

**Responses to Major Comments on
Technical Support Document**

**Public Health Goal
For
Hexavalent Chromium (Cr VI)
In Drinking Water**

Prepared by

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TABLE OF CONTENTS

TABLE OF CONTENTS	II
INTRODUCTION	4
RESPONSES TO MAJOR COMMENTS RECEIVED FROM UNIVERSITY OF CALIFORNIA PEER REVIEWERS (SEPTEMBER, 2009)	
Roberto Gwiazda, University of California, Santa Cruz.....	5
Leonard Bjeldanes, University of California, Berkeley.....	10
Michael Kelner, University of California, San Diego.....	12
REFERENCES	17
RESPONSES TO MAJOR COMMENTS RECEIVED FROM PEER REVIEWERS (2009)	
Sharada Balakrishnan, Practical Innovators Inc.....	18
Mitchell Cohen, New York University.....	22
Tobey Rossman, New York University.....	24
William Shotyk, University of Heidelberg.....	28
Elizabeth Snow, University of Tasmania.....	29
RESPONSES TO MAJOR COMMENTS RECEIVED, FIRST COMMENT PERIOD (2009)	
Silvio De Flora, University of Genoa.....	31
Andrew DeGraca, San Francisco Public Utilities Commission.....	37
Michael Rogge, California Manufacturers & Technology Association.....	37
Mark Johnson, Coachella Valley Water District.....	75
C.L. Stathos, Department of Defense.....	76
Robert Hollander, Western Coalition of Arid States.....	82
Andria Ventura, Clean Water Action.....	84
Kristy Morrison, American Chemistry Council.....	84
Renee Sharp, Environmental Working Group.....	85
Christy Marani, Central Water District.....	86
Gary Buchanan, New Jersey Department of Environmental Protection.....	87
Thomas LaHue, Soquel Creek Water District.....	87
Anthony Zampielo, Raymond Basin Management Board.....	88
J. Eric Tynan, Castroville Community Services District.....	90
David Koch, City of Watsonville.....	91
Danielle Blacet, Association of California Water Agencies.....	92

Ronald Gastelum, Southern California Water Committee.....	94
RESPONSES TO MAJOR COMMENTS RECEIVED, SECOND COMMENT	
PERIOD (2011)	
Ann Mason, American Chemistry Council.....	115
Michael Rogge, California Manufacturers & Technology Association.....	135
Timothy Quinn, Association of California Water Agencies.....	145
David Chang, California-Nevada Section, American Water Works Association.....	148
Elliott Rothman, City of Pomona.....	148
Kevin Milligan, City of Riverside.....	150
Steve Bigley, Coachella Valley Water District.....	151
David Luker, Desert Water Agency.....	154
Ron Hunsinger, East Bay Municipal Utility District.....	155
Rebecca Sutton, Environmental Working Group.....	155
Dan Askenaizer, Glendale Water and Power.....	156
David Chang, Golden State Water Company.....	157
Mic Steward, The Metropolitan Water District of Southern California.....	157
Richard Atwater, Souther California Water Committee.....	157
Michael Sovich, Three Valleys Municipal Water District.....	161
REFERENCES.....	163

INTRODUCTION

The following are the combined responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on a 2008 pre-release draft of the proposed public health goal (PHG) technical support document for hexavalent chromium and on two later public review drafts of that document. The pre-release draft was reviewed by three University of California peer reviewers. Their comments and OEHHA's responses were posted on the OEHHA Web site on September 10, 2009. They are included here for completeness. The first public review draft PHG document was released for public comment on August 20, 2009. A public workshop on the first PHG draft technical support document for hexavalent chromium was held on October 19, 2009. The public comment period on that draft document closed on November 2, 2009. The Association of California Water Agencies and Honeywell International, Inc. subsequently requested an external scientific peer review pursuant to Health and Safety Code section 116365(c)(3)(D). Public comments on that draft document, including comments from five additional peer reviewers, are included here along with OEHHA's responses. A revised PHG draft document was released for public review on December 31, 2010. The public comment period on the second PHG draft technical support document for hexavalent chromium closed on February 12, 2011. Public comments received in response to that second draft document are also included here along with OEHHA's responses. Changes have already been made in response to these comments, and have been incorporated into the final PHG document posted on the OEHHA website. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS ON 2008 PRE-RELEASE DRAFT RECEIVED FROM UNIVERSITY OF CALIFORNIA PEER REVIEWERS (POSTED ON OEHHA WEB SITE SEPTEMBER 2009)

Comments from Roberto Gwiazda, University of California, Santa Cruz

Comment 1: *Sensitive population issues.*

From page 1. “However, the weakest aspect of the estimate of the human protective level is the very crude approach followed to calculate it. The slope factor calculated via a linear extrapolation to zero of the lower boundary level of the ED₁₀ ignores two issues that are not incorporated under this approach but that may yield a different protective level (lower or higher) if included: namely, the existence of sensitive populations and the extent to which the reducing capacity of the gastrointestinal tract may have different efficiencies in the conversion of CrVI to CrIII depending on the amount of CrVI in the stomach. Because of these unknowns it is uncertain whether the PHG provides adequate public health protection.”

And from page 3 “There are two sensitive populations that are not included in the estimate of the one in a million lifetime cancer risk: carriers of *Helicobacter pylori* and people with anomalous stomach pH regulation. It is noted that animals in the NTP 2007 study were free of *H. Pylori*. As noted at the end of the document, a more realistic scenario, at least to evaluate the oral carcinogenicity of CrVI in carriers of *H. pylori* would utilize infected animals. This study would most likely yield a lower point of departure for linear extrapolation to zero and result in a lower PHG estimate.

The document recognizes the existence of other groups of sensitive individuals: those with a variety of conditions that result in reduced gastric capacity production. The equation of page 97 does not consider these sensitive subpopulations either. At this point there is no sufficient information to quantify the higher risks that these populations may be exposed to due to CrVI in drinking water. The only certainty is that their inclusion in the cancer risk estimate would yield a lower protective level of CrVI in drinking water than the current one that does not incorporate them specifically.”

Response 1. OEHHA is mandated by statute to protect sensitive populations. The PHG identifies two sensitive populations; 1) individuals with high stomach pH, which may result in less reduction of Cr VI to Cr III in the stomach and therefore a likely increase in the amount of Cr VI in absorption in the intestine, and 2) individuals infected by *Helicobacter pylori*.

While OEHHA is mandated by statute to protect sensitive population, there are no studies found that specifically evaluate these identified sensitive populations, and therefore no data that could be used to develop a dose-response relationship in these populations. The results of the NTP animal bioassay (NTP, 2007) did not yield findings that are informative regarding a dose-response relationship in the sensitive populations. An adjustment to the potency estimate based on differences in absorption of chromium VI in sensitive humans and rodents is problematic given it is unclear how much

hexavalent chromium was absorbed in the mouse relative to how much would be absorbed in individuals with high stomach pH.

However, the methods employed to develop a slope factor, using the most sensitive tumor site, sex and species, and using the lower bound estimate of the dose associated with a 10 percent incidence of tumors (and not the mean), are aimed at protecting sensitive populations.

From U.S. EPA (2005) guidance:

“Slope factors generally represent an upper bound on the average risk in a population or the risk for a randomly selected individual but not the risk for a highly susceptible individual or group. Some individuals face a higher risk and some face a lower risk. The use of upper bounds generally is considered to be a health-protective approach for covering the risk to susceptible individuals, although the calculation of upper bounds is not based on susceptibility data.”

Comment 2: *Reduction capacity of saliva and gastric fluids.*

From page 1: “and the extent to which the reducing capacity of the gastrointestinal tract may have different efficiencies in the conversion of CrVI to CrIII depending on the amount of CrVI in the stomach.”

From Page 2: “It was my opinion that in the process of calculating the oral cancer slope factor by extrapolating to zero a CrVI dose that is associated with a certain incidence of cancer in an animal study, there is an unwarranted assumption that the efficiency of saliva and gastric fluids to reduce CrVI to CrIII is the same in the presence of nanogram amounts of CrVI in the human stomach resulting from exposure to drinking water as it is in the presence of milligram amounts of CrVI in the rodent stomach resulting from high CrVI doses in the rodent studies. There is no information to support this assumption of linearity. ... It is assumed with the approach followed in 2005 and here in this PHG estimate that the fraction of CrVI that is reduced to CrIII is the same at high exposures, at the point of departure, at lower exposures and at the protective level.”

Response 2. The amount of reduction of Cr VI to Cr III in the stomach is a very important issue. Some risk assessors have suggested or concluded that the reducing capacity of stomach fluids is so vast that all Cr VI would be immediately reduced and therefore there is no cancer risk associated with oral exposure to hexavalent chromium. This opinion is not supported by the findings of pharmacokinetic studies in animals and humans (reviewed in the PHG document) and studies that have observed significant increases in tumors in animals and humans exposed to Cr VI (NTP, 2007; Borneff *et al.*, 1968; Beaumont *et al.*, 2007; Zhang and Li, 1987).

The rate of chromium reduction could be a function of concentration in the GI tract, but the reduction does not appear to be an enzymatic process and therefore not limited by the amount of an enzyme in the stomach. The reducing equivalents appear to be from dietary protein (and not the acid) in the stomach and in sufficient quantities that are not rate limiting. Thus mechanisms that would limit the rate of Cr VI reduction in the stomach (saturation of available enzymes or limited availability of reducing equivalents)

do not appear evident in the stomach. Studies by Donaldson and Barreras (1996), Kerger *et al.* (1996), Finley *et al.* (1996, 1997) do not indicate that the amount of absorption increases with increasing doses of hexavalent chromium in humans. A new paragraph in the absorption section of the PHG now discusses this issue.

This comment raises a concern that is similar to other concerns related to interpreting the results of animal cancer bioassays. Because of statistical considerations (the ability to detect tumors), high doses of agents are routinely tested in animal cancer bioassays. High doses may alter the rates of absorption, metabolism (activation and detoxification), and elimination as well as differences in ability to prevent or repair DNA damage, all of which could influence the occurrence of tumors. The use of high doses in bioassays and the consequences of using high doses have been discussed elsewhere (U.S. EPA, 2004); use of high doses is generally thought to help offset the statistical limitations of the relatively small animal study used to estimate human risk for the entire California population.

Comment 3, page 4: “The document extensively discusses the unknowns involved in many of the parameters that are to be considered and included in the PHG estimate. However, this discussion does not translate into a quantifiable measure of uncertainty. In other words: what is the degree of confidence in the PHG value? Can OEHA quantify the uncertainty and say “There is X probability that a value as low as this PHG would protect 1 in a million”?”

Response 3. 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.

Comment 4, page 4: “The absorption section is muddled and could be improved. The paragraphs are not thematically separated nor are the arguments built consistently on the basis of the previous paragraphs. These could be rewritten by leading each paragraph with the main point that is being made and each conclusion built on the foundation set by the previous paragraph.”

Response 4. This section of the PHG document has been rewritten to address the issue.

Comment 5, page 5: “The observation that there is absorption of CrVI when administered in the 6+ species is supported by a different tissue distribution and urinary half-lives after CrVI and CrIII administration. However, there is an apparent inconsistency in the fact that the half life of Cr in RBC’s after intraperitoneal or intravenous CrVI dosing does not match the half life of Cr in RBC’s after oral CrVI

administration. It is argued that blood carries Cr immediately from the point of oral absorption to the liver preventing a blood buildup of CrVI. Critics would argue that the Cr RBC time profile is not consistent with CrVI in blood and the increase in liver CrVI is in fact evidence for absorption of complexes of CrIII-organic ligands.”

Response 5. The difference in the tissue distribution and half-life of Cr following oral vs intraperitoneal administration is not unexpected. Given that oral absorption is a slower process, most of the orally absorbed chromium VI is probably rapidly reduced to Cr III in the plasma before it can get into cells. Being relatively insoluble, Cr III associates with proteins in the plasma and proteins on the outside of the RBC. Thus immediately following oral administration, a larger fraction of Cr in the blood is Cr III, which does not move into cells (RBCs) and is rapidly eliminated by the kidney. Intraperitoneal injection delivers Cr VI much more rapidly and at higher concentrations so immediately after an ip injection, more Cr VI would be expected to have the opportunity to move into RBCs before it is reduced to Cr III in the plasma.

Neither of these observations provides any evidence that orally administered Cr VI is absorbed because it is converted in the stomach to a CrIII-organic ligand complex nor has such a ligand been identified or isolated. The revised absorption section in the PHG document highlights two studies where oral absorption of inorganic trivalent chromium and various organic complexes of trivalent chromium was about the same. If oral absorption occurred via such a ligand complex, then the amount of oral absorption of Cr III and Cr VI should be about the same given most Cr VI is reduced to Cr III in the stomach.

Comment 6, page 5: “The case is made that despite the fact that the reducing capacity of the stomach should completely reduce the dose a human receive from drinking California waters, genotoxic effects were observed in distant tissues in rodents chronically administered by gavage doses...not likely to overwhelm the reductive capacity of the stomach, intestines, and blood, ... such as 1 mg/kg-d or 2.5 mg/kg-d. Further, at the end of the page this information is quoted again indicating that in these oral studies CrVI was not fully reduced, and DNA damage was observed. First, it is not known what the reducing capacity of the rodent stomach is. Second, this argument fails to account for the peculiarities of a gavage study.”

Response 6. The findings of this study indicate that at the doses given, Cr VI administration resulted in a genotoxic effect. Given that Cr III is not associated with genotoxicity, this finding indicates that not all of the administered Cr VI was reduced or converted in the stomach to Cr III. Otherwise, no genotoxicity would have been observed.

Comment 7, page 6: “The document discusses extensively the Borneff et al., 1968, study. The amount of space devoted to this study is not justified and it appears that this extensive presentation and discussion are a leftover from previous PHG’s documents were Borneff et al. 1968, was the only animal study that could be used to demonstrate that oral CrVI is carcinogenic and to calculate an oral cancer slope factor. This is not

the case anymore and it is puzzling that given the amount of uncertainty surrounding the results of this study so much space and speculation is devoted to it, in contrast to the study of Beaumont et al 2008, which is the only human study that shows a relationship between CrVI environmental exposure and oral cancer, but receives a mere two paragraphs of attention.”

Response 7. Point taken. The extensive discussion of the Borneff *et al.* (1968) study has been removed from the body of the PHG document and placed in an Appendix. While there are more recent studies available, conducted with more current study guidelines, a weight of the evidence approach for evaluating the carcinogenicity of Cr VI necessitated considering the findings of Borneff *et al.* (1968). Understanding/explaining the findings of Borneff *et al.* (1968) can help us better understand why Cr VI is an oral carcinogen. The discussion of the CrVI exposure in China which is the subject of Beaumont *et al.* (2008) has been expanded.

Comment 8, page 6: “The analysis of the occupational studies is fairly inconclusive and at most suggestive of a link between CrVI exposure and stomach cancer. Given the very little weight that this analysis carries OEHHA should consider not including this analysis in the PHG document...”

Response 8. The text in the PHG was revised to indicate that evaluation was undertaken “to determine if there may be a link between occupational exposure to hexavalent chromium and cancers of the digestive organs.” The results section of the analysis was changed to indicate that the rate ratio for stomach tumors exceeded 1 in a majority of studies (18/25) but was below 1 in some studies (7/25). Rate ratios for other sites in the digestive system are now included. The interpretation of the findings of this study was modified as suggested in the Examination of Evidence for Chromium Carcinogenicity section of the PHG document.

Comment 9, page 7: “The Beaumont et al. 2008 study deserves much more attention than two paragraphs and meaningless map!”

Response 9. The discussion of Beaumont *et al.* (2008) in the PHG and the underlying data has now been expanded in the PHG document.

Comment 10, page 7: “The modeling of the female data of the NTP 2007 study is not used for the calculation of cancer potency because “the male data used in the modeling was more robust”. OEHAA should reconsider this. Examination of the cancer incidence response with dose from the NTP study suggests a different response according to gender, with males appearing to have a more linear response through the dose range and with female data showing an apparent higher sensitivity at lower doses and saturation in cancer incidence at a lower dose than the males. Does this indicate a gender specific difference in the response shape and sensitivity? Female data should be considered, the LED₁₀'s are lower than those derived from the male data, and the most conservative approach would suggest taking that data into account.”

Response 10. The NTP bioassay consisted of three dose groups of male and female mice plus a control group. Statistically significant increases in tumors were observed in the two highest dose groups. Given the limited number of data points for each sex (only two points were significantly different than control), any comparison of the shape of the dose–response relationship in males and females is problematic, particularly in the low dose region where the incidence of tumors was no different than background.

None of the models yielded acceptable fits in female mice when all of the doses were used. After dropping the high dose, all of the models yielded acceptable fits with a LED_{10} similar to that obtained in male mice (which was based all dose groups). Given that in both sexes only the two high dose groups yielded statistically significant increases in tumors, a dose-response relationship based on both high dose groups (male mice) appeared to be preferable to a dose response relationship where one of the high dose groups had to be censored to obtain an acceptable fit (female mice). Thus the proposed PHG was based on the findings in male mice.

Saturation of the response is not evident in males or females, as at most 50 percent of the animals exhibited tumors in the highest dose groups.

Comment 11: “Page 60: ‘The reduced water consumption appears to be consistent with the reduced weight gain in these animals...’ This is not the case. Female mice drank as much as controls from week 15 and never gained enough weight. Male mice drank less than controls from week 15 but gained as much weight.”

Response 11. The paragraph was rewritten.

Comments from Leonard Bjeldanes, University of California, Berkeley

Comment 1, page 2: “A further cautionary note in the interpretation of the human cancer data apparently comes from a study in 453 communities in Nebraska (Bednar CM and Kies C, J Am Water Resour Assoc. 1991;27:631-635). No association was found in this study between low levels of Cr(VI) in drinking water (up to 10 ppb) with total cancer mortality. This study, to which this reviewer does not have ready access, seems to be highly relevant for the development of safe standards for Cr(VI) in water with relatively low contamination levels, and without obvious exacerbating factors, but was not discussed in the current PHG proposal. Indeed, this latter study apparently can provide dose-response data that could test the validity of the various extrapolation methods used in the PHG proposal to project low dose effects in humans based on high dose exposures in rodents.”

Response 1. The Nebraska study evaluated a number of inorganics including chromium. While the precise analytical methods used in this study are unclear, it is likely that the analysis (conducted by the Nebraska Public Health Department and not the authors) in 1986 and 1987 used standard U.S. EPA analytical methods of the time and therefore measured total chromium and not hexavalent chromium. Low levels of

chromium were detected in the municipal supplies (average level of 0.002 mg/L or twice the detection limit), 80 percent of which came from groundwater (authors). The Nebraska study did not find a relationship between chromium in drinking water and cancer. These data could be examined regarding statistical power and ability to detect an effect at the reported chromium levels, but lack of identification of the chromium species present makes it difficult to compare the findings to those of Beaumont *et al.* (2008) of a relationship between hexavalent chromium in water and increased risk of stomach cancer.

Comment 2, page 2: “The effort to develop a safe dose standard for Cr(VI) in drinking water, however, is complicated by the fact that the human and rodent cancer studies that were considered in the proposal involved only very high doses of Cr(VI). These high exposures are likely to overwhelm the strong reductive capacity of saliva and gastric juices that have been well documented (c.f. De Flora S, *Carcinogenesis* 2000;21; 533-541). Published work also suggests that rodents may be more sensitive to oral Cr(VI) toxicity than humans. Thus, published pharmacokinetic studies have reported a several fold greater level of gastric absorption of Cr(VI) in rodents compared to humans, possibly due to the higher pH of rodent gastric juice.”

Response 2. The absorption portion of the pharmacokinetic section of the PHG was rewritten and Appendix A was added to the document to address this important issue. The available evidence does not support the notion that hexavalent chromium only is absorbed when GI reduction capacity is exhausted. No marked increase in oral absorption of hexavalent was observed with dose, which would be expected if the reducing capacity of the GI tract had been overwhelmed.

The oral absorption of hexavalent chromium appears to be quite similar in rodents and humans. From page 10 of the PHG document: “The amount of hexavalent chromium recovered in urine was below ten percent of the administered dose of hexavalent chromium in humans (6.9 percent, Kerger *et al.*, 1996a), (3.4 percent, Finley *et al.*, 1996b), (1 to 4 percent, Finley *et al.*, 1997), (2 percent, Paustenbach *et al.*, 1996); or in the rat (2 percent, Febel *et al.*, 2001).”

