalent chromium considered occupational exposures where the route of administration was primarily via the inhalation pathway. Thirty-one studies were chosen where digestive tract [primarily stomach] tumors were reported. None of the studies cited addressed the oral route contribution to the potential tumor incidence and none of these studies focused on consumption of hexavalent chromium. However, in all of the studies that were cited, tumors of the respiratory tract were observed. In a meta- analysis of chromium exposure and cancer mortality [Cole and Rodu, 2005], at least 84 papers were reviewed relating hexavalent chromium exposure to 10 causes of cancer mortality [lung, stomach, prostate, kidney, central nervous system, leukemia, Hodgkin's disease, lymphatohematopoietic cancers, all cancer and all causes]. Based on the meta-analysis, there is only a weak association between inhaled Cr^{+6} and lung cancer; moreover, there was no significant association of inhalation Cr^{+6} exposure to any of the seven other cancers evaluated [note that the Cole & Rodu (2005) study was excluded by OEHHA].

13. There are limited epidemiological investigations of hexavalent chromium exposure via the ingestion route. Six papers were reviewed that addressed one area in China where a documented exposure to Cr^{+6} in the drinking water occurred. Zhang and Li (1987) evaluated potential relationships between drinking water exposure to hexavalent chromium and the incidence of various cancers and mortality. The OEHHA analysis concluded that the study showed significant increases in stomach and lung cancer and OEHHA reported (Table 8) a summary of epidemiological investigations and concluded there was a relationship between occupational exposure to chrome and increased stomach cancer. OEHHA then calculated rate ratios for the incidence of stomach tumors for these 19 investigations that ranged

from 0.95 to 5.0. However, analyses of these same data by Cole and Rodu [2005] indicated there were no significant increases in stomach or GI tumors associated with Cr^{+6} ingestion and only a very weak association between Cr^{+6} exposure and lung tumors.

14. Based on the tumor data for the F344/N rats and the B6C3F1 mice [NTP, 2008], the mouse appears to be more sensitive to the hexavalent chromium treatment. Hyperplasia was observed in the two year study in the mouse forestomach in a dose-dependent pattern strongly implicating regenerative hyperplasia as a mode of action for the small intestine tumors. Species-specific variability in GI parameters are critical to understanding the relationship between the observations in mice and relevance to low concentration exposures in humans. In contrast, oral cavity tumors are rare in the F344/N rat. Additionally, one cannot expect concordance between the site(s) of tumor development between rodents and humans given the great species-specific variability.

15. OEHHA employed the U.S. EPA BMDS model to fit a dose response curve for tumor incidence in the male B6C3F1 mice and extrapolated from the lower bound to the origin. The combined adenoma and carcinoma data for duodenum or small intestine data were used to generate a mean and lower-bound estimate of the Cr^{+6} exposed mice (ED_{10} and LED_{10}) associated with a ten percent increase in tumors. OEHAA also calculated a dose response curve for female B6C3F1 mice for tumors of the small intestine. Presumably, although not explicitly stated, OEHHA used the data from the male mice for determination of an oral slope factor due to the lower tolerated dose for the male mice.

16. The BMDS generated dose associated with a 10 percent increase in tumor incidence was scaled to a human equivalent dose based on body weight to the 4/3 power [$TD = \alpha \times BW^{4/3}$; allometric scaling]. Subsequently, the data were evaluated using the linearized multistage model [LMS] to develop a slope factor for the oral potency of hexavalent chromium. The OEHHA used the LMS to estimate an oral potency factor for male B6C3F1 mice of 0.6 $mg/kg\text{-}day^{-1}$ and calculated an oral slope factor of 0.8 $mg/kg\text{-}day^{-1}$ for female mice. The NTP [2008] data clearly illustrate evidence for carcinogenicity in the small intestine of the mouse and oral cavity of the rat. However, the MOA for Cr^{+6} tumorigenicity in the gut is not clear from the NTP data and it has not been addressed by the OEHHA. The tumors of the gastrointestinal tract appear to be related to regenerative hyperplasia [NTP, 2007a] in the target tissue followed by progression to benign tumors and finally carcinoma. This is highly indicative of a promotional mechanism that begs the discussion of a threshold dose-response relationship. The NTP studies cannot provide a basis for the MOA to direct a technical basis for the proper selection of a model to evaluate

the carcinogenic potency of Cr^{+6}. The default application of the LMS model makes the assumption that there is no threshold or dose below which there is no tumor response or increased carcinogenic risk. The LMS model is highly conservative and may greatly over-estimate the potency of Cr^{+6} via the oral route. Without understanding the MOA, it is not possible to assign a rigorous dose-response relationship or develop a justifiable oral slope factor.