The pHs of the rodent and human stomach fluids are quite acidic and it is unclear if small differences in acidity would cause a difference in absorption given that the reducing equivalent appears to come from protein and not directly from the acid. Infusion of hexavalent chromium directly into the human jejunum (bypassing the stomach) resulted in considerable absorption of hexavalent chromium (roughly 30 percent). Preincubation of hexavalent chromium with HCl alone (which was then neutralized) did not prevent the absorption in the jejunum but preincubation with acidic stomach contents (and then neutralization) prior to infusion into the jejunum largely prevented the absorption (Donaldson and Barreras, 1966).

Comment 3, page 3: “[T]he proposed PHG for Cr(VI), which is fully six orders of magnitude lower than the active concentrations in mice, is well below current safety standards, appears to be lower than levels in uncontaminated waters, is near the limits

of detection with currently available analytical methods, and apparently does not consider the likelihood of a threshold for Cr(VI) biological activity, requires further justification.”

Response 3. Carcinogens are routinely tested in rodent bioassays at high doses, orders of magnitude above levels where exposures typically occur. The need to use high doses in rodent bioassays, discussed elsewhere (Safe Drinking Water Committee, 1977; Committee on Risk Assessment Methodology, 1993), is due to the lack of sensitivity of these tests and mandates to protect public health from low levels of cancer risk (e.g., 10^{-6} risk).

PHGs, by statute, only consider health impacts. Development of the Maximum Contaminant Limit for Cr VI by the California Department of Public Health will address other issues such as background levels, detection limits and cost and feasibility. The possibility of a threshold for carcinogenic effects of Cr VI is an important consideration. For this risk assessment, OEHHA has followed the most recent carcinogen guidelines of the U.S. EPA (2005) and OEHHA’s own principles (OEHHA, 2005). Basically, if there is evidence that an agent acts through a genotoxic mechanism (as there is for Cr VI), no threshold for effect is assumed.

Also, because Cr VI is reduced to Cr III in the GI tract, it has sometimes been asserted that no portion of a dose is absorbed in the Cr VI form. An inability to absorb Cr VI could be considered a pharmacokinetic threshold (independent of genotoxicity considerations). However, all the available pharmacokinetic studies indicate that a portion of the Cr VI is orally absorbed, at the doses studied, with results far too variable to indicate or estimate a threshold. Thus, while we acknowledge the possibility of a dispositional threshold, we have no quantitative basis for the extrapolation, and have felt constrained to utilize the standard cancer risk assessment methodology in this case.

Comments from Michael Kelner, University of California, San Diego

Comment 1, page 1: “The first [salient point] is that only selected data from the NTP studies is used (reference 2007b) to derive the target value. By selected data, I mean only one subset of data from a single study out of the entire NTP database is deemed relevant. This is the one study describing the combined incidence of adenomas and carcinomas in male B6C3F1 mice. The data from all other rodent studies involving chromium-6 ingestion is not utilized.”

Response 1. Most cancer potency estimates that utilize animal data are derived based on the most sensitive species and strain. This is a health-protective assumption, intended to ensure that the cancer risk in humans is not underestimated. The most recent U.S. EPA guidelines (2005) acknowledge a variety of choices for selection of data for the potency calculation, including adding up tumors at various sites, combining data from different datasets (in various ways), presenting the potency as a range, choosing a single dataset “if it can be justified as most representative of the overall

response in humans,” or a combination of these options (U.S. EPA, 2005, section 3.3.5).

OEHHA evaluated the cancer incidence in rats and mice from the NTP (2007) study and concluded that the rat data were inferior for dose-response modeling (poor fits with the common models). We calculated the cancer potency for male and female mice combined intestinal tumors using several different models, finding reasonably good fits and estimated cancer potencies within the same range for both data sets with the various models. The most common model, the linear multistage, gave LED₁₀ values within the range of the other model outputs for both male and female mice, although the highest dose was eliminated from the model for female mice, to achieve best fit. These linear multistage estimates were selected as representative values; the slope factors calculated from them were nearly the same for males and females. Because the male mice data were statistically more robust (no discarded data points), we selected the cancer slope factor for males for calculation of the proposed PHG. The value derived from the female mice data would have been slightly smaller (0.04 versus 0.06), but in a statistical sense should not be thought of as any better or more accurate than the chosen approach. An average of the two values could also have been chosen for the proposed PHG, which would have been within the spirit of the U.S. EPA guidelines, but this seemed to us to add complexity with no added value. Thus, we believe that all the available data from the best studies were considered, and the most appropriate data set was chosen for calculation, with a result that is consistent with the intent of the U.S. EPA guidelines as discussed above.

Comment 2, page 1: “The second [point] is the equation on page 97. This is where the 0.06 ppb threshold is derived, from oral intake and ‘shower inhalation.’ ... Contribution from ‘shower inhalation’ is negligible in comparison to oral (drinking intake), so one needs to focus primarily on the oral intake value and its derivation.”

Response 2. OEHHA typically considers three possible pathways of exposure when developing a PHG: ingestion and dermal contact with water and inhalation in the shower. Because hexavalent chromium is carcinogenic by the inhalation pathway with a very high potency, inhalation exposure in the shower was a possible concern. Therefore, this pathway was addressed and the results showed that the inhalation exposure’s contribution to the overall cancer risk was negligible.

Comment 3, page 2: “The third [point] is the oral intake value for the LED10 on page 80 of 1.1 mg/kg-day(mouse). It is this value that drives the 0.06 ppb limit. ... Is it reasonable to use rodent data versus human? ... The answer to the ... question appears to be yes, based on the paucity and poor quality of human data.”

Response 3. We agree. The only available human study with demonstrable exposure to hexavalent chromium is Zhang and Li (1987). The exposure was not adequately characterized for a dose-response determination.

Comment 4, page 2: “Should an LED10 be used (versus an ED10)? If so, is the LED10 derived appropriately? The answer to [these questions] appears to be “no” as their use and derivation appear to conflict directly with guidelines in the EPA publication 630/P-03/001B, Guidelines for Carcinogen Risk Assessment (March 2005).”

Response 4. The U.S. EPA (2005) guidelines extensively discuss use of various endpoints within the observable range, such as LED10, and we believe that the calculations in the PHG document are well within the scope of recommended options. The specific discussion in the U.S. EPA document uses LED01 for the example of extrapolation from an appropriate point of departure (POD), but this is clearly only an example:

“The POD for extrapolating the relationship to environmental exposure levels of interest, when the latter are outside the range of observed data, is generally the lower 95% confidence limit on the lowest dose level that can be supported for modeling by the data. (Section 1.3.4, p. 1-14)”

“The slope of this line, known as the *slope factor*, is an upper-bound estimate of risk per increment of dose that can be used to estimate risk probabilities for different exposure levels. The slope factor is equal to $0.01/LED_{01}$ if the LED_{01} is used as the POD.” (Section 3.3.3, p. 3-23)”

Comment 5, page 2: *The approach appears to overestimate risk because:*

“#1) The mouse is a susceptible strain (vs even another rodent strain such as a rat that was concurrently tested by the NTP). Why was the data for the rat excluded? Furthermore, the results from this one single mouse experiment, used to derive all factors in the text, appears to be have a higher tumor incidence rate than even other mouse studies performed by the NTP. In essence, the data used represents the most sensitive gender of the most sensitive study of the most sensitive strain, and all other NTP results are discarded.”

“#2) Linear extrapolation was used to derive an LED10 at 95% confidence interval (not an ED10).”

“#3) The largest of several slope factors was chosen as the sole parameter to derive the slope (rather than the mean of all experiments).”

“The latter two are critical as #2 vastly overestimates true risk even for the model used. Regarding #3, not only was the largest slope factor [chosen], but this factor is vastly higher than other slope factors for other rodent studies done by the NTP (perhaps by over a magnitude).”

Response 5. The methods used in a cancer dose-response assessment are intended to be health-protective, but whether the methods result in an underestimate or overestimate of “actual” risk is usually unknown. For example, it is not known whether the most sensitive strains of rats and mice have been chosen for the carcinogenicity study, since only one strain of each species was studied. All the applicable data were considered, as discussed above. The linear extrapolation method for calculating cancer potency is the method of choice when the mode of action is unknown (U.S. EPA, 2005),

and the 95th percentile lower confidence limit on the benchmark dose for a 10% tumor response (i.e., LED₁₀) is the most common benchmark for extrapolation.

OEHHA did not choose the largest available slope factor from the models evaluated, nor calculate the proposed PHG based on the most sensitive sex, as described in the response to comment 1 above. It is unclear whether the commenter may have been alluding to the NTP studies on chromium picolinate as other data available. OEHHA did not consider these data relevant because this compound is an organic complex of Cr III.

OEHHA sought examples to determine how the U.S. EPA is using the 2005 guidance (or an earlier draft version of this guidance) in conducting cancer risk assessment. Only one example was identified for an analogous situation (vinyl chloride, where tumors occurred in males and females of two species; U.S. EPA, 2000). The U.S. EPA developed four slope factors based on the results in male and female rats and mice. The most conservative estimate was recommended, with this statement:

“The oral slope factor and inhalation unit risk calculated for VC are presented in Table 9 (LMS model) and Table 10 (95% lower bound on the ED₁₀). The values calculated using these two methods were very similar. The oral slope factor using the LMS model was determined to be 7.2×10^{-1} per (mg/kg)/day. Inhalation unit risk estimates of 2.6, 2.1, 1.0, and 4.4×10^{-6} per g/m³ for male mice, female mice, male rats, and female rats, respectively were derived. The more conservative estimate of 4.4×10^{-6} per-g/m³ is recommended.”

When developing health-based criteria, OEHHA routinely selects the data set from the most sensitive species and sex if multiple data sets (of sufficient quality) are available. In addition, when tumors are observed in more than one site, the site with the highest incidence of tumors or which yields the highest cancer potency is routinely selected. This approach is taken because the actual carcinogenic potency in humans is unknown, because of the variability of effects in humans, and because of the mandates to protect sensitive human populations.

Recommendations and guidelines supporting this approach include:

- “Since humans vary widely in sensitivity and some individuals are likely to be as sensitive as the most sensitive animal species, a common procedure is to use the most sensitive system as the basis for extrapolation. This procedure was explicitly recommended by the U.S. Inter-Agency Regulatory Liaison Group (IRLG) which stated, ‘the use of data from less sensitive species is justifiable only if there are strong reasons to believe that the most sensitive animal model is completely irrelevant to a segment of the exposed human population.’ OSHA justified the same procedure on grounds of prudence: It is prudent for public health reasons to use the data for the most sensitive system as the basis for extrapolation.” From California’s Guideline for Chemical Carcinogen Risk Assessments and Their Scientific Rationale (CDHS, 1985).
- “For a given chemical, the model was fit to a number of data sets. As discussed in the section above, the default was to select the data for the most sensitive target organ in the most sensitive species and sex, unless data indicated that this

was inappropriate.” From OEHHA Air Toxics Hot Spots Program Risk Assessment Guidelines (OEHHA, 2005).

- “(3) Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality. (4) The results obtained for the most sensitive study deemed to be of sufficient quality shall be applicable to all routes of exposure for which the results are relevant. (5) The absence of a carcinogenic threshold dose shall be assumed and no-threshold models shall be utilized. A linearized multistage model for extrapolation from high to low doses, with the upper 95 percent confidence limit of the linear term expressing the upper bound of potency shall be utilized. Time-to-tumor models may be appropriate where data are available on the time of appearance of individual tumors, and particularly when survival is poor due to competing toxicity.” From California Code of Regulations, Title 27, Chapter 3. Safe Drinking Water and Toxic Enforcement Act of 1986, Article 7. No Significant Risk Levels, §25703. Quantitative Risk Assessment.

Comment 6, page 3: “However, all the NTP2007 studies need to be analyzed and slope factors derived for each study by an accepted methodology. Then the mean median (preferably) slope factor is to be utilized for subsequent calculations. NOT the 95% confidence interval.”

“Note that the use of a mean or median ED₁₀ (not a 95% confidence interval) is also described in the EPA document.”

“Furthermore, the average slope factor (not the upper and lower limits) is to be used to generate the slope factors. Thus, risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decision makers.”

“The ED₁₀ used to generate a human equivalent dose) should be calculated by using all available rodent data considered reliable (e.g. all data in NTP2007B report). Do not restrict the data to one gender from one experiment from one species that is highly susceptible compared to other rodent species (or even other strains of the species).”

“Then the mean value for all studies determined and this value is used to derive the human equivalent dose, which is then used to generate the desired standard.”

Response 6. As described earlier, the U.S. EPA (2005) guidance recommends that the LED₁₀ value be employed to derive the slope factor. OEHHA presents the ED₁₀ values (the “central estimate” referred to above) as well as the LED₁₀ values in Tables 10 and 11, but in accordance with the U.S. EPA guidance, the LED₁₀ value is employed as the point of departure (POD) to generate the slope factor. Given OEHHA’s statutory mandate to be health protective and to protect sensitive populations, the LED₁₀ is the appropriate value to use as the basis of the POD.

The discussion in U.S. EPA (2005) of central estimates is in the context of a formal uncertainty analysis, as follows:

“For example, it may be appropriate to emphasize the central estimate in activities that involve formal uncertainty analysis that are required by OMB

Circular A-4 (OMB, 2003) as well as ranking agents as to their carcinogenic hazard. Thus, risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decisionmakers.”

Guidelines for conducting such an uncertainty analysis for cancer risk extrapolation from animal data have never been provided, and no cancer risk assessment meeting the OMB criterion has yet been produced by U.S. EPA. However, OEHHA does acknowledge in the Risk Characterization section of the PHG document the various uncertainties inherent in cancer risk assessment.

Combining or pooling the results of individual studies can be appropriate under various conditions, especially when the endpoint appears to be a measure of the same effect in independent experiments. Combining or pooling data on different effects (different tumor sites in different species, for example) is very problematic. One could envision combining or pooling data from sites and studies where no significant increase in tumors was observed with sites where there were tumors. This approach would be subject to manipulation, as the dose-response relationship (and therefore the cancer potency) would be a function of the sites and experiments that were selected to be pooled.

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AUGUST 2009 PUBLIC-REVIEW DRAFT

Comments from Sharada Balakrishnan, Practical Innovators Inc.

General Comment and Response

Comment: "Overall, this draft report is a well documented compilation of information on the metabolism and toxicity of Cr(VI) and on the evidence of the carcinogenic potential of Cr(VI) via the oral route."

Response. Comment acknowledged. No response needed.

Specific Comments and Responses

Comment I-1: “Although the Felter and Dourson study did show no responses are likely to be detected below 4 ppm of Cr(VI), there are several factors that affect the interpretation of the results – individual susceptibility, different compounds used in the testing and the fact that levels required to elicit a reaction in previously sensitized persons will be quite variable.”

Response I-1. The Immunotoxicity section has been revised as suggested.

Comment I-2: “The average value of Cr(VI) in the urine of the 4 volunteers is listed. What is the standard deviation of this value?”

Response I-2. The standard deviation (7.7 µg) has been added.

Comment I-3: In the Summary section, page 2, last paragraph, it is mentioned that “Review of occupational studies in which humans were exposed to hexavalent chromium primarily by the inhalation route revealed an increase in stomach cancer, which suggests that cells in the stomach are being exposed to hexavalent chromium, although the primary exposure route was inhalation.” As detailed in the Results section (page 61) of Cancers of ingestion- and digestion-related organs reported in occupational studies, this data is indicative but not all-conclusive. Therefore, the summary statement must be revised to reflect that.”

Response I-3. The Summary has been revised accordingly.

Comment I-4: “As presented in Appendix II, it is believed that infection with *Helicobacter pylori* is likely to increase susceptibility to the occurrence of stomach cancers, this hypothesis should not be relegated to the Appendix section or to a small comment in the Sensitive subpopulations section but at least a summary-synopsis should be discussed within Sensitive subpopulations.”

Response I-4. OEHHA has received a number of different opinions concerning whether the discussion of *Helicobacter* and Cr VI is too speculative to include in the main body of the PHG. The current consensus is to keep it in the Appendix.

Comment I-5: “Comments by reviewer Dr. Robert Gwiazda, (Detailed review, point A) has raised an important point ‘It is assumed that the fraction of Cr(VI) that is reduced to Cr(III) is the same at high exposures, at the point of departure, at lower exposures and at the protective level.’ What is the authors’ view on this? Currently it is not clear if low doses of Cr(VI) will also evade reduction and/or cause DNA damage in the oral cavity or GI tract.”

Response I-5. It is true that the dose-response curve in mice for intestinal tumors versus ingested dose of Cr VI is assumed to be linear from the point of departure down to zero dose. It is also true that such an extrapolation assumes that the same fraction of ingested Cr VI dose is available (i.e., not reduced to Cr III) to induce tumors as the dose is decreased. Unfortunately, we do not have data in the mouse to know exactly what fraction of ingested Cr VI is reduced to Cr III at low dose levels. Therefore, in accordance with standard risk assessment practice for a genotoxic carcinogen (U.S. EPA, 2005; OEHHA, 2009), we assume a linear relationship between ingested dose and tumor incidence. The PHG document discusses a number of studies in which

doses of Cr VI below the point of departure (LED₁₀) resulted in toxicity and/or measurable tissue uptake of Cr VI, indicating that some fractions of administered Cr VI evaded reduction.

Comment I-6: "I think it is not correct to argue that the absorption [of Cr VI] is similar. Looking at the data, one can argue that there is high variability in humans and this is likely in rats as well. There is not enough evidence to assume that the absorption is the same."

Response I-6. We agree. The PHG document presents the limited data but makes no judgment as to whether absorption is similar or different between the two species.

Comment III-1: "Evidence in literature suggests increased susceptibility to cancer from early-life exposure, particularly for chemicals acting through a mutagenic mode of action (Barton et al, 2005, USEPA Supplemental Guidance 2005 and OEHHA 2009)...The PHG derivation should take into account an age dependent adjustment factor (ADAF) or age sensitivity factor (as also recommended by OEHHA's own guidelines). The PHG needs to be recalculated accordingly."

Response III-1. We agree. The PHG was revised to address early in life exposures to carcinogens. The mutagenic mode of action described by McCarroll et al. (2010) has been cited as well.

Comment III-2: "There is no explanation in the draft document on why the multistage model and corresponding LED 10 value was picked for derivation of the cancer slope factor when there are other LED 10 values with higher potency (such as the Quantal linear model in male and female mice) that could have been more conservative and health protective."

Response III-2. The document was revised to only present the multistage model results. As now stated in the document, this is the model preferred by OEHHA (2009) and U.S. EPA (2010) for conducting cancer dose-response assessments (U.S. EPA, 2005; OEHHA, 2009). This is primarily due to the multistage model's generally good fit of the data in the relatively high dose range used in rodent bioassays (Armitage and Doll, 1961).

Comment III-3: "On page 43 under the NTP 2007b study, the body weight gains of the rat are discussed but there is no mention about the water consumption. Please add a few sentences to explain the water consumption, which presumably is just like the mice data which was reduced in the highest dose groups (this is mentioned in the Mice section, Page 47)."

Response III-3. Water consumption was also reduced in the rat. This information has been added to the text.

Comment III-4: "As detailed on Page 46 under the section Neoplasms, it is indicated that in the NTP 2007b study there were other tumors in male rats (benign pheochromocytomas) and female rats (adenomas in the clitoral gland). The authors have not indicated how many animals were affected and what is the historical rate of such tumors in male and female rats? Has NTP addressed these tumors? Is there an

explanation on their occurrence and their significance? Can they be dismissed even though they were statistically significant?."

Response III-4. For both of these tumor types there were more tumors at lower Cr VI concentrations than at the higher concentrations. This precluded their use in dose-response assessment, as discussed in the PHG document. NTP stated "the relationship of these changes to exposure is uncertain." The historical occurrence of pheochromocytomas in male rats is 12 percent and adenomas of the clitoral gland in female rats is 4 percent.

Comment IV. None of these comments required a response.

Comment V-1: "The subheading Physiologic and Nutritional role (page 21) under the section on Metabolism and Pharmacokinetics seems unnecessary. The last sentence (about dietary intake of chromium) of this point on nutritional role has been discussed under Food (page 6). I think that there is no specific need to mention it again here. The first two sentences of this paragraph can also be mentioned under Food and this heading eliminated from this section."

Response V-1. The PHG document has been revised accordingly.

Comment V-2: "The heading on Page 22 is Toxicological effect in Animals and Plants but there are no effects in plants discussed anywhere in the document. The index should also be changed accordingly."

Response V-2. The PHG document has been revised accordingly.

Comment V-3: "On page 56, the last sentence in the first paragraph under the heading Non-oral routes reads "Although the data are rather sparse, it appears that rodents are relatively insensitive to hexavalent chromium when it is administered by inhalation." Did the authors mean to write trivalent chromium since it is apparent that hexavalent chromium causes toxicity via inhalation in rodents?."

Response V-3. Our reference to Cr VI is correct. Cr VI is clearly carcinogenic in humans via inhalation. Few studies have been performed with rodents exposed via inhalation. Those that have been performed suggest that it is not a potent carcinogen in rodents, but more data are required.

Comment V-4: "...for completeness, a small paragraph of Discussion/Conclusion/Summary should be included at the end of this section that indicates the conclusion of the authors based on the results i.e the presence of a "suggestive link between inhalation exposure in epidemiological studies and ingestion related cancer."

Response V-4. The PHG document has been revised as suggested.

Comment V-5: It appears as if undue time/space is devoted to the Helicobacter hypothesis and Borneff study...this can be represented in a short summary in the main document itself."

Response V-5. Discussion of Borneff et al. (1968) was moved to the Appendix per the recommendations of peer reviewers. We find it appropriate as it was not used directly for the calculation of the PHG, but its inclusion serves as a scientific resource and as a

record of the issues that have been addressed in the research for and preparation of this PHG document.

Comment V-6: “Under the section Vagotomy (page 133), it would be clearer to add 1-2 sentences to describe what it is and why it is used.”

Response V-6. The PHG document has been revised as suggested.

Comments from Mitchell D. Cohen, New York University School of Medicine

General Comment and Response

No general comment was made.

Specific Comments and Responses

Comment 1: “In response to the 2008 Reviewer’s comments, the OEHHA modified the PHG to contain a new section (c.f. Appendix A) dealing with the issue of Cr6+ absorption and its relation to any potential ‘carcinogenic threshold’, and to revise the ‘Metabolism and Pharmacokinetics’ portion of the document to better address this issue. OEHHA also indicated in these responses that the reducing equivalents that may be key to the reduction of Cr6+ to Cr3+ appear to come from dietary proteins rather than from gastric acid. This is an important point for deriving the PHG in light of the increased consideration of sensitive populations (i.e., those with anomalous pH regulation due to disease or medications). However, there is no mention of this potential alternative pathway for reduction of ingested Cr6+ in this version of the Draft.”

Response 1. It is not an alternate pathway. The acidic environment appears to act like a catalyst for the reduction of Cr VI to Cr III. We used the word “appears” in our response to the 2008 Reviewer’s comments because it is not certain what factor or factors limit Cr VI reduction in the human stomach. Therefore, we prefer not to speculate on this subject in the PHG document.

Comment 2: “This revised portion of the Draft, in citing the Finley et al. (1997) study showing that administration of Cr6+ (over a range of 0.1 – 10 mg Cr6+/d, for 4 d) did not cause dose-related changes in the percentage of Cr6+ in the urine of human subjects, concludes that “results of these studies do not indicate that oral absorption of administered Cr6+ begins to occur when the reducing capacity of the stomach is exhausted.” This Reviewer questions if insertion of the term “only” before “begins” would be more in keeping with the intention of the OEHHA. As it currently reads, this statement could be interpreted to suggest that there is *always* some Cr6+ that will pass into the GI tract intact rather than only occurring if/when the local ability to reduce ingested Cr6+ is overwhelmed, an outcome with its own toxicologic ramifications (Editorial note: the Finley results are in ‘total Cr present in urine’, not Cr6+ as could be inferred from the corresponding sentence on Page 12).”

Response 2. The PHG document has been revised by inserting the word “only” and indicating that total chromium and not hexavalent chromium was measured in the urine.

Comment 3: “There clearly are more studies on the immunotoxicologic impact of Cr6+ exposure than are provided here – some of these unexplored studies have dealt with effects upon host resistance, changes in functionality of macrophages, etc. Many of the

Cr-induced alterations induced in phagocytes have the potential to also impact on host resistance against tumor cells. Thus, an expansion of the Immunotoxicity section of the document would have greatly strengthened the overall accuracy and completeness of the Draft.”

Response 3. The Immunotoxicity section of the PHG document has been expanded. How effects on immunologic parameters such as host resistance and macrophage functions could affect tumor occurrence resulting from oral Cr VI exposure is not known.

Comment 4: “Nevertheless, as noted in some of the comments from the Public sector, the ‘lack’ of negative results could be disconcerting...However, it is also essential that non-toxic outcomes be reported to provide the proper context and completeness necessary for valid conclusions to be made about the overall toxicity of any given agent, including Cr6+.”

Response 4. The Genotoxicity section of the PHG document has been rewritten. It now includes the in vivo studies that yielded negative results, as suggested in some of the Public Comments.

Comment 5: “The sentiment that only a full explanation of all MOA for Cr6+ should be presented before any PHG can be derived and accepted is illogical. This would be akin to stating that any government-based warnings about smoking and cancer should not be offered even at this point in time since the precise MOA are still evolving [after >50 years].”

Response 5. OEHHA agrees. It should be pointed out that the Cr VI cancer mechanism is discussed in detail in the document, in particular where the weight of the evidence carcinogenicity determination is made (see “Examination of Evidence for Chromium Carcinogenicity” section of the PHG).

Comment 6: “Another study discussed by the 2008 Reviewers for possible inclusion in the Draft was that of Bednar and Kies (1991) which found no relationship between exposure to “Cr6+ in drinking water” and total cancer mortality...This Reviewer believes that inclusion of this study (as an example of a ‘non-outcome’-type study that the 2008 Reviewers felt necessary to include to provide scientific balance to all the other studies indicating Cr6+-induced effects and thereby mitigate any perceived “selective bias”) would have greatly strengthened the overall accuracy and completeness of this Draft.”

Response 6. Discussion of Bednar and Kies (1991) and Fryzek et al. (2001) has been added to the document.

Comment 7: “Optimally, the OEHHA should have presented calculated PHG values based upon both the ED₁₀ and the LED₁₀ (thereby giving rise to a PHG range of 0.06 - 0.11 ppb). However, as noted above, a most conservative approach should be used when dealing with a risk for the potential for causing cancer in exposed populations. Thus, **the determination has been made that use of the LED₁₀ was appropriate for generating the PHG for human exposures to Cr⁶⁺ in drinking water.**”

Response 7. Revised tables in the PHG document contain both the LED₁₀ and ED₁₀ values used for the cancer potency estimates in male (Table 10) and female (Table 11)

mice. Only the LED₁₀ was used to develop the PHG. Developing multiple final PHG values was judged not useful.

Comment 8: “It is clear that the data presented in the Draft document (c.f. Figure 13; Editorial note: abscissa needs the addition of units as the values shown do not correspond to any of the reported doses in Table 5 and 6) shows that tumor formation in the mice as a function of Cr⁶⁺ level in drinking water is not linear.”

Response 8. In the 2008 NTP study statistically significant increases in tumors of the small intestine were observed for both male and female mice at the two highest drinking water concentrations. Exact trend tests were positive for both sexes. The absence of statistically significant increases in tumors at the two lowest drinking water concentrations may be due to the small number of animals tested. The use of high doses in cancer bioassays is generally thought to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors). Figure 13 from the draft PHG document referred to here has been removed.

Comment 9: “Reviewer comment: The information provided in the OEHHA response to the Reviewer noted here [2008 Peer Reviewer Michael Kelner] should also be placed in the Draft document to provide critical clarity for readers and others who will rely upon the Draft for making important decisions regarding Public Safety/Health matter.”

Response 9. This information has been added to the “Dose-Response Assessment” section of the PHG document.

Comment 10: “The second issue is about the use of the 2 L/day value for modifying the 0.6 (mg/kg-day)⁻¹ slope factor value (originally derived on Page 78) in the final PHG estimate. This conflicts with the fact that in the Table 17 data displaying the HPD values for non-cancer endpoints, an adult consumption of water is presumed to be ~ 3.7 L/day (to yield 0.053 L/day value noted in the footnote).”

Response 10. The water consumption values associated with Table 17 (non-cancer endpoints) and Table 18 (cancer endpoint) are now correct.

Comments from Toby Rossman, New York University

General Comment and Response

Comment: “Attached is my review of the chromium document. I have some serious reservations about the mechanistic aspects, as you will see.”

Response. See below for OEHHA’s responses to each specific comment made by this reviewer.

Specific Comments and Responses

Comment 1-1: “DNA damage *per se* does not inform us about eventual heritable change, which is the true issue. Assays that do not depend on the survival of genetically-altered offspring (i.e. chromosome aberrations, SCE, micronuclei) are only suggestive.”

Response 1-1. The *in vivo* genotoxicity studies reported in Table 2 of the PHG document are short-term assays that do not depend on the long-term survival of the

genetically-altered cells. For mutation induction by Cr VI, which generally does depend on long-term survival, see the first paragraph of the “Genetic Toxicity” section of the PHG document for references to recent reviews that discuss experiments with cultured mammalian cells and bacteria. Nonetheless, evidence of chromosome breakage implied by the appearance of chromosome aberrations, micronuclei or SCE (Table 2 of the PHG document) has traditionally been considered an important part of the discussion concerning mechanism of action.

Comment 1-2: “The description of an agent as a “genotoxic carcinogen” is out of date. What we really need to know is whether an agent has a mutagenic mode of action (MOA).”

Response 1-2. Genotoxicity continues to be an important consideration in discussions of MOA. The *in vivo* evidence for genotoxicity is presented in Table 2 of the PHG document. The evidence for mutation induction by Cr VI is presented in some recent review articles cited in the first paragraph of the “Genetic Toxicity” section of the PHG. We now note in the document that a mutagenic mode of action has been fully described and justified by McCarroll et al. (2010). Further, the described mode of action is consistent with extrapolation procedures used in the risk assessment.

Comment 1-3: “Cr(VI) is only weakly mutagenic in mammalian cells, rarely giving more than a 3-fold increase in mutant fraction over background levels (in endogenous genes), and in a very narrow (and toxic) dose-range with a strong threshold (reviewed in Nickens et al., *in press*)...Mutations can result from DNA damage, but can also result from loss of mismatch repair and other types of genomic instability, and in some cases “mutations” are actually epimutations resulting from altered DNA methylation...Salnikow and Zhitkovich also discuss the lack of p53 mutations in Cr-induced lung tumors (which usually have p53 mutations when associated with other agents such as tobacco smoke), and the fact that the few mutations found do not correspond to the types of mutations caused by Cr in *in vitro* systems...Thus, the actual increase in mutant fraction reached only about 1.5-fold over background.”

Response 1-3. There are a number of published studies which report robust (in excess of 3-fold increases) mutagenic responses of cultured mammalian cells to Cr VI (see Paschin et al. (1983) *Mut Res*103(3-6):345-347; Mitchell et al. (1988) *Environ Mol Mutagen* 12(Suppl 13):37-101; Myhr and Caspary (1988) *Environ Mol Mutagen* 13(12):103-194; McGregor et al. (1987) *Environ Mutagen* 9(2):143-160; Oberly et al (1982) *J Toxicol Environ Health* 9(3):367-376). Reviews discussing these studies are cited in the first paragraph of the “Genetic Toxicity” section of the PHG document. Cr VI also caused mutations in bacteria, yeast, *D. melanogaster* and mice (U.S. EPA, 2010). Loss of mismatch repair could hardly be responsible for the findings reported in Table 2 of the PHG document. Lastly, we would not rule out the plausibility that Cr VI causes tumors by a mutagenic MOA as described by McCarroll et al. (2010).

Comment 1-4: “It is of interest that most of the *in vivo* drinking water experiment described in the document gave negative results for genotoxicity, except for the high dose of 100-200 ppm (Coogan et al., 1991).”

Response 1-4. Table 2 in the PHG document updated with the results of NTP (2007) now cites nine drinking water studies of which three are positive for genotoxicity, and 21

total studies (drinking water or gavage) of which 10 are positive for genotoxicity. OEHHA believes these data demonstrate that Cr VI is genotoxic by the oral route.

Comment 1-5: "In the case of Cr(VI), most of the micronuclei are kinetecore-positive, meaning that they arise from malsegregation (Seoane and Delout, *Mutat. Res.* 490:99-106, 2001; Figgitt et al., *Mutat. Res.* 688:53-61, 2010)."

Response 1-5. Ten *in vivo* studies were positive for genotoxicity (Table 2 of the PHG document). Of these, one was a micronucleus study (NTP, 2007). Micronuclei were not assayed for the presence of kinetochores in this study. In addition, both studies cited in this comment also reported increases in cells with chromosome fragments relative to controls, demonstrating genotoxicity.

Comment 1-6: "There is evidence that food contains Cr(VI) as well as Cr(III). In fact, all parts of grain contain Cr(VI) and 10% of the Cr in bread is Cr(VI) (Mishra et al., *Food Chem. Toxicol.* 33:393-397, 1995; Soares et al., *J. Agric. Food Chem.* 58:1366-1370). It is possible that dietary Cr(VI) is significant and should be evaluated."

Response 1-6. Mishra and associates studied the uptake of Cr VI into the corn plant but did not speciate the form of Cr in the plant. Soares and coworkers did speciate between total chromium and Cr VI in finished bread and this paper has been added to the "Food" section of the PHG document. For non-carcinogens, a relative source contribution (RSC) factor is used to derive the PHG. The choice of the RSC is based on how much exposure comes from sources other than drinking water. A public health-protective concentration for Cr VI in drinking water based on noncarcinogenic effects is based on 20 percent of the total daily exposure to Cr VI coming from other (non-water) sources. The health protective dose (HPD, referred to as acceptable daily dose or ADD in the final PHG document) of 0.0002 mg/kg-day or 14 µg/day was for an adult male. Twenty percent of the ADD is 2.8 µg/day which is considerably higher than the level of 0.6 µg/day due to intake from bread reported by Soares and coworkers (now discussed in the "Food" section of the PHG document).

Comment 1-7: "It is incorrect to say the relative contribution of the various species to DNA damage is unknown when the most recent reference given is 2000...The intracellular reduction of Cr(VI) is non-enzymatic. Reductants are ascorbate (major), GSH, other thiols, maybe NADH...The second paragraph on p. 42 should be deleted and replaced with up-to-date material."

Response 1-7. The section entitled "Mechanism of Genotoxicity and Carcinogenicity" has been revised and updated.

Comment 1-8: "The experiment by Davidson et al. is not a non-oral route, it is a cocarcinogenesis experiment with solar UV and Cr(VI) in drinking water."

Response 1-8. We reported this study together with non-oral studies because its protocol is not typical of oral studies (highlighting this fact). It is a co-carcinogen type study, many of which were done by skin painting of two carcinogens together.

Comment 2-1: "The data set is probably the best available. However, the calculations are confusing...Concerning the dose/response relationship in Fig. 13: What are the units on the axes? Where are the error bars or 95% C.I.?"

Response 2-1. Figure 13 from this draft has been dropped from the PHG document. The mouse tumor data are now presented in Tables 5 and 6. The discussion has been revised.

Comment 2-2: “The paragraph on the historic rate of small intestine tumors is confusing...In any case, the final sentence in the first paragraph is nonsense. Statistical analysis decides.”

Response 2-2. This paragraph has been revised. A sentence has been added to clarify that tumors are for 1) duodenum, or, 2) for the entire small intestine. While statistical analysis is important, increases in rare tumors are often a concern even when the increase is not statistically significant. In this case the increase was for a rare tumor that also happened to be statistically significant.

Comment 3-1: “The assumption is that Cr(VI) in drinking water has a mutagenic MOA with no threshold.”

Response 3-1. OEHHA does not know the mechanism by which Cr VI causes cancer in humans or animals. The review of possible mechanisms includes a number of genotoxicity studies that are consistent with a non-threshold mechanism. As the reviewer indicates, there are studies that suggest other mechanisms. The document now cites the mutagenic mode of action described by McCarroll et al. (2010).

Comment 3-2: “A “genotoxic” agent does not necessarily cause tumors by a mutagenic MOA. Cr(VI) is only weakly mutagenic in animal cells (it is more mutagenic to bacteria). Furthermore, the mutagenicity occurs only at toxic doses in a narrow range (i.e. it has a threshold).”

Response 3-2. It is not unusual for mutagens to also cause some cell killing in the dose range where mutations are induced. See Response 1-3 for a discussion of the magnitude of the mutagenic response of cultured mammalian cells to Cr VI. With regards to experimental thresholds, this is to be expected. As the dose is lowered, at some point the experimental system will not be sufficiently sensitive to measure the change.

Comment 3-3: “Other MOA’s have not been considered. These include, for example, selection for Cr-resistance (involving epigenetic changes) and aneuploidy. These events generally show thresholds.”

Response 3-3. Various effects of Cr VI on DNA are discussed in the PHG document. However, given the evidence of reactions between Cr VI and DNA that could result in a non-threshold dose response relationship, the dose response relationship for calculation of the PHG is based on a non-threshold mechanism.

Comment 3-4: “In the NTP study, there is no statistically significant increase in tumors below 85.7 mg/L. Is this taken into account in deriving the slope? What would happen if a threshold were included?”

Response 3-4. In many NTP studies, statistically significant increases in tumors are not detected in the lowest dose group. This may be due to the inability to detect a low number of tumors at the low dose levels (too few animals), not a mechanistic threshold. The multistage model used to derive the dose response relationship in male mice used

all dose groups. If a different model were used that gave a threshold at the lower dose levels, the PHG would be different.

Comment 3-5: "Please consider the recent meta-analysis of cancers of the G.I. tract among those occupationally exposed to Cr(VI), which concludes that these workers are not at greater risk than the general population (Gatto et al., Cancer Epidemiol. 34:388-399, 2010). Inhalation exposure usually also leads to G.I. exposure, so this also suggests a possible threshold if the ingested dose can be estimated."

Response 3-5. The study by Gatto et al. (2010) is discussed in the "Toxicological Effects in Humans" section of the PHG document. Its conclusions as quoted above may or may not be evidence of a threshold. The inability to detect significant increases in GI tract tumors may be due to the small population studied or the low doses of Cr VI swallowed. GI tract tumors may have been detected if the population comprising the study had been larger.

Comment 3-6: "Using the LED₁₀ is overly conservative."

Response 3-6. Use of the LED₁₀ is recommended for cancer risk assessment (U.S. EPA, 2005; OEHHA, 2009).

Comment 4: "I would just add that Cr(VI) in food may be more significant than assumed. The fact that Cr is essential also implies that oral Cr(VI) could supply the necessary Cr(III), again implying a threshold."

Response 4. The study by Soares et al. (2010) on the Cr VI content of bread has been added to the "Food" section of the PHG document. The knowledge on the essentiality of chromium in the mammalian diet is still being developed and chromium essentiality has recently been questioned by Di Bona et al. (2010, J Biol Inorg Chem 16(3):381-90).

Comments from William Shotyk, University of Heidelberg

General Comment and Response

Comment: "In general, the PHG report is excellent and I have no significant criticisms. However, I have some minor, general comments which are made below, and a few specific remarks about the PHG of 0.06 parts per billion of Cr in drinking water; these comments are based on my experience measuring Cr in natural freshwaters, including ground waters and surface waters."

Response. Specific responses to each comment are provided below.

Specific Comments and Responses

Comment 1: "The units employed for concentration are inconsistent, sometimes on the same page, including mg/L, mg/kg, and ppm (parts per million); this probably reflects the concentration units employed in the original publications and is a general problem in reviewing scientific literature, not something unique to this report."

Response 1. The reviewer is correct. The PHG document utilizes the units provided by the study's authors so there is no confusion as to which dose is discussed by OEHHA when describing the study. So when NTP presents tumors at various dose levels (in mg/L) the PHG document uses the same units to discuss the study. When OEHHA

then develops a dose response relationship from the study, the units are often transformed. For the NTP study, the dose in mg/kg-day was derived using water consumption rates and body weights provided by NTP.

Comment 2: “Also, given the number of abbreviations used throughout the report, a Table summarizing and defining these would also be helpful.”

Response 2. Each abbreviation is spelled out the first time it is used in the document.

Comment 3: “On p.21 it is indicated that “trivalent chromium is an essential mineral”, but “element” would be more appropriate than “mineral”...The occurrences of CrO₃ (there are at least two) should be replaced by Cr₂O₃.”

Response 3. The PHG document has been revised accordingly.