17. Evaluation of noncarcinogenic effects associated with dichromate ingestion were based on the classical NOAEL/LOAEL approach based on six selected studies. The NTP [2007a] study was chosen as the study given the most weight for a determination of an RfD for oral Cr^{+6}. The OEHHA chose an uncertainty factor of 1000 [10x for using a LOAEL, 10x for extrapolation between species, and 10x to protect sensitive species]. The default 10x interspecies scaling factor is a practice in regulatory assessments where PBPK is not available or has been rejected. In the present situation, PBPK models are available and if utilized would reduce the uncertainty and increase the accuracy of the Cr^{+6} health risk assessment.

18. The carcinogenic potency discussion of the inhalation route of exposure on pages 79 to 89 would be more appropriate in a separate PHG document for establishing an inhalation toxicity factor. There are published studies (Crump et al. 2004; Gibb et al. 2000; Park et al. 2004; Park & Stayner, 2006) that could be used, or directly provide updated inhalation unit risk factors for Cr^{+6} rather than the current OEHHA slope factor that is based on dated information. The more recent studies were used by OSHA for their 2006 rulemaking.

19. OEHHA Appendix A Carcinogenic Threshold. It is not clear how does this discussion contributes to the understanding of a threshold-based dose-response relationship for ingested dichromate. Clearly, the NTP studies do not indicate the absorption of hexavalent chromium is a consequence of over burdening the ability of the GI tract's capacity to reduce Cr^{+6} to Cr^{+3}. Given the tumor response in the rat and mouse, the most likely threshold effect is the ability of the hexavalent chromium to elicit dose-dependent overt tissue damage, chronic inflammation and local regenerative hyperplasia.

20. OEHHA Appendix B Borneff et al. (1968). As noted above, the Borneff study has many limitations due to confounding factors such as ectromelia and lack of a dose-response relationship. The study is qualitative and the results have not been reproduced and should be viewed as anecdotal. The NTP chronic two-year bioassay is a full GLP investigation with rigorous quality control and assurance and pathology review. The NTP is a much stronger investigation and should be the primary basis for any assessment of carcinogenic risk associated with ingested Cr^{+6}.

21. OEHHA Appendix B Helicobacter Hypothesis. There is no information on the presence of *Helicobacter pylori* in the F344/N or the B6C3F1 animals used in the NTP bioassay. While *H. pylori* affects a significant human population and it may influence the stomach pH, it has not been shown experimentally to affect the ability of the stomach to reduce Cr^{+6} to C^{+3} or to affect absorption of chromium across the gut. Appendix B is speculative, lacks relevance to developing the PHG and it should be eliminated from the document as it is speculation.

Recommendations

The NTP bioassays do not address the MOA of hexavalent chromium via the ingestion pathway. Given the lack of data on the Cr^{+6} MOA in the gut, generation of a PHG for hexavalent chromium at this time may be premature as it is not possible to assign a dose-response relationship – other than the default OEHHA assumptions and methods used since 1985. Additional investigations are indicated and should be considered before public release of the PHG value or its documentation.

Subsequent to the 2007 publication of the National Toxicology Program report on the lifetime carcinogenicity bioassay in rats and mice, the Hamner Institute for Health Sciences (Research Triangle Park, North Carolina) initiated pilot studies to update and revise the rodent: human Cr^{+6} PBPK model and to investigate the Cr^{+6} mode of action (MOA) at the genomic level in order to support rigorous human health risk assessments. At the present time, those pilot studies are only just beginning as well as re-evaluation of the 14 day acute and the 90 day subchronic studies in rats and mice upon which the dose selection for the lifetime bioassay was based. The goal of the preliminary studies are to gain sufficient data to inform the design of protocols designed to define more accurately the risk assessment approach which should be taken with ingested Cr^{+6}. It may well be that at the high doses used in the NTP bioassay, that the properties of chemical oxidation are responsible for the upper gastrointestinal tract tumors, whereas, it may be that a genotoxic MOA may be operational in the small bowel where chronic inflammation may be the initiating event. The hexavalent chromium MOA has simply not been established.