Comment 4: “Again, I have no question about how the authors of this report arrived at the PHG value of 0.06 parts per billion hexavalent chromium. I simply wish to indicate that this concentration may be low, relative to the abundance of Cr in natural freshwaters, even when the natural waters are tested using “clean lab” methods.”

Response 4. OEHHA will forward these data to the Department of Public Health so they have these data when they develop the MCL for hexavalent chromium.

Comment 5: “One final, personal remark about Cr and contact dermatitis...I have no data about Cr release rates from these materials, only these observations, but it is difficult to imagine parts per million levels of Cr being released from a stainless steel watch bracelet coated with either Au/Rh or Ti.”

Response 5. In addition to chromium other metals such as Ni are components of stainless steel. Nickel is also associated with skin sensitization. Thus, it is difficult to know what is precipitating skin sensitivity. Also, it is not clear how much of the Cr in stainless steel is in the form of Cr VI.

Comments from Elizabeth Snow, University of Tasmania

General Comment and Response

Comment: “Having carefully read and evaluated the above mentioned document (PHG for Cr6) it is my considered opinion that the document is based on the best available scientific knowledge and that the conclusions reached are to the best of my knowledge and understanding both accurate and complete.”

Response. Comment noted.

Specific Comments and Responses

Comment 1: “Based on these data it is clear that environmental exposure to Cr6 in drinking water can pose a potential risk for human carcinogenesis.”

Response 1. OEHHA agrees.

Comment 2: “A cancer potency estimate of 0.6 (mg/kg-day)⁻¹ derived following standard guidance from the U.S. EPA and OEHHA (U.S. EPA 2005, OEHHA 2009), resulted in an extrapolated 1 in 10⁶ lifetime cancer risk level for Cr6 in tap water of 0.06 ppb.”

Response 2. The PHG document now has a slightly lower cancer potency estimate (calculated from the LED_{10}) of $0.5 \text{ (mg/kg-day)}^{-1}$ compared to 0.6 in the previous draft. This is due to rounding and use of the NTP (2008) study values for ingested dose of Cr VI in the December 2010 draft and final PHG documents rather than ingested dose as calculated by OEHHA in the August 2009 draft. The PHG value in the current document is 0.02 ppb due to correction for early-in-life exposures to carcinogens (as described in OEHHA, 2009).

Comment 3: “Based on this study, along with very limited evidence of tumor response at lower levels of Cr6, there is very limited evidence for a linear dose response.”

Response 3. This is the case with most carcinogens. Dose-response data are not available in the low dose region where human exposures are expected.

Comment 4: “It is more likely, due to the high probability of extracellular conversion of the Cr6 to the much less toxic Cr3, that uptake and bioavailability of the Cr6, in itself, will exhibit a non-linear (threshold) dose response.”

Response 4. This may or may not be true. The PHG document contains examples of Cr VI absorption at dose levels that are far below the calculated capacity of the GI tract of humans and rodents to reduce all ingested Cr VI to Cr III. The PHG document also discusses examples where Cr VI absorption was not concentration dependent.

Comment 5: “A low dose, linear response also assumes a lack of DNA repair and other protective mechanisms with an expected maximum protective effect at low dose.”

Response 5. A linear cancer response at low dose levels is consistent with DNA repair. Consider radiation induced carcinogenesis, the best data set we have covering cancer induction by low dose levels of any genotoxic carcinogen (radiation-induced cancer in human A-bomb survivors). The cancer incidence responds linearly at low doses of radiation despite the well-characterized ability of mammalian cells to repair potentially lethal DNA damage (PLD repair). The linear dose response is also recommended by U.S. EPA Cancer Guidelines (2005) based on the described mutagenic mode of action (McCarroll et al., 2010).

Comment 6: “The essential nature of Cr3 as a required trace element should also be considered as oral Cr6 is expected to be reduced to Cr3 for which there must be some sort of uptake mechanism in order to supply this nutrient to the body.”

Response 6. The presumption is that the chromium needed by the body is absorbed at a slow rate as Cr III and not as Cr VI. The understanding of the essentiality of Cr is still developing and this essentiality in the mammalian diet has recently been questioned by Di Bona et al. (2010, J Biol Inorg Chem 16(3):381-90).

RESPONSES TO MAJOR COMMENTS RECEIVED ON AUGUST 2009 DRAFT, FIRST COMMENT PERIOD (2009)

Comments from Silvio De Flora, University of Genoa

Comment 1: “Although it is evident that Cr(VI) detoxification mechanisms represent formidable barriers against Cr(VI) toxicity, genotoxicity, and carcinogenicity, I do not pretend that they are infinite and cannot be saturated. Under certain conditions, especially in animal models, they may be overwhelmed as a function of the dose and of the administration route (see Comment #9). Therefore, the statement, reported on page 17 of the OEHHA Document, that according to my studies the Cr(VI) detoxifying mechanisms in the organism are “essentially inexhaustive” does neither reflect my opinion nor what is written in my papers.”

Response 1. The sentence was revised and quotes from the investigators are now included in the text.

Comment 2: “On page 37 is stated that no study to date has looked for DNA damage in the oral cavity or gastrointestinal tract following oral administration of Cr(VI). It is also stated that these studies are needed. The authors of the document overlooked our *ad hoc* study (S. De Flora *et al.*, *Mutat. Res.* 659, 60-69, 2008), in which we demonstrated that the daily administration of sodium dichromate to SKH-1 mice, at the doses of 5 or 20 mg/L for 9 consecutive months, failed to enhance the frequency of DNA-protein crosslinks and did not cause oxidative DNA damage, measured in terms of 8-oxo-dGuo, in mouse forestomach, glandular stomach, and duodenum.”

Response 2. The Genotoxicity section of the document has been revised and now discusses De Flora *et al.* (2008). However, judging from the responses of the positive controls in De Flora *et al.* (2008), it is likely that their methodology lacked the sensitivity to measure DNA damage at the dose levels tested. In addition, McCarroll *et al.* (2010) noted that the levels tested in this study may in part explain the negative results because they are below the exposure levels used in the NTP 2-year drinking water study.

Comment 3: “Table 2 and pages 37-41 of the OEHHA Document summarize studies on the genotoxicity of Cr(VI) administered by the oral route. Again, relevant literature data were overlooked. In a study of mine (S. De Flora *et al.*, *Mutat. Res.* 610, 38-47, 2006)...”

And “Surprisingly, unless I missed them somewhere else in the document, even the NTP studies evaluating the frequency of micronucleated erythrocytes in peripheral blood were not cited. ... ”

Response 3. The Genotoxicity section of the document has been revised and now includes these studies.

Comment 4: “As noted in the OEHHA Document, a statistically significant increase of oral cancers only occurred at the highest dose tested (516 mg/L sodium dichromate) in both male and female rats [NTP, 2008]. A statistically significant increase of small intestine tumors only occurred at the highest dose tested in male mice (257.4 mg/L) and at the two highest doses tested in female mice (172 and 516 mg/l) [NTP, 2008]. These are huge doses! One should go to the lab and see the color and appearance of water containing hundreds or even tens mg/L Cr(VI). Nobody would drink this water unless for suicidal purposes (which probably would be unsuccessful, see Comment #8). No effect was observed at the lowest doses tested in the NTP study, corresponding to 5-30 mg Cr(VI)/L water (which still are quite high doses), which is in agreement with the conclusions of our genotoxicity study (S. De Flora *et al.*, *Mutat. Res.* 659, 60-67, 2008), ruling out that DNA damage may occur not only in the forestomach and glandular stomach but also in the duodenum of mice receiving sodium dichromate with the drinking water, at the doses of 5 and 20 mg Cr(VI)/L (see Comment #2).”

Response 4. In the 2008 NTP study statistically significant increases in tumors of the small intestine were observed for both male and female mice at the two highest drinking water concentrations. Exact trend tests were positive for both sexes. The absence of statistically significant increases in tumors at the two lowest drinking water concentrations should not be interpreted as a threshold for tumorigenicity, since the number of animals may have been too low to detect tumors at the two lowest drinking water concentrations. The use of high doses in cancer bioassays is generally thought to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors). In addition, the study by De Flora *et al.* (2008) assayed only a narrow subset of the different types of DNA damage Cr IV can cause (discussed in the PHG). Also, judging from the responses of their positive controls, it is likely that their methodology lacked the sensitivity to measure DNA damage at the dose levels tested. Lastly, McCarroll *et al.* (2010) noted that the levels tested in this study may in part explain the negative results because they are below the exposure levels used in the NTP 2-year drinking water study.

Comment 5: “It should be noted that in the NTP study there were significant decreases of certain tumors in Cr(VI)-treated rodents, such as a decrease of total benign tumors in both rats (females only) and mice (males only), which by the way was the only concomitant change in the two rodent species, a decrease of pituitary gland tumors in both male and female mice, and a decrease of liver adenomas in both male and female mice, which was the only effect observed at 2 or 3 Cr(VI) concentrations. Clearly, although these decreases are statistically significant, they do not mean that Cr(VI) is protective but highlight the fact that, likewise, significant increases at high doses are not biologically significant and do not bear relevance to the human situation.”

Response 5. First, OEHHA agrees that a decrease in tumor incidence does not mean that Cr VI protects against cancer. Second, biological significance does not follow from occasional increases or decreases in tumors. Rather, OEHHA looks for a dose-responsive change exhibiting statistical significance. In mice such a pattern was observed for intestinal tumors. Decreased tumor incidences at higher dose levels have been observed for a number of chemicals tested at the NTP (Haseman and Johnson, 1996; Haseman et al., 1997). In many cases the decreases in tumors were significantly correlated with decreased bodyweights, also commonly observed at higher dose levels. This may well be the reason for the decreases in some tumors observed in the two-year Cr VI bioassay.

Comment 6: “On page 58, last paragraph, it is stated that IARC (1990) concluded that Cr(VI) is a ‘strong’ carcinogen for the respiratory system. This statement is not correct. As quoted on page 42 of the OEHHA Document, the IARC concluded that ‘there is sufficient evidence in humans for the carcinogenicity of Cr(VI) compounds as encountered in the chromate production, chromate pigment industry and chromium plating industries.’”

Response 6. This reference to IARC (1990) has been deleted. IARC conclusions regarding carcinogenicity are reported in the “Toxicological Effects in Animals, Carcinogenicity” section of the PHG document.

Comment 7: “The need for high Cr(VI) doses to induce lung cancer is confirmed by more recent study, such as the Gibb *et al.* (2000) study, which is extensively reported and discussed in the OEHHA Document.”

Response 7. Exposures are often higher in occupational studies than what occur in the ambient environment. The ability to detect effects such as cancer in such a small population typically the subject of occupational studies is likely related to the high levels of exposure. This does not suggest that cancer would not occur at lower levels of exposure, but rather one may not be able to detect an increased incidence of cancer in a small population. This is similar to the problem of conducting bioassays in small populations of animals and is addressed by using high doses in these bioassays.

Comment 8: “As everybody knows, the Mancuso’s data, that U.S. EPA used for the potency estimate, are highly biased.

Response 8. The strengths and weakness of both the Mancuso (1997) study and the Gibb et al. (2000) study are discussed in cancer potency for the inhalation route section of the PHG document. Our analysis indicates that the two studies are consistent.

Comment 9: “In the last paragraph of page 72, the OEHHA Document concludes that “a summary of the findings of multiple studies where workers were exposed to Cr(VI) by the inhalation route (conducted by OEHHA) was suggestive of a link between inhalation exposure to Cr(VI) and cancer of the digestive organs”. This conclusion is surprising and

contrasts with the actual results of the OEHHA study, which are reported in Tables 7 and 8 on pages 62-69. In fact, taking into account statistically significant variations, the analysis of 30 studies led to the following results for cancers of the digestive system ...”

Response 9. A new Table 8 shows cancers of a variety of organs as well as nonmalignant respiratory diseases, all in persons occupationally exposed to Cr VI via inhalation. As indicated in the PHG document, for several studies the rate ratios for stomach cancer exceeded one, and in three the associations were statistically significant.

Comment 10: “In addition to the considerations on the carcinogenic potency (see Comment #5) and on the link between inhalation exposure to Cr(VI) and cancer of digestive organs (see Comment #7), the OEHHA Document relies on the Chinese study, whose limitations are extensively discussed on pages 69-71. Note that this controversial study was further examined in a recent article (B.D. Kerger *et al.*, *J. Toxicol. Environ. Hlth*, 72, 329-44, 2009), which is not quoted in the Document.”

Response 10. Discussion of the Kerger *et al.* (2009) study has been added to the PHG document. It is not clear what is meant by “the OEHHA document relies on the Chinese study.” Cancer potency was calculated from the rodent data in NTP (2008). Zhang and Li (1987) was one of two studies identified in which humans were exposed to Cr VI via their drinking water and in which organ-site-specific results were available. The exposed population exhibited a statistically significant increase in stomach cancer mortality. These findings suggest that Cr VI is carcinogenic in humans via the oral route.

Comment 11: “As to the Borneff *et al.* (1968) study, which is extensively reported and discussed both in the text and in Appendix D of the OEHHA Document, this study was so obsolete, inadequate and full of problems that the IARC Working Group (including myself and other 20 scientists) decided not even to cite it in the 1990 Monograph. Incidentally, it is noteworthy that the Borneff *et al.*, study suggested an increase of forestomach tumors in mice (that even the author interpreted with a great caution) while the NTP study suggested an increase of small intestine tumors in mice. Who is right?”

Response 11. It is not uncommon that different studies detect tumors at difference sites, particularly if different genders and strains were employed.

Comment 12: “Genotoxicity. As previously discussed (Comments #2 and #3), the data reported in the OEHHA Document are largely incomplete.”

Response 12. This section of the PHG document has been updated to include discussions of the studies mentioned in Comments #2 and #3 above.

Comment 13: “Toxicokinetics. As previously discussed (Comment #1), I do not pretend that detoxification mechanisms are infinite. In any case, they are formidable barriers that imprint a threshold character to Cr(VI) carcinogenesis (see Comment #9).”

Response 13. OEHHA agrees that the ability to reduce CrVI to Cr III is not infinite. However, there appears to be sufficient reducing capacity (84 mg/day according to the estimates of DeFlora and coworkers) to adequately reduce the amount of chromium VI that was administered to humans in several pharmacokinetic studies. Therefore, the observed absorption of hexavalent chromium in these studies did not occur because the reducing capacity of the GI tract was exhausted. In a recent study of rats and mice exposed to Cr VI via their drinking water, there was no threshold for its accumulation in a variety of tissue (Collins *et al.*, *Tox Sci* 118: 368-379, 2010). Rather, its accumulation was either linearly related to its concentration in the drinking water over the entire concentration range tested, or linearly related at low concentrations with indications of a plateau at higher concentrations. These data are discussed in Appendix A of the PHG.

Comment 14: “This section of the Document summarizes some mechanisms of Cr(VI). Regarding the meaning of the intracellular Cr(VI) reduction, when in 1989 I prepared a review (cited in the Document) together with the late Karen Wetterhahn, the best researcher on Cr(VI) biochemical toxicology ever, we agreed on the interpretation that when Cr(VI) reduction occurs close to DNA target molecules, it is an activation mechanism (uptake-activation theory). However, when Cr(VI) reduction occurs in the cell cytoplasm or in any case far away from DNA, it is a detoxification (uptake-detoxification theory), due to the myriad of intracellular ligands that block Cr(VI) or its derivatives before reacting with DNA. Here is a further mechanism responsible for the occurrence of thresholds in Cr(VI) toxicology.”

Response 14. OEHHA has considered your work in the PHG document and finds it informative. While considerable mechanistic research has yielded several plausible mechanisms by which Cr VI may be causing tumors (reviewed in the PHG document), the exact mechanism remains unclear.

Comment 15: “It is surprising that this chapter reaches the conclusion that ‘the findings of available human, animal, genotoxic, and toxicokinetics studies all indicate that Cr(VI) is a possible human carcinogen by the oral route.’ It is intriguing that all data that were evaluated to be either incomplete or heavily criticized in the document itself now become the starting point to reach the above conclusion and to develop a proposal of PHG.”

Response 15. The document does discuss the weaknesses of key studies such as the Zhang and Li (1987) study in China. However, the evidence that Cr VI is carcinogenic by the oral route is compelling. The evidence from various types of studies (toxicokinetic, genotoxic, mechanistic, animal bioassays and epidemiology) is internally consistent, and points to carcinogenesis. Toxicokinetic studies indicate absorption and cellular uptake of Cr VI, the genotoxic and mechanistic studies provide a plausible

mechanism for carcinogenesis and both animal and humans studies reveal evidence of an increased incidence of tumors. In particular, four recent animal bioassays meeting quality standards were positive for tumors in two rodent species, in both males and females, at two sites (NTP, 2008).

Comment 16: “The lack of thresholds, as claimed in APPENDIX A of the OEHHA Document, would imply that even a single Cr(VI) molecule, introduced in the organism, would be able to reach the DNA of target cells, which is unbelievable. It should be added that threshold mechanisms occur not only at toxicokinetic and metabolic levels but also after DNA damage, e.g., due to DNA repair and apoptosis. My lab investigated these processes by analyzing *in vivo* both transcriptome (A. Izzotti *et al.*, *Mol. Carcinogenesis*, 35, 75-84, 2002) and proteome (A. Izzotti *et al.*, *Int. J. Oncol.*, 24, 1513-22, 2004).”

Response 16. The issue of thresholds in carcinogenesis has been discussed in detail (U.S. EPA, 2005; OEHHA, 2009). It may be difficult to envision a single molecule of Cr VI in a liter of drinking water causing significant damage to a human. However, at the PHG for Cr VI of 0.02 micrograms per liter, there would be 2.3×10^{14} molecules of Cr VI per liter of drinking water, any one of which has the potential to damage DNA. While detoxification and DNA repair can reduce the potency of genotoxic carcinogens, it is not evident that these mechanisms result in a threshold for Cr VI or other carcinogens.

Comment 17: “However, starting from inconsistent epidemiological and experimental data and denying the occurrence of threshold mechanisms in Cr(VI) toxicity and carcinogenicity lead to unrealistic figures.”

And,

“The results of the NTP carcinogenicity study in mice and rats that, as noted in Comment #7, were not consistent with the results of epidemiological studies, were used as a major conceptual base for claiming that Cr(VI) is carcinogenic also by the oral route and for calculating the proposed PHG.”

Response 17. As discussed above, both the findings of animal studies and the results of epidemiological studies were consistent with a statistically significant increase in tumors associated with exposure to Cr VI. This suggests that Cr VI is carcinogenic by the oral route.

Comment 18: “The concentrations of Cr(VI) in water that produced significant variations of tumor incidence in the NTP study were in the range of hundreds mg/L, i.e., millions of times higher than the proposed 0.06 µg/L PHG.”

Response 18. The use of high doses in cancer bioassays is traditionally used in toxicological testing to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (e.g., tumor occurrence).

OEHHA employed standard procedure to estimate the dose associated with 10^{-6} risk which was employed to derive the proposed PHG (U.S. EPA, 2005; OEHHA, 2009).

Comments from Andrew DeGraca, San Francisco Public Utilities Commission

Comment 1: Our principal concern is that OEHHA has relied on the results of National Toxicology Program's 2007 study to derive the PHG for carcinogenic effects. Although this study found that chromium VI in drinking water was carcinogenic in mice and rats, there are unresolved questions about the applicability of these results to humans. It is well accepted that chromium VI is reduced to non-toxic chromium III in the human stomach, a transformation that does not occur in rodents."

Response 1. Cr VI is also reduced to Cr III in the rodent stomach. This is discussed in detail in the PHG document in the sections "Hexavalent Chromium Reduction by Saliva and Gastric Fluids", "Absorption" and "Pharmacokinetics of Trivalent versus Hexavalent Chromium." See also Appendix A. While Cr VI reduction in the GI tract of rodents compared to humans has not been fully described, the U.S. EPA (2010), the New Jersey Department of Environmental Protection (NJDEP, 2009) and OEHHA (this PHG document) have all found that they are similar enough to allow calculation of a human cancer slope factor for Cr VI based on the NTP two-year bioassay.

Comments from Michael Rogge, California Manufacturers and Technology Assc.

General Comment 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."

General Response 1. The literature considered in the PHG document has been updated and expanded by the addition of relevant journal articles that we could identify and retrieve in the update, and were either missing from the August 2009 draft or were published after that draft was posted. All recognized errors have been corrected and omissions rectified where warranted.