The Hamner Institute is willing to cooperate with Cal/EPA, provided sufficient funding is identified to support collection of the genomic and pharmacokinetic parameters that are necessary to determine the MOA and to scale properly the delivered Cr^{+6} dose to target tissues properly from rodents to humans. Using Magnetic Image Resolution (carried out at the University of North Carolina), the Hamner Institute has been able to measure and quantify the relative contributions of Cr^{+3} and Cr^{+6} in the target tissues. The Hamner Institute already has in hand the original O'Flaherty PBPK model for chromium in rats. As of today's date, there is no PBPK model for mice.

These studies are prerequisites to any revisions to the OEHHA public health goal for Cr^{+6}. In the absence of the empirical data, it is speculative to suggest values other than the default 60 nanogram/L PHG are equally, more or less protective of the public health. Taking the most recent Hamner Institute re-evaluation of the pathogenesis and genomics of formaldehyde-induced nasal carcinomas in rodents as an example, the minimum budget required to measure the genomic changes and to develop and implement the PBPK model for one (1) species was $870,000 (direct and indirect costs combined) over 2 years. Thus, one can anticipate a total cost for collection of the required mode of action data and refinement of the PBPK models for rats and mice would be ~$1.8 M over 2 years.

Relative Source Contribution and Bioavailability

The more common commercially important forms of hexavalent chromium include: the oxide (CrO_2), chromyl chloride, ammonium dichromate, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate, potassium chlorochromate, silver chromate, barium chromate, strontium chromate and lead chromate. Their solubilities in water varies from the completely insoluble lead salt to the very soluble oxide. Chromic oxide (the trivalent Cr_2O_3) predominates in ores (e.g. chromites) from which metallic chromium is produced is completely insoluble in water. Thus, one cannot generalize materials as "hexavalent" chrome; rather, the exact form of the element must be taken into account in human health risk assessments - a situation not unlike that applied to other inorganic elements (e.g., arsenic).

It is common practice to take into account xenobiotic exposures incident to bathing, showering and all other domestic uses of potable water (e.g., toilets) when establishing a maximum contaminant level (MCL) for inorganic (e.g., 22 CCR 64431) and organic (e.g., 22 CCR 64444.5) materials. The contribution to total exposure associated with volatile organics like perchloroethylene, carbon tetrachloride, trichloroethylene and related materials has been quantified and it can be substantial (up to 50%of lifetime average dose in the case of chloroform) (McKone, 1987; McKone and Knezovich, 1991). However, none of the common chromium compounds (either as present naturally in ores or as refined commercially important forms) are volatile.

The fact none of the chromium compounds are volatile begs the question of exposure during use of potable domestic water. Given the lack of volatility and the relative water solubility, the only physical form in which a potassium or sodium chromate can be present in water would be as an aerosol. The OEHHA analysis appears to assume the bioavailability of a dilute chromium aerosol is equivalent to that of chromium fume that can arise during welding, cutting or plating or ore processing. All of the temperature

conditions under which chromium fume or aerosols are generated are substantially greater than those encountered in routine household use of potable water for bathing.

There are no empirical data to substantiate the presence of chromium aerosols (regardless of oxidation state) in drinking water intended for domestic consumption or other incidental use. Therefore, it is not possible to assign a relative source contribution for chromium present during bathing in calculation of potential risk to the public health. No reference to peer-reviewed empirical data concerning bathing and showering contributions to total daily chromium dose was provided in the materials submitted for review. Most important, it is necessary to divide chromium and its inorganic compounds into a number of chemical-specific groupings, each with a specific MCL based on the available exposure, toxicological and epidemiological evidence.

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