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

General Response 2. OEHHA has carefully reviewed the peer reviewer comments and the DTSC memorandum. Responses to the UC peer reviewers are included in this document. Responses to specific CMTA comments regarding the UC peer reviewers and the DTSC memorandum are included below in OEHHA's responses to those comments.

General Comment 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.”

General Response 3. The mechanism of action (MOA) of Cr VI is discussed in the following sections of the PHG document: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Genetic Toxicity,” “Mechanism of Genotoxicity and Carcinogenicity,” and “Examination of Evidence for Chromium Carcinogenicity.” The section entitled “Mechanism of Genotoxicity and Carcinogenicity” concludes:

“OEHHA could not discern a consistent pattern of histiocytic infiltration, inflammation, hyperplasia and the occurrence of tumors in the mouse or rat duodenum, oral cavity or liver in the NTP (2008) study. Therefore, an MOA other than that of genotoxicity or mutagenicity is not supported by these findings. The standard approach for carcinogens operating via a genotoxic or mutagenic MOA is to apply a linearized multistage model to calculate the cancer potency (U.S. EPA, 2005; OEHHA, 2009).”

The human relevance of the mouse tumor data are discussed in the section entitled “Examination of Evidence for Chromium Carcinogenicity.” The section concludes:

“The findings of available human, animal, genotoxic and toxicokinetic studies all indicate that Cr VI is a possible human carcinogen by the oral route. Given these observations and until more human and/or animal studies become available that clearly indicate otherwise, it is prudent to consider this hazard in the development of a proposed PHG for Cr VI.”

Note that OEHHA employed the same allometric scaling methodology as NTP (Stout et al., 2009) and U.S. EPA (2010) to extrapolate from mice to humans.

OEHHA acknowledges that new research is on-going and looks forward to the new data when available for consideration. The Safe Drinking Water Act of 1996, amended 1999 (Health and Safety Code [H&SC], Section 116365) contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. When new research data are published in a finalized, peer-reviewed format, OEHHA will consider them in the development of a revised PHG for hexavalent chromium. OEHHA acknowledges that new studies may alter a PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

General Comment 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.”

General Response 4. The NTP (2008) study, an *ad libitum* drinking water study, was used to calculate the cancer slope factor for Cr VI. It was performed at Cr VI concentrations that are generally much higher than those to which Californians are exposed in their drinking water. The use of high concentrations in cancer bioassays is designed to offset the statistical limitations of using small numbers of animals

(50 /sex/dose level) to measure a relatively rare event (tumors) (U.S. EPA, 2005; OEHHA, 2009).

General Comment 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.”

General Response 5. Two epidemiologic studies were located which measured organ-specific mortality from cancer in humans exposed to Cr VI in their drinking water. The study by Zhang and Li (1987) was already in the August 2009 draft document, while a recent study by Linos et al. (2011) was added. Both studies are evaluated in detail in the PHG document according to standard epidemiologic methods. The older study was judged to have accurately identified the exposed population, but the magnitude of the exposure was considered unclear. The more recent study provided exposure concentrations that varied widely, with the five highest concentrations being 44, 48, 51, 53, 54, and 156 µg/l. Comparing these values to those measured in California drinking water and presented in the “Environmental Occurrence and Human Exposure” section of the PHG document demonstrates that this study’s results are relevant to persons in California.

General Comment 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.”

General Response 6. Only a single PHG is developed for each chemical that is evaluated. For Cr VI in drinking water one PHG was developed in this document: that of 0.02 µg/L based on tumor data. A health protective concentration of 2.0 µg/L was calculated based on non-cancer effects. However, this latter value was not adopted as the PHG because the value protective of both cancer and non-cancer effects is 100-fold lower (i.e., 0.02 µg/L).

OEHHA will be applying the BMD approach in future analyses of the non-cancer data. Our preliminary analysis applying the BMD approach to the non-cancer data followed by an uncertainty factor of 100 yielded a final value that was more than 100-fold higher than the current PHG (0.02 µg/L) based on cancer effects. Thus, the current PHG is more protective and would not change.

General Comment 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.”

General Response 7. OEHHA acknowledges that new research is on-going and looks forward to the new data when available for consideration. The Safe Drinking Water Act of 1996, amended 1999 (Health and Safety Code [H&SC], Section 116365) contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. When new research data are published in a finalized, peer-reviewed format, OEHHA will consider them in the development of a revised PHG for hexavalent chromium. OEHHA acknowledges that new studies may alter a PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

General Comment 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.”

General Response 8. The uncertainty associated with the development of the PHG for Cr VI in drinking water is discussed in the “Risk Characterization” section of the document. OEHHA is not aware of an established methodology for quantifying the uncertainty associated with cancer risk extrapolation.

Specific Comment 1: “The PHG document does not adequately address the comments of the UC peer reviewers [of the 2008 pre-release draft].”

Specific Response 1. The PHG document has been revised as appropriate in accordance with each substantive comment from each UC peer reviewer (see below).

Specific Comment 1-1: “The peer reviewers [of the 2008 pre-release draft] 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.”

Specific Response 1-1. The approach taken in the PHG document to calculate a cancer slope factor using high dose rodent tumor data is the up-to-date approach used by U.S. EPA (2005; Davis et al., 2010) and OEHHA (2009). One University of California peer reviewer (Dr. Gwiazda) suggested that this approach may have **underestimated** the cancer potency of Cr VI, not overestimated it.

Specific Comment 1-2: “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 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.”

Specific Response 1-2. 1) Systemic absorption of Cr VI may or may not be required for tumor induction, as it simply is not known at present and 2) Part of OEHHA’s analysis of the relationship between GI tract reduction capacity and carcinogenicity is presented in Appendix A. Data from NTP (2008) in Figures A.3-A.6 show increased Cr accumulation in a variety of mouse tissue at drinking water concentrations ranging from 5 to 180 mg/L of Cr VI. The dose response for Cr accumulation was generally linear over the dose range tested, indicating that Cr VI reduction did not saturate. Collins et al. (2010) reached the identical conclusion. Importantly, this range of Cr VI concentrations includes the drinking water concentrations causing increased mouse intestinal tumors in the two-year bioassay (30 to 180 mg/L). Sutherland et al. (2000) measured significant increases in tissue Cr of rats relative to controls at drinking water concentrations of 3 and 10 mg/l Cr VI. No increases were observed at the lowest concentration tested:

0.5 mg/L of Cr VI. Some have interpreted this as an indication that at low Cr VI concentrations in drinking water, reduction of ingested Cr VI to Cr III is sufficient to prevent significant tissue accumulation of Cr VI or toxicity (Proctor et al., 2011; Thompson et al., 2011). However, since the amount of tissue Cr in control animals was near or below the detection limit in the study by Sutherland et al. (2000), an increase in tissue Cr at this low drinking water concentration (0.5 mg/L of Cr VI) may not have been measurable. The currently available data do not permit evaluation of whether reduction of Cr VI in the GI tract is sufficient to prevent significant entry of Cr VI into tissue at drinking water concentrations below approximately 1 mg/L. As discussed in the “Metabolism and Pharmacokinetics” section of the PHG document, there are a number of studies, some performed with radioactively labeled chromium compounds administered at dose levels below 1 mg/L, in which oral administration of Cr VI or Cr III (to rodents or humans) resulted in different patterns of absorption, distribution and excretion, indicating that not all Cr VI was reduced to Cr III following ingestion.

Specific Comment 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”

Specific Response 1-4. See Response 1-2. More discussion of the study by Sutherland et al. (2000) has been added to the PHG document.

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

Specific Response 2. See below for responses to specific issues raised by DTSC and cited by this commenter.

Specific Comment 2-1: "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."

Specific Response 2-1. We agree that development of the PHG would be enhanced if more information were available on the target tissue dose of Cr VI in mice and humans. Absent such data, we have performed allometric scaling according to standard risk assessment practice to extrapolate between species. A similar approach was taken by the New Jersey Department of Environmental Protection (2009; see PHG document) and the U.S. EPA (2010).

Specific Comment 2-2: "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."

Specific Response 2-2. No inflammation was reported in the key tumor bioassay in mice. Hyperplasia is consistent with the appearance of tumors and is considered a precursor to tumor formation. These issues are discussed in the text describing Table 7 of the PHG document.

Specific Comment 2-3: "OEHHA's highly conservative approaches substantially overestimate the carcinogenic potency of ingested Cr(VI)."

Specific Response 2-3. OEHHA used standard procedures to derive potency (U.S. EPA, 2005; OEHHA 2009; Davis et al., 2010).

Specific Comment 2-4: "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."

Specific Response 2-4. The discussion of Table 8 now includes a statement that cancer of the oral cavity and pharynx was not significantly elevated in exposed workers.

Specific Comment 2-5: "The MOA for small-intestine tumors in mice has not been adequately addressed. The NTP data suggest that an MOA associated with chronic 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."

Specific Response 2-5. The PHG document contains a detailed discussion of the relationship between tissue damage, inflammation, hyperplasia and tumors (see Table 7

and its accompanying discussion). It is noted that tissue damage was not observed in the 2-year bioassay in either the mouse or the rat. Also, chronic inflammation was not observed in tissues where tumors increased. Lastly, the hyperplasia that was observed in the mouse duodenum was not regenerative in nature. The NTP scientists who performed the 2-year bioassay published a report in which they stated, “We observed no increase in non-neoplastic histopathology lesions in either species suggestive of overt tissue damage due to the oxidant properties of Cr (VI)” (Stout et al., 2009).

Specific Comment 2-6: “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 of GI anatomy and physiology are critical to understanding the relationship between observations in mice and relevance to low-concentration exposure in humans.”

Specific Response 2-6. We agree that the risk assessment of Cr VI via the oral route would benefit from more information on its pharmacokinetics in humans and mice. Absent these data, OEHHA has utilized allometric scaling to extrapolate dose from mice to humans. A similar approach has been taken by the New Jersey Department of Environmental Protection (NJDEP, 2009) and the U.S. EPA (2010).

Specific Comment 2-7: “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.”

Specific Response 2-7. See the “Carcinogenic Effects” section of the PHG document located within the “Calculation of the PHG” section for the relative contributions of the inhalation and ingestion risks to the total risk posed by Cr VI in drinking water. Inhalation contributes less than 1 percent of the total risk. Therefore, refinements of the inhalation potency of Cr VI, as suggested in this comment, will not significantly affect the final PHG value.

Specific Comment 2-8: “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.”

Specific Response 2-8. The title of Appendix A has been revised to indicate that the discussion pertains to whether thresholds were observed over the dose range used in the NTP (2008) bioassay. The data in NTP (2008) suggest that the GI tract’s ability to reduce Cr VI to Cr III was not exceeded over the dose range tested. As discussed in the PHG document (see discussion of Table 7) no overt tissue damage was observed in this study, and inflammation was not observed at the sites where tumors arose. These findings also indicate that the observed hyperplasia was not regenerative.

Specific Comment 2-9: “The analysis of the Borneff et al. (1968) study and the Helicobacter hypothesis is highly speculative, lacks relevance, and should be deleted.”

Specific Response 2-9. The PHG does not rely on the Helicobacter hypothesis or Borneff et al. (1968) in the development of the PHG. The hypothesis is located in Appendix B and clearly indicated as such. The Helicobacter hypothesis was formulated by OEHHA as part of an effort to obtain a better understanding of the findings of diverse studies such as the occurrence of tumors in the first generation of the Borneff et al. (1968) study and stomach tumors following a relatively short term exposure to Cr VI in rural China. These discussions serve as a scientific resource and are attached in the Appendix as records of the issues that have been addressed in the research for and preparation of this PHG document.

Specific Comment 2-10: “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 Response 2-10. OEHHA acknowledges that new research is on-going and looks forward to the new data when available for consideration. The Safe Drinking Water Act of 1996, amended 1999 (Health and Safety Code [H&SC], Section 116365) contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. When new research data are published in a finalized, peer-reviewed format, OEHHA will consider them in the development of a revised PHG for hexavalent chromium. OEHHA acknowledges that new studies may alter a PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

Summary and Introduction

Specific Comment 3: “Page 2 of August 2009 draft PHG document, ‘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 De Flora et al. indicate that all Cr(VI) is completely reduced at any dose. OEHHA has misunderstood and misrepresented this research.”

Specific Response 3. Quotes from papers published by these investigators have been added to the text of the PHG document.

Environmental Occurrence and Human Exposure

Specific Comment 4: “This information (water monitoring data in California) is out of date. CDPH data for Cr(VI) monitoring is current through February of 2009 and is available on the CDPH website at...”

And,

"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)."

Specific Response 4. The data covering Cr VI concentrations in California drinking water have been updated.

The use of high doses in cancer bioassays is traditionally used to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors). OEHHA employed standard procedure to estimate the dose associated with 10^{-6} risk which was employed to derive the proposed PHG (U.S. EPA, 2005; OEHHA, 2009). As required by law, PHGs are based on scientific assessments of health risks posed by drinking water contaminants, and not the actual contaminant levels measured in drinking water.

Metabolism and Pharmacokinetics

Specific Comment 5-1: "(Page 11 of August 2009 draft PHG document) '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."

Specific Response 5-1. The reference Kerger et al. (1996a) has been added to the text. Although OEHHA used a level a little lower than Kerger and coworkers (1996a), it is consistent with their statement, "The findings of this study may have important mechanistic implications applying to detoxification of Cr(VI) at plausible concentrations in drinking water (i.e., <10 mg/liter)."

Specific Comment 5-2: "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."

Specific Response 5-2. The concentrations of Cr VI at the target tissues are not known. In the absence of such data, OEHHA has followed the standard procedure of calculating cancer potency using the drinking water concentrations of Cr VI (U.S. EPA, 2005; OEHHA, 2009).

Specific Comment 5-3: "Finley et al. (1997) found no dose-related increases in plasma and red-blood-cell 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."

Specific Response 5-3. In the study by Finley et al. (1997), five subjects received a dose of 100 ug/day of Cr VI for 3 days. Red blood cell (RBC) Cr levels increased in 4 out of the 5 subjects while the plasma Cr level increased only slightly in only 2 individuals. As for dose-response relationships, the changes were too variable even within the same individual, so not much can be concluded regarding the effect of dose. But increases in RBC Cr levels were observed following the administration of as little as 100 ug VI for 3 days. Sutherland et al. (2000) measured significant increases in tissue Cr of rats relative to controls at drinking water concentrations of 3 and 10 mg/l Cr VI. No increases were observed at the lowest concentration tested: 0.5 mg/L of Cr VI. Some have interpreted this as an indication that at low Cr VI concentrations in drinking water, reduction of ingested Cr VI to Cr III is sufficient to prevent significant tissue accumulation of Cr VI or toxicity (Proctor et al., 2011; Thompson et al., 2011). However, since the amount of tissue Cr in control animals was near or even below the detection limit in the study by Sutherland et al. (2000), an increase in tissue Cr at this low drinking water concentration (0.5 mg/L of Cr VI) may not have been measurable.

Specific Comment 6: “Page 12 of August 2009 draft PHG document), ‘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.”

And,

“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.”

And,

“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.”

Specific Response 6. From Finley et al. (1997): urinary Cr recovery (means) of 1.7 % at 100; 1.2 % at 500; 1.4 % at 1000; 1.7 % at 5000 and 3.5 % at 10,000 ug/day. To test if there is a dose related increase of urinary excretion, a comparison using only the high dose and low dose is inappropriate because it ignores all the intermediate doses. Comparisons should use all of the dose levels. No increase in absorption was evident (in all the intermediate doses) with the possible exception of the high dose, and absorption at the high dose still remained quite low. The text has been revised to include urinary recoveries at the various dose levels.

As indicated in the PHG document, there is considerable variability between individuals, which makes modeling these limited data using PBPK particularly problematic.

As noted in the PHG document both Cr VI and Cr III are absorbed. Kerger et al. (1996) demonstrated that a lot more Cr VI is absorbed, demonstrating that Cr VI is not completely converted to Cr III in the stomach. Otherwise the amount of absorption should have been the same.

Specific Comment 7: “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.”

Specific Response 7. The different forms being referred to are Cr VI versus Cr III. OEHHA agrees that there is a difference in pharmacokinetic patterns which indicates that Cr VI is being absorbed as Cr VI and is not all reduced to Cr III in the stomach prior to its absorption. Otherwise, the pharmacokinetic patterns would be the same.

Specific Comment 8: “(Page 12 of the August 2009 draft document) ‘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).’ OEHHA is not correctly citing this study.”

Specific Response 8. The text of the PHG document has been revised to read, “Finley and associates observed marked increases in RBC chromium levels in some individuals (but not in others) that ingested three daily doses of Cr VI, at total doses as low as 0.1 mg/day, while plasma chromium levels were less affected (Finley et al., 1997).”

Specific Comment 9-1: “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.”

Specific Response 9-1. There is no statement in the PHG document that there is no difference in the kinetics associated with differing routes of exposure. For most xenobiotics, the route of administration will influence the pharmacokinetics.

Specific Comment 9-2: “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...The entire discussion of toxicokinetics should be refocused and rewritten.”

Specific Response 9-2. Sutherland et al. (2000) measured significant increases in tissue Cr of rats relative to controls at drinking water concentrations of 3 and 10 mg/L

CrVI. No increases were observed at the lowest concentration tested: 0.5 mg/L of Cr VI. Some have interpreted this as an indication that at low Cr VI concentrations in drinking water, reduction of ingested Cr VI to Cr III is sufficient to prevent significant tissue accumulation of Cr VI or toxicity (Proctor et al., 2011; Thompson et al., 2011). However, since the amount of tissue Cr in control animals was near or below the detection limit in the study by Sutherland et al. (2000), an increase in tissue Cr at this low drinking water concentration (0.5 mg/L of Cr VI) may not have been measurable.

Specific Comment 9-3: “Second, the discussion of Cr(III) binding on page 14...indicates that there is considerable uncertainty in concluding whether Cr(VI) or Cr(III) is systematically absorbed...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 systematic absorption of Cr(VI).”

Specific Response 9-3. The levels of Cr excreted in the urine and its urinary half life are the key data that demonstrate that Cr VI is absorbed as Cr VI. As indicated in the PHG document (“Metabolism and Pharmacokinetics” section), little increase in RBC Cr levels occur when Cr VI is administered by the oral route in humans or animals. It appears that non-RBC sites are the depots for absorbed Cr VI.

Specific Comment 10-1: “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.”

Specific Response 10-1. It is not unusual to observe differences in absorption between different species. With regard to differences in reducing capacity, NTP addressed this issue and indicated no data are available but calculations based on allometric considerations indicate no marked differences.

Specific Comment 10-2: “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 increased ability to detoxify Cr(VI).”

Specific Response 10-2. We were unable to identify documentation in support of the commenter’s statement that humans will have an increased ability to reduce ingested Cr VI relative to the rat. However, the ability to reduce Cr VI to Cr III does not appear to be strictly a function of pH, as the reducing equivalents come from small molecules such as ascorbate, GSH and proteins. Reduction appears to be facilitated by low pH.

Specific Comment 10-3: “Second, in this paragraph, OEHHA sites Sutherland et al. (2000) but ignores the findings at the lowest dose by the relevant route of exposure.”

Specific Response 10-3 Sutherland et al. (2000) measured significant increases in tissue Cr of rats relative to controls at drinking water concentrations of 3 and 10 mg/L Cr VI. No increases were observed at the lowest concentration tested: 0.5 mg/L of Cr VI. Some have interpreted this as an indication that at low Cr VI concentrations in

drinking water, reduction of ingested Cr VI to Cr III is sufficient to prevent significant tissue accumulation of Cr VI or toxicity (Proctor et al., 2011; Thompson et al., 2011). However, since the amount of tissue Cr in control animals was near or below the detection limit in the study by Sutherland et al. (2000), an increase in tissue Cr at this low drinking water concentration (0.5 mg/L of Cr VI) may not have been measurable.

Specific Comment 11: "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."

Specific Response 11. OEHHA disagrees. The prolonged urinary half-life following Cr VI administration compared to following Cr III administration is consistent with the absorption of Cr VI, not Cr III.

Specific Comment 12: "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."

Specific Response 12. We know of no evidence that "Cr III bound to an organic matrix" exists. However, the occurrence of Cr VI absorption does explain a prolonged half-life for chromium. See the discussion of the work of O'Flaherty et al. (2001) in the "Metabolism and Pharmacokinetics" section of the PHG document.

Specific Comment 13: "(Page 17 of the August 2009 draft PHG document) '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...' 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."

Specific Response 13. The phrase "essentially inexhaustible" has been removed.

Specific Comment 14: "(Page 17 of the August 2009 draft document) '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 1000 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 Roloids 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(III). 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 discussions of kinetics to focus on rates of reduction and rates of absorption, rather than speculation regarding absolute quantities.”

Specific Response 14. The discussion of this paper has been expanded. However, the original discussion in the PHG document quoted above was accurate. Antacid had little effect on the reducing properties of the simulated stomach fluid. Regarding dilution, the authors of Proctor et al. (2002a) stated, “Thus, diluted stomach fluid reduces approximately the same amount of Cr (VI) as full strength stomach fluid when put in terms of actual gastric fluid/enzymes.”

Specific Comment 15: “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.”

Specific Response 15. The tumor studies cited above may well be site of contact tumors. Ingested Cr VI also causes non-carcinogenic toxicity following absorption and systemic distribution. The PHG document discusses many of these types of toxicity in the “Toxicological Effects in Animals” section. The work of Kerger and colleagues is useful in understanding the pharmacokinetics of Cr VI and these types of systemic toxicity.

Specific Comment 17: “The most meaningful data by Sutherland et al., which finds 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 Response 17. Sutherland et al. (2000) measured significant increases in tissue Cr of rats relative to controls at drinking water concentrations of 3 and 10 mg/L Cr VI. No increases were observed at the lowest concentration tested: 0.5 mg/L of Cr VI. Some have interpreted this as an indication that at low Cr VI concentrations in drinking water, reduction of ingested Cr VI to Cr III is sufficient to prevent significant tissue accumulation of Cr VI or toxicity (Proctor et al., 2011; Thompson et al., 2011). However, since the amount of tissue Cr in control animals was near or below the detection limit in the study by Sutherland et al. (2000), an increase in tissue Cr at this low drinking water concentration (0.5 mg/L of Cr VI) may not have been measurable.

Specific Comment 19: “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.”

Specific Response 19. The PHG document now mentions the commenter’s point that cytoplasmic vacuolization in hepatocytes in NTP (1997a) was not observed in the chronic mouse study (NTP, 2008). Note that the Health Protective Concentration for non-carcinogenic effects calculated in Table 17 of the PHG document is based on inflammation and fatty changes to the livers of females rats treated for two years with drinking water containing Cr VI, not on the effects discussed in this specific comment.

Specific Comment 20: “Note that the Chopra et al. (1996) and Acharya et al. (2001) studies were conducted by the same laboratory using nearly identical study protocol, 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.

Specific Response 20. The strengths and weaknesses of both studies are discussed in Table 1.

Specific Comment 22: “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.”

And,

“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.”

And,

“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.”

Specific Response 22. The MTD is discussed in detail in the “Carcinogenicity” section of the document in the discussion of the NTP (2008) study. This study (NTP, 2008), and not the subchronic study described in Specific Comment 22, was used to develop the health protective concentrations of hexavalent chromium for cancer and non-cancer

effects. Considering water intake (Figure 13), body weights (Figure 11) and various other indicators of animal hydration, the dose levels of Cr VI administered to male mice appear not to have exceeded the MTD. A similar conclusion was reached by NJDEP (2009) and U.S. EPA (2010).

Chronic Toxicity

Specific Comment 24: “(Page 32 of the August 2009 draft PHG document) ‘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.”

Specific Response 24. A detailed discussion of the two-year bioassay in rodents (NTP, 2008) is presented in the “Carcinogenicity” section of the draft PHG. The specific issue of whether the MTD was exceeded in either rats or mice is included. OEHHA determined that the MTD was not exceeded in male mice. This is important because male mouse tumor incidence was used to calculate the cancer potency of ingested Cr VI in the PHG document. NJDEP (2009) and U.S. EPA (2010) also concluded that the MTD was not exceeded in the male mice in NTP (2008).

Specific Comment 25: “(Page 33 of the August 2009 draft PHG document) ‘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.”

Specific Response 25. We have changed “appeared to recover” to “appeared to be recovering.”

Specific Comment 26-1: “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).”

Specific Response 26-1. See Appendix A of the PHG document for a discussion of the data indicating that the capacity of the rodent GI tract to reduce Cr VI to Cr III was not exceeded in the NTP (2008) two-year bioassay.

Specific Comment 26-2: “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.”

Specific Response 26-2. With regard to Finley et al. (1997), humans exposed to drinking water concentrations of Cr VI as low as 0.1 mg/L exhibited increased urinary chromium compared to controls, indicating that Cr VI had been absorbed. The authors suggested that this was due to absorption of Cr III. These data are discussed in the “Absorption” subsection of the “Metabolism and Pharmacokinetics” section of the PHG document. In rats, Sutherland et al. (2000) found no increased tissue chromium after giving rats drinking water containing 0.5 mg/L Cr VI. The PHG document discusses the likelihood that the rat study’s detection limit was too high to detect increased tissue chromium at 0.5 mg/L (see Specific Response 1-2).

Specific Comment 26-3: “Second, the NTP (2007b) expressed clear reservations concerning the biological significance of the chronic liver inflammation observed in the Cr(VI) study animals...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.”

Specific Response 26-3. We did not find any statements in the NTP study that expressed reservations concerning its findings of an increased incidence of minimal to mild inflammation in the livers of female rats. It is true that similar changes were observed in the livers of aged, control animals. However, when a concurrent control population is available, as was the case here, OEHHA would not discount an effect that was significant relative to the concurrent control, even if the values fell within the historical control range.

Specific Comment 26-4: “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.”

Specific Response 26-4. OEHHA acknowledges that there is uncertainty associated with the calculation of the health-protective concentration of Cr VI for non-cancer effects. This is discussed in the “Risk Characterization” section of the PHG document. Chronic liver inflammation in female rats, measured in the two-year bioassay (NTP, 2008), was the most sensitive non-cancer endpoint. As discussed in Collins et al. (2010) and in Appendix A of the PHG document, the dose responses for chromium

accumulation in tissue (NTP, 2008) indicate that the reductive capacity of the rat GI tract did not become saturated over the concentration range used in the study (5 to 180 mg/L of Cr VI). In addition, we know of no data indicating that the liver effects observed in rats in a number of Cr VI drinking water studies (discussed in the PHG document) are not valid. Lastly, we know of no data demonstrating that rats are either more or less sensitive than humans to the non-cancer, chronic effects of Cr VI in drinking water.

Specific Comment 27: “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 than are not relevant at lower, environmentally relevant doses.”

Specific Response 27. Part of OEHHA’s analysis of the relationship between GI tract reduction capacity and carcinogenicity is presented in Appendix A. Data from NTP (2008) in Figures A.3-A.6 show increased Cr accumulation in a variety of mouse tissue at drinking water concentrations ranging from 5 to 180 mg/L of Cr VI. The dose response for Cr accumulation was generally linear over the dose range tested, indicating that Cr VI reduction did not saturate. Collins et al. (2010) reached the identical conclusion. Importantly, this range of Cr VI concentrations includes the drinking water concentrations causing increased mouse intestinal tumors in the two-year bioassay (30 to 180 mg/L). Sutherland et al. (2000) measured significant increases in tissue Cr of rats relative to controls at drinking water concentrations of 3 and 10 mg/l Cr VI. No increases were observed at the lowest concentration tested: 0.5 mg/L of Cr VI. Some have interpreted this as an indication that at low Cr VI concentrations in drinking water, reduction of ingested Cr VI to Cr III is sufficient to prevent significant tissue accumulation of Cr VI or toxicity (Proctor et al., 2011; Thompson et al., 2011). However, since the amount of tissue Cr in control animals was near the detection limit in the study by Sutherland et al. (2000), an increase in tissue Cr at this low drinking water concentration (0.5 mg/L of Cr VI) may not have been measurable. Due to the absence of data, OEHHA is currently unable to evaluate whether reduction of Cr VI in the GI tract is sufficient to prevent significant accumulation of Cr in tissue at drinking water concentrations below approximately 1 mg/L. As discussed in the “Metabolism and Pharmacokinetics” section of the PHG document, there are a number of studies in which oral administration of dose levels below 1 mg/L of Cr VI or Cr III (to rodents or humans) resulted in different patterns of absorption, distribution and excretion, indicating that not all Cr VI was reduced to Cr III following ingestion.

Specific Comment 30: “The “weaknesses” for NTP (2007a), the subchronic 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.”

Specific Response 30. The subchronic rodent study (NTP, 2007) was partly performed as a range-finding study prior to the two-year bioassay. Good range-finding studies should exceed the MTD. This is not a weakness of the study.

Genetic Toxicity

Specific Comment 32: “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.

Specific Response 32. The genotoxicity data presented by NTP (2007) have been added to Table 2. Table 2 now cites nine drinking water studies of which three are positive for genotoxicity, and 21 total studies (drinking water or gavage) of which 10 are positive for genotoxicity. See the “Genotoxicity” section of the PHG document for a discussion of these studies and presentation of OEHHA’s reasons for concluding that Cr VI is genotoxic via the oral route.

Specific Comment 33: “De Flora 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 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.”

Specific Response 33. The results of De Flora (2008) have been added to the “Genotoxicity” section. However, judging from the responses of their positive controls, it is likely that their methodology lacked the sensitivity to measure DNA damage at the dose levels tested. In addition, McCarroll *et al.* (2010) noted that the levels tested in this study may in part explain the negative results because they are below the exposure levels used in the NTP 2-year drinking water study.

Specific Comment 34: “OEHHA provides no basis for concluding that genotoxic effects occur at doses that do not overwhelm the reductive capacity of the stomach.”

And,

“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.”

Specific Response 34. The basis for the statement that genotoxicity has been observed at drinking water concentrations not likely to overwhelm the reductive capacities of the stomach, intestines and blood is discussed in De Flora (2000), as cited in the PHG document in the “Genetic Toxicity” section.

Sutherland et al. (2000) were not able to detect chromium in the brain tissue of any of their rats, including controls. Clearly, the amount of chromium in brain tissue was below the detection limit of their methodology, and their failure to measure increases in the chromium levels of brain tissue from dosed animals is uninformative.

Carcinogenicity

Specific Comment 35-1: “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.”

Specific Response 35-1. This information has been added to the text where Tables 5 and 6 are discussed.

Specific Comment 35-2: “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 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...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.”

Specific Response 35-2. Calculation of the denominators of the tumor incidence data now conforms to standard procedure (U.S. EPA, 2005; OEHHA, 2009). This is discussed in the text in the “Carcinogenicity” section, subheadings “NTP, 2008; Mouse; Neoplasms.” The intestinal tumor data were normalized to the number of mice alive at the time of occurrence of the first tumors in the small intestine: day 451 for males and day 625 for females.

Specific Comment 37: “(Page 53 of the August 2009 draft PHG document) ‘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...Rates of chronic inflammation of the liver were also high in the control groups of females and males (24% and 28% respectively).”

Specific Response 37. The discussion of chronic inflammation observed in rat liver has been revised. Reference to liver inflammation in control animals has been added to this discussion.

Specific Comment 38: “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.”

Specific Response 38. No epithelial cell injury or irritation of the small-intestinal epithelium was observed in the two-year bioassay conducted by NTP. These observations, and their implications for an MOA, are discussed in the “Carcinogenicity”

section of the draft PHG (see Table 7). In addition, judging from the responses of their positive controls, it is likely that the methodology used by De Flora et al. (2008) lacked the sensitivity to measure DNA damage at the dose levels tested. Also, McCarroll *et al.* (2010) noted that the levels tested in this study may in part explain the negative results because they are below the exposure levels used in the NTP 2-year drinking water study.

Specific Comment 39: “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 numbers of tumors per animal, both of which are the appropriate parameters for reporting results.”

And,

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

And,

“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.”

Specific Response 39. With regards to the study limitations cited in Specific Comment 39: 1) The paper states that the UV radiation contained less than one percent in the UVC range, 2) The discussion of the study in the PHG document states that the observed dose-response was for chromate concentration, not chromate dose. To make this clearer the phrase “concentration in the drinking water” has been added to the document, 3) The PHG states that the observed dose-response was for skin tumor formation. To make this clearer the phrase “increased numbers of skin tumors” has been added, 4) The PHG document does not discuss the study’s findings regarding what fractions of tumors were malignant, 5) With regards to skin effects in humans, note the “Toxicological Effects in Humans”, subheading “Carcinogenicity” section of the PHG document, which discusses dermatitis in Portland cement workers due to exposure to Cr VI in the cement. We located very few epidemiological data to either support or refute a link between exposure to Cr VI and increased risk of skin cancer. Thus, we would not discount the observations of Davidson et al. (1994) in mice and their potential implications for human exposures to Cr VI.

Toxicological Effects in Humans

Specific Comment 40: “The discussion of allergic contact dermatitis is dated and incomplete.”

Specific Comment 41: “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.”

Specific Responses 40 and 41. PHG documents are not intended to be comprehensive reviews of the literature and in the case of Cr VI focuses on the oral pathway. The inhalation studies discussed were judged to be the best available at the time of the calculation. To clarify that the review is not comprehensive, OEHHA has added the phrase “selected studies.”

Specific Comment 42: “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.”

Specific Response 42. The commenter makes a valid scientific suggestion that the unpublished results for stomach cancer from the Gibb et al. (2000) study be included in the OEHHA review. At this time, however, the review contains only published results. If unpublished results were to be included, an effort would have to be made to contact the investigators of all published studies and ask them if they can provide unpublished results. The scope of that effort is beyond the resources of OEHHA.

Specific Comment 43-1: “Although there are limitations to the Cole and Radu (2005) study, those limitations identified by OEHHA are not meaningful.”

Specific Response 43-1. OEHHA believes that the limitations are meaningful because, as discussed in the PHG document, the analysis included studies in which there was no exposure to Cr VI, did not include studies in which there was Cr VI exposure, and included a study that was retracted by the journal that published it.

Specific Comment 43-2: “OEHHA should include a review of SES and stomach cancer, or cite the findings of Cole and Radu (2005)”.

Specific Response 43-2. The following sentence was added to the PHG document: “A common limitation of the studies was lack of data on socioeconomic status, which may be associated with stomach cancer as noted by Cole and Radu (2005).”

Specific Comment 44-1: “OEHHA’s review of occupational epidemiology data is riddled with errors and does not reflect a thorough review.”

Specific Response 44-1. OEHHA acknowledges that it was not able to identify with 100 percent certainty all occupational studies with relevant exposure and excluded all studies with little exposure. A sentence about this has been added to the PHG document.

Specific Comment 44-2: “Virtually all of the papers identified in this section are not included in the reference section.”

Specific Response 44-2. OEHHA has updated the PHG document. All cited occupational studies are now listed in the reference section.

Specific Comment 44-3: “OEHHA states...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.’”

Specific Response 44-3. To lessen the implication of causality, the PHG document now says “consistent with an association between” instead of “suggestive of a link between.”

Specific Comment 45-1: “OEHHA missed many papers...These include {studies of} tannery workers.”

Specific Response 45-1. Since approximately World War II tanneries have switched to a single bath process that does not involve exposure to Cr+6. OEHHA has examined the tannery papers mentioned by the commenter and has concluded that Cr+6 exposure was unlikely for the workers studied in those papers.

Specific Comment 45-2: “OEHHA...missed the Guberan (1989) study of painters.”

Specific Response 45-2. OEHHA carefully examined the Guberan (1989) study of painters in the general population of Geneva, Switzerland. The painters were identified during a national census. Based on information provided in the article, OEHHA’s best professional estimate by two staff members with degrees in industrial hygiene is that less than 50% of the painters in Geneva were significantly exposed to Cr+6.

Specific Comment 45-3: “Also not included were a study of mild-steel and stainless-steel welders in France (Moulin et al 1993).

Specific Response 45-3. The Moulin 1993 article did not include results for digestive system cancers for stainless-steel welders, and mild-steel welders are not of interest to the PHG document because mild steel contains very little chromium compared to stainless steel.

Specific Comment 45-4: “{Also not included was} a study of deaths among die-casting and electroplating workers in the U.S. (Silverstein et al 1981).”

Specific Response 45-4. The Silverstein (1981) population included chrome platers, but results were not presented for chrome platers and they were probably a small portion of the entire population. OEHHA judged the study to be not useful.

Specific Comment 45-5: “{Also not included was} a study of stainless-steel, mild-steel, and shipyard welders in nine European countries (Simonato et al. 1991).”

Specific Response 45-5. The Simonato (1991) article did not include results for digestive system cancers for stainless-steel welders, and mild-steel welders and shipyard welders are not of interest to the PHG document because mild steel contains very little chromium compared to stainless steel.

Specific Comment 45-6: “{Also not included was} a study of chrome platers in Japan (Takahashi et al. 1990).”

Specific Response 45-6. The Takahashi (1990) cohort was updated by Itoh et al. (1996) and those results are already included in the PHG document.

Specific Comment 46: “How did OEHHA determine that at least half of the population likely has been exposed to Cr+6? What papers/findings were included or excluded on this basis?”

Specific Response 46. OEHHA made its best professional estimate as to which papers/findings should be included or excluded based on industrial hygiene-related information provided in the articles.

Specific Comment 47: “{The category} ‘all digestive system cancers’...should be removed from the summary...This represents a broad category... OEHHA’s review should consider only individual cancers, not the digestive system as a whole.”

Specific Response 47. OEHHA agrees that the broad category of digestive system cancers is much less useful than organ-specific results. While less useful, OEHHA believes that the results for all digestive system cancers combined should be included in the PHG document because Cr VI could cause cancers in multiple digestive organs.

Specific Comment 48: “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.”

Specific Response 48. OEHHA does not understand this concern about standardization, because the whole point of standardization is to control for differences in age, race, and gender distributions. Rate standardization methods are not “often questioned” in the opinion of OEHHA.

Specific Comment 49-1: “OEHHA twice included the same occupational cohort in the German chromate industry – Korallus et al. (1993) and Birk et al. (2006)... Birk et al. represents the most recent follow-up.”

Specific Response 49-1. OEHHA agrees that there was overlap of populations between the two studies and has added a footnote to the entries for these studies in the PHG document.

Specific Comment 49-2: “OEHHA reported data from an unknown paper (Raffnsson 1984”) concerning concrete mixers in Iceland...There is a more recent publication to Raffnsson et al. (1997) that could be the same cohort... Data from the more recent study should be included.”

Specific Response 49-2. The commenter is correct that Raffnsson et al. (1997) is a more recent update and OEHHA has updated Table 8 to reflect the newer data.

Specific Comment 50: “OEHHA appears to have extracted relative risk estimates for more highly exposed subcohorts within the individual studies, but the approach taken appears random.”

Specific Response 50. OEHHA has attempted to be consistent in judging the relative exposure levels of subcohorts within studies. With regard to the Axelsson *et al.*(1980) paper, for clarification OEHHA has added the following text to the PHG document: “ In the Axelsson *et al.*(1980) study of ferrochromium manufacturing, arc furnace workers

were exposed to higher levels than other workers (0.25 mg/m³ Cr VI versus a maximum of 0.05 mg/m³ in other subcohorts), thus the results for the arc furnace workers were abstracted.” With regard to Horiguchi et al. (1990) chrome platers, OEHHA confirmed that it abstracted the results for all chrome platers. With regard to Sorahan et al., (1987), OEHHA added text as follows: “In the Sorahan *et al.* (1987) study of metal platers, chrome bath workers were said to be ‘more heavily exposed,’ thus the results for the subcohort of workers whose first employment was ‘chrome bath’ were abstracted.”

Specific Comment 51-1: “It should be recognized that OEHHA’s literature review is incomplete.”

Specific Response 51-1. OEHHA has attempted to perform a complete literature review, but acknowledges possible limitations in any literature searches. Thus OEHHA has added the following statement to the PHG document: “OEHHA cannot say with 100% certainty that all occupational studies with relevant exposures were included and that no studies with little exposure were included”.

Specific Comment 51-2: “A conclusion regarding the number of studies with risk ratios less than or greater than one is not reliable.”

Specific Response 51-2. OEHHA agrees and has removed all text and a table in which risk ratios were compared to 1.00.

Specific Comment 51-3: “Exposures to Cr+6 are low compared to other industries...Mixtures...added to cement...are sometimes carcinogenic—for example asbestos.”

Specific Response 51-3. While exposures to Cr+6 may have been relatively low, OEHHA believes that the exposures were significant enough to warrant inclusion of cement industries. With regard to asbestos, the PHG documents states that the review excluded studies with workers exposed to asbestos-containing cement.

Specific Comment 51-4: “Rosenman and Stanbury (1996)...is a proportionate mortality ratio (PMR) study. OEHHA reported the PMR for stomach cancer. However, the PCMR (proportionate cancer mortality ratio) from the same study was not significantly increased for stomach cancer.”

Specific Response 51-4. The commenter raises a valid scientific issue about whether the PMR or PCMR in a study is preferable. In this study, the overall risk of cancer was substantially elevated (~40%), primarily due to large excesses of lung cancer. OEHHA concluded that comparing proportions within all cancers (the PCMR method) would cause the ratio for stomach cancer to be biased downward because of the overall excess of cancer. Comparison to all other deaths (the PMR method) was judged by OEHHA to be the preferred measure of association in this study.

Specific Comment 52: “Evaluating the risk by counting the number of studies with risk ratios greater or less than one is not a valid scientific method.”

Specific Response 52. OEHHA agrees and has removed text and a table in which the numbers of rate ratios above and below 1.00 were compared.

Specific Comment 53-1: “OEHHA has ignored..{studies of} environmental exposure to Cr+6 via ingestion, {including} Armienta-Hernandez and Rodriguez-Castillo (1995), Fryzek *et al.* (2001), and Bednar and Kies 1991).”

Specific Response 53-1. All three of these studies are now discussed in the PHG document.

Specific Comment 53-2: “The recent paper by Kerger *et al.* (2009) should be added to the discussion.”

Specific Response 53-2. Kerger *et al.* (2009) has been added to the discussion.

Specific Comment 54-1: “Beaumont et al (2008) argues that Cr+6 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 the Cr+6 exposure caused the cancers reported.”

Specific Response 54-1. OEHHA agrees that Cr+6 might have promoted rather than initiated cancer. The point of Beaumont’s argument was that it may not be reasonable to assume that Cr+6 exposure initiated the cancers. This agrees with the commenter’s view.

Specific Comment 54-2: “An ecological measurement of exposure ... was used to assign a level of Cr+6 exposure to the individuals included in the study.”

Specific Response 54-2: OEHHA did not assign levels of Cr+6 exposure; rather, it only classified geographic regions as to yes or no with regard to contaminated water having been present.

Specific Comment 54-3: “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.”

Specific Response 54-3. OEHHA agrees that the exposure may have been self limiting because of color and taste, and has added a paragraph to the PHG document regarding data on the color of the water in the Armienta-Hernandez and Rodriguez-Castillo (1995) study.

Specific Comment 54-4: “OEHHA should...focus on those studies most representative of California drinking water exposures (Fryzek et al.2001; Bednar and Kies 1991).”

Specific Response 54-4. Those studies did not provide useful results as explained in new text in the PHG document.

Specific Comment 55: “OEHHA is attributing these effects {oral ulcers, diarrhea, and abdominal pains in the villagers} to Cr+6 exposure. It can be surmised that the exposures of the villagers are not representative of Cr+6 exposures in California.”

Specific Response 55. OEHHA has removed the paragraph about the acute symptoms reported by the Chinese investigators because the methods used for the symptom study are not clear. OEHHA agrees that the concentrations of Cr+6 in groundwater encountered by the villagers were not representative of typical exposures in California.

Specific Comment 56: “What evidence exists that Cr+6 in water causes an increase in lung cancer {among the Chinese villagers}?”

Specific Response 56. The PHG document has never claimed that Cr+6 in water causes lung cancer. OEHHA has added to the PHG text that cigarette smoking is an uncontrolled risk factor in the Chinese study.

Specific Comment 57: “We concur that more information is clearly needed to provide an adequate exposure assessment for Cr+6 {exposure in drinking water in the Chinese study}, and without such the study is of questionable reliability... Is OEHHA going to conduct more research to better assess exposure?”

Specific Response 57. OEHHA has no plans to further investigate exposure to the Chinese villagers. OEHHA did not use data from the Chinese study to calculate the PHG.

Specific Comment 58: “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...Hence, this statement appears to be speculative and should be supported or struck.”

Specific Response 58. See Donaldson and Barreras (1966) for data showing increased Cr VI absorption in humans with pernicious anemia and achlorhydria. This citation has been inserted in the PHG document after the statement referred to in Specific Comment 58.

Examination of Evidence for Chromium Carcinogenicity

Specific Comment 59: “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.”

Specific Response 59. It is true that the mice in the NTP study did not develop tumors of the forestomach. However, different strains of mice were used in the NTP and Borneff et al. (1968) study. Mouse strain differences in tumor induction have been reported for other chemicals. As discussed in Appendix B of the PHG document, Borneff et al. (1968) suggested that tumor growth may have been inhibited in the F₁ and F₂ generations due to exposure to mousepox vaccine.

Specific Comment 60: “For accuracy and clarity, OEHHA should insert the word “lung” before “cancer” in this statement.”

Specific Response 60. This change has been made.

Specific Comment 61: “As described above in detail, this conclusion is based on a flawed analysis and is not correct.”

Specific Response 61. To lessen the implication of causality, the PHG document now says “consistent with an association between” instead of “suggestive of a link between.”

Specific Comment 62: “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.”

Specific Response 62. The studies cited in this comment (Fryzek et al, 2001; Bednar and Kies, 1991) are both discussed in the PHG document in the sub-section “Carcinogenicity” located in the “Toxicological Effects in Humans” section. Also discussed is a new epidemiology study of a geographic population exposed to Cr VI in drinking water in Greece. The limitations of these studies, discussed in the PHG document, did not allow conclusions to be drawn concerning organ-specific cancers.

Specific Comment 63: “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.”

Specific Response 63. The discussion of Borneff et al. (1968) was moved to the Appendix on the advice of some reviewers. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

Specific Comment 64-1: “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 De Flora 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.”

Specific Response 64-1. When making MOA determinations, OEHHA, U.S. EPA and others commonly consider the results of genotoxicity tests in tissue not yielding tumors (OEHHA, 2009; U.S. EPA, 2005). The mutagenic MOA described by McCarroll et al. (2010) has also been added to the document. The data of De Flora et al. (2008) have been added to the PHG document. It is now noted in the PHG document that De Flora et al. (2008) are the only investigators known by OEHHA to have looked for genotoxicity in the GI tract of rodents exposed to Cr VI in drinking water. However, judging from the responses of their positive controls, it is likely that their methodology lacked the sensitivity to measure DNA damage at the dose levels tested. In addition, McCarroll et al. (2010) noted that the levels tested in this study may in part explain the negative

results because they are below the exposure levels used in the NTP 2-year drinking water study.

Specific Comment 64-2: “Further, OEHHA cites the genotoxicity study of Bigaliev et al. (1977), conducted by gavage dosing, seven 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 Kuykendall et al. (1996), which is a study in humans exposed by drinking water 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 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.”

Specific Response 64-2. The ambiguity in Bigaliev et al. (1977) related to the part of the study that was conducted for one year. The uncertainty regarding exactly how the dose was applied is described in the footnote to Table 2. The part of that study in which the animals were administered a single dose by gavage was clearly understandable from the translation. Table 2 presents all the genotoxicity studies considered in the PHG document. Some of these were positive for genotoxicity and some were negative. The PHG document summarizes these results as follows:

Fifteen primary studies of the potential genotoxic effects following ingestion of Cr VI by humans or other mammalian species were located. A summary of these studies is provided in Table 2. Nine of the fifteen studies reported positive genotoxicity findings in various tissues.

We believe this is an even-handed evaluation of the findings of the available studies. The studies listed in Table 2 were judged to have been of sufficient quality to be included in the weight-of-evidence consideration of whether Cr VI is genotoxic. It is not clear why the studies by Mirsalis et al. (1996) and Kuykendall et al. (1996) are considered “far more meaningful” than the other studies cited in Table 2.

Specific Comment 65: “(Page 73 of the August 2009 draft PHG document) ‘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.”

Specific Response 65. A recent publication by the NTP authors (Collins et al. 2010) is discussed in Appendix A of the PHG document. Figures A3 to A6 show the accumulation of chromium in different tissues of female mice administered drinking water containing Cr VI ranging from 5 to 180 mg/L. Chromium accumulation was either linearly related to the concentration of Cr VI in the drinking water over the entire concentration range tested, or linearly related at low concentrations with indications of a plateau at higher concentrations. These data suggest that the reductive capacity of the GI tract was not exceeded in the two-year bioassay (NTP, 2008). The conclusion that the reductive capacity was not exceeded is compatible with the statement of Stout et al. (2009) that a portion of Cr VI escaped reduction since, as recognized earlier in these comments from the CMTA, Cr VI reduction and absorption are considered to be competing processes.

Mechanism of Genotoxicity and Carcinogenicity

Specific Comment 66-1: “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, De Flora 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.”

Specific Response 66-1. See the discussion of NTP (2008) and Table 7 in the PHG document. No inflammation or chronic tissue damage (including intestinal epithelial cell injury) was observed in the tumor-bearing tissue in either mice or rats. Hyperplasia was observed in mouse intestine but there were no indications that it was regenerative. With regard to De Flora et al. (2008), the DNA-protein crosslinks and 8-oxo-dG adducts they assayed (see Table 2 of the PHG document) comprise only a small subset of the types of DNA damage caused by Cr VI. In addition, judging from the responses of their positive controls, it is likely that their methodology lacked the sensitivity to measure DNA damage at the dose levels tested. Lastly, McCarroll *et al.* (2010) noted that the levels tested in this study may in part explain the negative results because they are below the exposure levels used in the NTP 2-year drinking water study.

Specific Comment 66-2: “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.”

Specific Response 66-2. The short-term tests presented in Table 2 of the PHG document were designed to determine whether ingested Cr VI is genotoxic in a variety of different tissues. Such genotoxicity data stand on their own, irrespective of whether tumors were detected in the same tissues in a two-year bioassay. We believe that the positive and negative studies comprising Table 2 are presented in an evenhanded manner.

Specific Comment 67: “The response of mice is likely due to non-genotoxic processes related to regenerative hyperplasia, which is secondary to epithelial injury and not operative at low doses.”

Specific Response 67. See the discussion of NTP (2008) and Table 7 in the PHG document. No inflammation or chronic tissue damage (including intestinal epithelial cell injury) was observed in the tumor-bearing tissue in either mice or rats. Hyperplasia was observed in mouse intestine but there were no indications that it was regenerative.

Specific Comment 68: “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 Response 68. The mechanism of action of Cr VI and its relevance to humans is discussed at length in the PHG document, especially in the following sections: “Mechanism of Genotoxicity and Carcinogenicity,” “Carcinogenicity (Animals), Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” and “Examination of Evidence for Chromium Carcinogenicity.” The document now cites the mutagenic mode of action described by McCarroll et al. (2010).

Dose-Response Assessment

Specific Comment 69: “The descriptions for these studies [Chopra et al., 1996 and Acharya et al., 2001] 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.”

Specific Response 69. These study shortcomings are listed in Table 1 of the PHG document entitled “Strengths and Weaknesses of Available Hexavalent Chromium Bioassays.”

Specific Comments 71 and 72: “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.”

Specific Responses 71 and 72. The discussion of the NTP (2008) study in the “Chronic Toxicity” section of the document has been revised. It now states that female rats exhibited another change in addition to inflammation at the lowest dose level; that of increased fatty changes to the liver. This discussion also notes that while fatty changes were increased at all dose levels, the increase was not statistically significant compared to the control at the lowest dose level.

Specific Comment 73: “OEHHA should use the current version of the BMD model for their PHG slope factor derivation.”

Specific Response 73. BMDS versions 1.4.1 and 2.1 gave identical risk estimates.

Specific Comment 74-1: “Comparisons of the results from Table 11 to those generated by the New Jersey Department of Environmental Protection, for the same data set, yields a different LED₁₀ 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...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.”

Specific Response 74-1. The cancer slope factors for male and female mice, as shown in Tables 10 and 11, are now the same as those calculated by both Stern (2010) and U.S. EPA (2010). The results for the duodenum only were dropped from both tables. The BMD modeling work consisted only of the results for the multistage model. The Chi-square statistics, P-values, ED₁₀ values and LED₁₀ values for that model are presented in Tables 10 and 11. Only the multistage model was used to model the tumor incidence data because this is the model preferred by OEHHA (2009) and U.S. EPA (2010) for conducting cancer dose-response assessment. This is primarily due to the multistage model’s generally good fit of the data in the relatively high dose range used in rodent bioassays (Armitage and Doll, 1961).

Specific Comment 74-2: “It is important to recognize that the uncertainty in the assumption of a linear dose-response is readily quantified here. The LED₁₀ can be used with a 30-fold uncertainty factor (3-fold factor for toxicodynamics and 10-fold for intraspecies variability) to derive a HPD that is 200-times higher than the value developed from the linear dose-response.”

Specific Response 74-2. OEHHA does not consider this a quantification of the uncertainty associated with its method for calculating the cancer risk. Rather, this is a choice to use a different model based on a different mechanism of action.

Specific Comment 75-1: “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 (rat).”

Specific Response 75-1. Standard cancer risk assessment practice is to assume that humans are at least as sensitive as the most sensitive species tested (U.S. EPA, 2005; OEHHA, 2009). It is not uncommon for a chemical to cause tumors in one rodent species and not in a second species. In the case of Cr VI, both rodent species tested yielded tumors.

Specific Comment 75-2: “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.”

Specific Response 75-2. OEHHA employed the same interspecies scaling methodology used by NTP (Stout et al., 2009) and U.S. EPA (2010) for the mouse tumor data.

Specific Comment 76: “New Jersey DEP (2009) used yet a different approach and applied the time-weighted average body weight at zero dose, which coincidentally equals 0.05 kg. OEHHA should provide justification for the approach used to scale to humans.”

Specific Response 76. The PHG document has been revised and now uses the time-weighted average bodyweight of the control male or female mice in the NTP (2008) study to scale from mice to humans (OEHHA, 2009). This is shown in the “Dose-Response Modeling” section of the document, where Tables 10 and 11 are discussed.

Specific Comment 77: “If there is no evidence of 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.”

Specific Response 77. As shown in Table 11 of the PHG document, the small intestine tumor data for female mice were modeled after excluding the high dose value. That the high dose tumor incidence data from female mice were dropped prior to BMD modeling is stated in the text and in the title of Table 10. As stated in the discussion accompanying Table 10, the high dose value was excluded because this yielded an acceptable fit of the model (according to Chi-square statistic and P value) to the data in the low dose region of the dose response curve. The low dose region is the region of importance for modeling the cancer risk, since the point of departure is in this region. There are many possible reasons for the bending of a dose response curve in the high dose region including pharmacokinetic, toxicodynamic and others. Dose response modeling, including dropping a high dose data point, is commonly performed when the biological basis for the bending over of the dose response curve is not known.

Specific Comment 79: “Hence, the upper confidence interval on the more refined dose-response assessment by Crump et al. (2003) is more than an order of magnitude lower than the value used by OEHHA of $0.15 (\mu\text{g}/\text{m}^3)^{-1}$...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.”

And,

“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.”

And,

“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.”

Specific Response 79. As shown in Table 18 of the PHG document, the proportion of the total cancer risk contributed by inhalation is very small: less than ~0.6%. Using a decreased estimate of the inhalation potency of Cr VI, as suggested in the comment, will have no significant effect on the final PHG value.

Calculation of the PHG

Specific Comment 82: “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 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.”

Specific Response 82. At present the Cr VI PHG based on cancer effects is 100-fold lower than if it were based on non-cancer effects (see “Calculation Of The PHG” section of the document). OEHHA will be applying the BMD approach in future analyses of the non-cancer data. Our preliminary analysis applying the BMD approach to the non-cancer data followed by an uncertainty factor of 100 yields a final value that is more than 100-fold **higher** than the proposed PHG based on cancer effects. Thus, the proposed PHG (0.02 ppb) for protecting against both cancer and non-cancer effects would not change.

Specific Comment 84: “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.”

Specific Response 84. The noncancer liver effects in female rats at the LOAEL were chronic inflammation and fatty changes (NTP, 2008). The incidence of animals with fatty changes was increased relative to controls at the lowest dose level, but was statistically significant only at the three higher dose levels (discussed in the PHG document). Since the health consequences of these effects are not known, OEHHA hesitates to classify them as “mild.” Even were they to be classified as “mild,” OEHHA would still use an uncertainty factor of 10 to extrapolate from a LOAEL to a NOAEL **for a chronic study** (see Table 4.4.1 in OEHHA, 2008). Since the study lasted two years, an uncertainty factor for less-than-lifetime duration is not needed.

Specific Comment 85: “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 the 2007b NTP study.”

Specific Response 85. The “problematic” study referred to in Specific Comment 85 is the subchronic study by NTP (1997a). We have expanded the discussion of NTP (1997a) and have now pointed out that similar liver effects were not observed in NTP (1997b), a subchronic study using the same strain of mouse and similar levels of Cr VI in the feed, or in the two year drinking water study (NTP, 2008).

Specific Comment 88-1: “For clarity, the only 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).”

Specific Response 88-1. Fatty changes to the liver were also increased relative to controls at the lowest dose level of 0.2 mg/kg-day; however, the fatty changes at the lowest dose level were not statistically significant relative to controls. This is now stated in the PHG document.

Specific Comment 88-2: “OEHHA should use the benchmark dose modeling approach for consistency with its own guidance and that of ATSDR.”

Specific Response 88-2. At present the Cr VI PHG based on cancer effects is 100-fold lower than if it were based on non-cancer effects (see “Calculation Of The PHG” section of the document). OEHHA will be applying the BMD approach in future analyses of the non-cancer data. Our preliminary analysis applying the BMD approach to the non-cancer data followed by an uncertainty factor of 100 yields a final value that is more than 100-fold **higher** than the proposed PHG based on cancer effects. Thus, the proposed PHG (0.02 ppb) for protecting against both cancer and non-cancer effects would not change.

Specific Comment 88-3: “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.”

Specific Response 88-3. We have not been able to locate data on the incidence of chronic liver inflammation in otherwise healthy humans. Without such data it is not possible to conclude that, “the endpoint of liver inflammation may not be biologically relevant to humans.”

Specific Comment 88-4: “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.”

Specific Response 88-4. As shown in Table 4.4.1 of OEHHA (2009), for extrapolating from a LOAEL to a NOAEL in a chronic study OEHHA recommends use of an uncertainty factor of 10.

Specific Comment 90-1: “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.”

Specific Response 90-1. As shown in Table 18 of the PHG document, the proportion of the total cancer risk contributed by inhalation is very small: less than ~0.6%. Using a decreased estimate of the inhalation potency of Cr VI, as suggested in the comment, will have no significant effect on the final PHG value.

Specific Comment 90-2: “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.”

Specific Response 90-2. PBPK modeling based on the limited data we currently have would add more uncertainty to the derivation of the PHG.

Specific Comment 90-3: “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.”

Specific Response 90-3. The issue of whether or not to use linear extrapolation to estimate the cancer risk is not an issue in uncertainty quantification. It is not clear what is meant by, “it is possible to quantify the PHG.” Also, it is not clear how a “non-cancer PHG” can “result in a cancer PHG.”

Specific Comment 90-4: “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 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.”

Specific Response 90-4. The results of this risk assessment are more certain than most PHGs. Cr VI is a known human carcinogen. A state-of-the-art chronic bioassay demonstrated carcinogenicity in two animal species in the relevant route of exposure, drinking water. There are extensive studies demonstrating the genotoxicity of Cr VI in vitro and in vivo. The description of uncertainty in the document is sufficient for the purpose of developing this PHG.

Appendix A – Carcinogenic Threshold?

Specific Comment 92-1: “Comment 92 OEHHA’s analysis of the lack of a carcinogenic threshold is flawed and should be removed.”

Specific Response 92-1. The use of the term “carcinogenic threshold” in the title of Appendix A has created confusion. It was meant to apply only to the results of the NTP (2008) bioassay and the dose range tested in that study. Over that dose range, the rodent GI tract’s ability to reduce Cr VI to Cr III was not exceeded. Therefore, the title has been modified to “Carcinogenic Threshold: Was the reductive capacity of the rodent GI tract exceeded in the NTP (2008) bioassay?”

Specific Comment 92-2: “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.”

Specific Response 92-2. OEHHA did not draw such a conclusion. However, the NTP (2008) study results do show that the apparent threshold for increased tumor incidence in that study was not due to exceeding the reductive capacity of the rodent GI tract over the dose range tested. This has been added to the discussion in Appendix A. Whether the rate of reduction of Cr VI to Cr III changes markedly over a much lower dose range is not known (discussed in the “Metabolism and Pharmacokinetics” section of the PHG document).

Specific Comment 92-3: “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 evaluations of tissue dose in the low dose range, which is relevant to environmental exposures.”

Specific Response 92-3 (repeat of General Response 4). Health and Safety Code Section 116365.5 required the department (now the Department of Public Health) to adopt a Cr VI Maximum Contaminant Level (MCL) by January 1, 2004. Section 116365 also mandates the development of PHGs as part of the process of adopting drinking water standards. Given the mandate to adopt a standard for hexavalent chromium by

January 2004 it is very difficult to justify additional delays in the development of a PHG for hexavalent chromium.

It is also difficult to predict the impact of future research on the development of PHGs. OEHHA does not know when the results of future research will become available, nor can OEHHA predict the outcome of future research, nor does OEHHA know how future findings could impact the development of PHGs in the future.

Section 116365 contains an important provision that addresses new scientific research when it becomes available: "(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data". When new research is completed and published in a peer-reviewed format, OEHHA will consider it in the development of a revised PHG for hexavalent chromium. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: "When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced."

OEHHA will review the Hamner Institutes PBPK model upon its completion. If the model produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Specific Comment 93: "Further, OEHHA must consider that, because tumors occurred only in the alimentary tract of the rodents, whether the observed tumors occurred at exposures that exceeded the reductive capacity of the rodent GI is actually not relevant (i.e., systemic absorption was not necessary for the observed effects to occur)."

Specific Response 93. If the reductive capacity is exceeded one would expect both more Cr VI to be absorbed into the systemic circulation and more to be transported directly from the intestinal contents into the epithelial cells that line the small intestines.

Specific Comment 94: "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."

Specific Response 94. The text has been revised accordingly.

Specific Comment 95: "(From page 115 of the August 2009 draft PHG document) '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). 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.”

Specific Response 95. The results of Sutherland et al. (2000) have been cited by some as a demonstration of a threshold for Cr VI absorption of between 0.5 and 3 mg/L. For reasons discussed in the PHG document, including methodological limitations and results from other studies performed with radioactive Cr VI, the Sutherland et al. (2000) data should not be used as a basis for concluding that essentially all Cr VI is reduced to Cr III at drinking water concentrations of 0.5 mg/L and below.

Appendix B

Specific Comment 96-1: “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...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.”

Specific Response 96-1. The discussion of the Borneff et al. (1968) study was moved to the Appendix on the advice of some reviewers. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

Specific Comment 96-2: “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.”

Specific Response 96-2. We have added this information to the discussion of Borneff et al. (1968) in Appendix B.

Comments from Mark Johnson, Coachella Valley Water District (CVWD)

Comment 1: “CVWD understands other studies exist and are referenced in the document providing evidence that complete reduction may not always occur, but believes the administered doses in the NTP study are so large they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in the rodents.”

Response 1. See Appendix A in the PHG document for a discussion of the data showing that the Cr VI reducing capacity of the rodent GI tract was not saturated over the dose range tested in the NTP (2008) two-year study.

Comment 2: “This is especially significant as the NTP study did not find excess cancers at the lowered doses in both rats and mice.”

Response 2. The absence of excess tumors at the lower dose levels may have been due to the use of too few animals to detect a relatively rare event (tumor formation).

Comment 3: “Equally as important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated and higher level of gastric juices than rodents.”

Response 3. See the “Metabolism and Pharmacokinetics” section and Appendix A of the PHG document for discussions of human data indicating that Cr VI escapes reduction and is absorbed into the circulation at drinking water concentrations below those used in the NTP (2008) two-year bioassay in rodents.

Comment 4: “After extensive review, an expert panel report concluded this study [Borneff et al., 1968] was seriously flawed due primarily to poor hygiene, which killed most of the parent and first generation mice and could have been the cause of the specific adverse effects that the authors attributed to hexavalent chromium. This study has no merit and should not be used to support the subject PHG.”

Response 4. The Borneff et al. (1968) study is not a key study in the derivation of the PHG for Chromium VI and was moved to the Appendix for that reason. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

Comment 5: “In the work completed in 1987 and 1997 by Zhang and Li, the data shows a negative dose-response between chromate exposure in drinking water and cancer rates found in about 10,000 villagers exposed to groundwater contaminated with hexavalent chromium levels as high as 2,600 ppb. The authors concluded there was no association between chromate exposure and any form of cancer in this population. Using a selective re-analysis of this study, the PHG document concludes a statistically significant increase in stomach cancer occurred based on unsupported assumptions about water consumption practices, plume migration and population distributions.”

Response 5. The commenter is in error in saying that the 1987 Zhang and Li paper concluded there was no association; only the 1997 paper, which has since been withdrawn by the journal that published it, concluded that there was no association. Although the names of the second authors of the two papers appeared to be the same, they are different individuals. The findings of Beaumont et al. (2008) replicated the findings of the original study: a statistically significant increase in stomach cancers. This is discussed in detail in the “Toxicological Effects in Humans, Carcinogenicity” section of the PHG document. See that discussion as well as the original publication by Beaumont et al. (2008) for a description of the assumptions and limitations of the OEHHA analysis. Another recent reevaluation of the Zhang and Li (1987) study by Kerger et al. (2009) has been added to the PHG document.

Comments from C. L. Stathos, Department of Defense

Cover Letter Comment 1: “To ensure complete transparency and improve understanding of the science underlying the proposed PHG, we urge the California Office of Environmental Health Hazard Assessment (OEHHA) to publish an analysis of the available weight-of-evidence for (a) the determination that Cr6+ is genotoxic and (b) epidemiological evidence of gastrointestinal cancer causation.”

Cover Letter Response 1. The issue of genetic toxicity is discussed at length in the PHG document in the “Genetic Toxicity” section. This discussion focuses on studies

performed *in vivo*, some of which were negative and some positive for genotoxicity. The PHG document also provides citations for a number of review articles which discuss Cr VI-induced genotoxicity in bacteria and cultured mammalian cells. Epidemiological studies of GI tract cancers in humans are discussed for exposure by inhalation (Table 8) in the “Cancers of ingestion- and digestion-related organs reported in occupational studies” section of the PHG, and for exposure by ingestion in the “Ingestion studies” section (Figure 15).

Cover Letter Comment 2: “We also recommend the publication of statistical analyses of the correlations between the State’s Cr6+ drinking water data and incidence of gastrointestinal cancers. We further recommend that OEHHA make available a comparison of these data to the cancer incidences predicted by the risk assessment on which the draft PHG is based. This will provide needed perspective on the proposed PHG for the public.”

Cover Letter Response 2. OEHHA is not aware of any published study or report comparing statewide Cr VI ingestion rates and incidences of GI tract cancers other than the very limited study of twelve families living in Hinkley, California. That study (DHHS, 2000) is discussed in the PHG document in the “Ingestion studies” section. We are unsure that a study such as that proposed in Cover Letter Comment 2 is feasible.

General Comment 1: “These data also strongly suggest that Cr+6 is a site-of-contact carcinogen. The data do not suggest that Cr+6 is a systemic carcinogen because...”

General Response 1. Given the types of tumors observed in the NTP (2008) bioassay (oral cavity in rats and small intestine in mice), Cr VI may be a site-of-contact carcinogen. However, Cr VI also caused systemic toxicity (see “Chronic Toxicity” section of the PHG) including genotoxicity in the liver (Table 2), indicating it was absorbed and bioavailable to distant tissues. Thus, we would not rule out the potential of Cr VI to cause cancer at sites distant from the GI tract.

General Comment 2: “Nevertheless, the data provide information that is useful and provide a biologically plausible alternative to the standard, default analysis that assumes systemic carcinogenicity. This alternative analysis could be part of the risk characterization that is presented to the decision-maker.”

General Response 2. Given the available data OEHHA is not able to distinguish between a point of contact or a systemic mechanism of carcinogenesis by Cr VI. We have added this information to the “Examination of Evidence for Chromium Carcinogenicity” section of the PHG document.

General Comment 3: “The dose-response curves for both cancer and mutagenicity are highly nonlinear, with statistically significant increases observed at only the highest doses, i.e., not at the lower doses. These would support a nonlinear extrapolation from the point of departure.”

General Response 3. The absence of statistically significant increases in tumors at the two lowest drinking water concentrations in NTP (2008) should not be interpreted as a threshold for tumorigenicity, since the number of animals may have been too low to detect tumors at the two lowest drinking water concentrations. The use of high doses in

cancer bioassays is generally thought to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors).

General Comment 4: “Point-of-contact carcinogens are usually caused by triggering events that only occur at high doses, e.g., irritation or cellular toxicity, rather than low-dose mutagenicity that is the historical basis for the linear extrapolation as a default for carcinogenesis.”

General Response 4. See discussion of Table 7 in the “Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice” section of the PHG document. Neither tissue damage nor inflammation was observed in the oral cavity of the rat or small intestine of the mouse, both sites where tumors were observed.

General Comment 5: “We should inquire as to whether OEHHA is considering Cr+6 to be acting by a mutagenic mode of action for carcinogenesis, as this would have additional implications for its risk assessment.”

General Response 5. As discussed in various parts of the PHG document (“Examination of Evidence for Chromium Carcinogenicity”, “Risk Characterization” sections), OEHHA finds that Cr VI is probably inducing tumors via a genotoxic/DNA-damaging mechanism of action that may or may not include mutations. The mutagenic mode of action described by McCarroll et al. (2010) has been added to the document.

General Comment 6: “Thus, if even 1% of the dietary chromium is Cr+6, our typical diet would expose a person to almost 10 times the proposed PHG. Information on the percentage of chromium in the diet that is Cr+6 should be obtained so that the previous estimate can be made. In particular, if typical, dietary exposure to Cr+6 greatly exceeds the draft PHG, one would expect higher GI tract tumors in the general population. This is a good and relatively easy method for determining how much the risk estimate (based on significant, but limited data) may overestimate the actual risk.”

General Response 6. As discussed in the PHG document in the “Food” section, the measurements of Cr in food rarely provide information on speciation. Were these data available, it would indeed be useful to use them to test an association between Cr VI intake and cancer.

General Comment 7: “The conversion performed by OEHHA from exposure to dose is only referenced as “OEHHA calculations.” If this was performed by a standard OEHHA procedure, that method should be publicly available and the reference provided. If it was specific to this study, it should be provided, perhaps as an appendix.”

General Response 7. The revised PHG document now uses the original daily Cr VI intake values provided by NTP (2008). That citation is now provided where the intake values are quoted.

General Comment 8: “Most of the human, non-lung cancers that were reported in the tables in the draft PHG document have a lower confidence limit of <1, indicating an absence of statistical significance. Four did not. Two of those involved cement or concrete workers that would have exposures to other potential carcinogens. The remaining two involved production of chromium materials. Nine other studies of similar

worker populations were negative. The weight of the evidence for carcinogenicity from epidemiological studies, therefore, is less than definitive.”

General Response 8. OEHHA agrees. The discussion of the worker studies in Table 8 has been revised to read, “These results are consistent with an association between occupational exposure to Cr VI (via inhalation) and stomach cancer.”

General Comment 9: “In all studies presented throughout the document, either human or animal studies, the doses of administered chromate are orders of magnitude higher than the doses that would be taken if drinking water were to meet the PHG guidelines.”

General Response 9. The use of high doses in cancer bioassays is generally thought to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors).

Specific Comment 1: “Therefore, it appears plausible that these NTP findings may support a nongenotoxic mode of action for initiation of the small intestine tumors observed in mice, as hyperplasia is usually associated with chronic tissue irritation in the “continuum-of-change”...Therefore, we believe that despite the data presented that Cr+6 can have “systemic” genotoxic effects distant from the site of carcinogenicity, the data presented in the draft document is not convincing that it operates via a mutagenic MOA for carcinogenesis during exposure to low environmental concentrations in drinking water.”

Specific Response 1. OEHHA found no evidence that the tumors observed in the two-year bioassay (NTP, 2008) were associated with epithelial cell damage or chronic inflammation (see discussion of Table 7 in the draft PHG). Also, it is not uncommon for carcinogens to stimulate cellular proliferation in the absence of cell killing. With regards to genotoxicity, ingested doses of Cr VI similar to those used by NTP (2008) caused a variety of genotoxic damage in rats and mice (Table 2). Thus, a genotoxic MOA is the only mode of action that is consistent with the available data.

Specific Comment 2: “As there is significant scientific concern associated with the results of the Borneff et al., 1968 animal study, it is not clear why this particular study is singled out and cited in the Summary and expanded upon at length in Appendix B; and why the draft PHG document does not elaborate on the weaknesses identified...Available studies, such as 2007 and the previous NTP rodent studies, and human population studies of drinking water ingestion reporting negative findings of increased population carcinogenicity (for example, June 2009 Texas Department of State Health Services, Evaluation of Chromium in Private Wells in Midland County Texas, ATSDR Letter Health Consultation and others), and on mode of action for digestive tract carcinogenicity, genotoxicity and mutagenicity, etc. should have been considered.”

Specific Response 2. The weaknesses of Borneff et al. (1968) are discussed in detail in Appendix B of the PHG document. The well contamination in Midland County Texas was discovered in 2009. The Letter Health Consultation states, “The site investigation and discovery has just started in the area. The source of contamination is not known, and the groundwater contamination has not been delineated or fully characterized at this time. Additionally, well water is being further assessed to determine if chromium is

the only contaminant of concern.” The letter goes on to cite the Texas Cancer Registry. For the period of 1997 to 2006, there were no excess cancers reported for the zip code of interest in Midland County. Since the concentrations of Cr VI were poorly characterized at the time this report was made, and the cancer monitoring period preceded the time-frame of contamination monitoring, OEHHA did not include this report in the PHG document.

Specific Comment 3-1: “Comparing the data derived from the 2007 NTP drinking water ingestion studies, and the potential exposures to Cr+6 from maintenance operations, such as welding stainless steel, with ingesting low levels of Cr+6 in drinking water, it appears that humans may be much less susceptible than other animals to Cr+6-induced gastrointestinal (GI) tract cancers, since the adenomas or carcinomas of the duodenum, jejunum, or ileum are only reported in mice exposed to about 6 orders of magnitude higher active concentrations of Cr+6 and rats stomach tumors at even higher administered doses than that for mice (NTP, 2007).”

Specific Response 3-1. The use of high doses in cancer bioassays is designed to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors) (U.S. EPA, 2005).

Specific Comment 3-2: “As stated in the ‘Comments Regarding NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate for May 16-17, 2007 Peer Review,’ ‘Many differences exist in the physiology and anatomy of the rat and mouse gastrointestinal tracts, with even greater differences in humans. One such difference of particular importance is basal rate of gastric acid secretion, which is approximately 1,200 times greater in the rat compared to the mouse (Friis-Hansen et al. 1998; Runfola et al. 2003; Wang et al. 2003). The human basal gastric acid secretion rate is approximately 8-times higher than that of the rat (Friis-Hansen et al. 1998).’ Thus, a more in-depth discussion of potential interspecies variability, as seen in the NTP 2007 rodent studies, is important to increase understanding of potential implications for human increased potential for carcinogenicity...Peer reviewers’ comments have further suggested that interspecies variability may be due to differences in the pH of human salivary glands (6.5-7.5) compared to the mouse (9.0-10.0). Other interspecies differences such as (a) acid secretion rate differences in humans 8,000-20,000 (µEq/4h) compared to 1-168 (µEq/4h) in the mouse; (b) stomach bacteria and protozoan species indigenous in the mouse and rat; and (c) a much larger stomach fraction of GI tract compartments compared to rodents, may result in greater conversion of Cr+6 to Cr+3 than in the human stomach at low environmental concentrations.”

Specific Response 3-2. Calculation of the human oral cancer slope factor in the PHG document was performed with tumor data collected from the mouse. Due to inadequate toxicokinetic and toxicodynamic data, it was only possible to adjust the mouse dose to a human equivalent dose with default methodology; i.e., scaling by bodyweight^{3/4} (U.S. EPA, 2005; OEHHA, 2009; Stern, 2010; U.S. EPA, 2010). The interspecies differences between rodents and humans in reduction, absorption and distribution of Cr VI are discussed in the “Metabolism and Pharmacokinetics” section of the PHG document. More discussion of interspecies differences has been added to the “Calculation Of The PHG,” subheading “Choosing Appropriate Uncertainty Factors” section and the “Risk Characterization” section of the document.

Specific Comment 3-3: “Regarding absorption, the 2008 ATSDR Draft *Toxicological Profiles for Chromium* states that less than 10% of Cr+6 ingested is absorbed from the stomach; the majority of ingested Cr+6 is absorbed from the stomach as Cr+3 via reduction by the acidic juices; and 0.5-2% of Cr+3 ingested is absorbed from the gastrointestinal tract.”

Specific Response 3-3. The PHG document contains extensive discussion of Cr VI and Cr III absorption and reduction.

Specific Comment 4: “Figure 12 indicates that, at the highest dose level, female mice had a body weight approximately 20% less than controls. This suggests that the maximum tolerated dose (MTD) was exceeded. Even if this decrease in body weight was due to a lower consumption of water, a decrease in body weight of > 10% for any reason is generally considered sufficient to raise concerns about the toxicity observed in those animals.”

Specific Response 4. The possibility that the MTD was exceeded in the high dose female mice is now discussed in the “Carcinogenicity,” subheading “Neoplasms” section of the draft PHG.

Specific Comment 5: “Therefore, we recommend that the document more clearly states that a causal link between exposure to Cr+6 in drinking water and tumors of the digestive tract has not been confirmed based on the data derived from human studies; and that the human data are considered “suggestive” of such a link, but not compelling.”

Specific Response 5. The final PHG document states, “In the only two studies of human exposure to Cr VI in drinking water that specifically measured organ-specific cancer, statistically significant increases in stomach cancer mortality (Zhang and Li, 1987; statistical analysis conducted by OEHHA) and primary liver cancer mortality (Linos *et al.*, 2011) were detected in the exposed population.”

Specific Comment 6: “It appears that CA OEHHA simply counted the numbers of human studies with relative risk ratios less than or greater than one, without giving any consideration to the range of the confidence intervals for each study. Generally, epidemiological studies with a lower confidence limit that includes “1” are not considered to be statistically significant. Thus, we recommend that CA OEHHA consider a more rigorous statistical approach to better understand the strength of these studies. The need for a statistical approach was also a recommendation made by one of the three university external peer reviewers on the 2008 PHG Draft, Dr. R. Gwiazda, Environmental Toxicology, University of California, Santa Cruz.”

Specific Response 6. We have added more discussion of Table 8 that includes the suggestions of Dr. Gwiazada to: 1) not compare the rate ratios to 1.00, and 2) conclude that the results are consistent with an association between occupational exposure to Cr VI (via inhalation) and stomach cancer.

Specific Comment 7-1: “The Beaumont et al 2008 study of the same Chinese villagers reported a statistically significant relationship between Cr+6 environmental exposure and oral cancer in 5 villages in China with high concentrations of Cr+6 in well water...The PHG Draft has also reported that this population was found to have been infected with *Helicobacter pylori* bacteria, which is much more prevalent in developing

countries and may be associated with the increased risk of stomach cancer in the entire province (even in regions without Cr+6 contaminated drinking water.”

Specific Response 7-1. *Helicobacter pylori* was not measured in the Zhang and Li (1987) study. Also, the study reported stomach cancer mortality, not oral cancer.

Specific Comment 7-2: “The draft PHG document does not emphasize in the main portion of the text the fact that well documented dietary and other environmental and genetic factors have been shown to lead to stomach cancer itself, in the absence of Cr+6 in drinking water...It would be beneficial to provide additional pertinent information concerning the prevalence of gastrointestinal cancer in developing countries versus the U.S...We also recommend including additional information on other potential environmental confounders that also may be associated with stomach cancer in humans in addition to those already discussed, such as ingestion of asbestos particulates in drinking water, etc., and should be discussed in greater detail, to help account for other potential confounders in future research designs and study evaluations.”

Specific Response 7-2. These suggestions for an expanded general discussion of human stomach cancer go beyond the scope of the PHG document.

Editorial Comment 1: “We believe it would increase clarity if the text were changed to indicate whether the chromium analysis in blood and plasma was speciated to differentiate between hexavalent chromium (Cr+6), trivalent chromium (Cr+3), or total chromium following administration of Cr+6.

Editorial Response 1. We have revised the “Summary” section of the PHG document accordingly.

Editorial Comment 2: “The reference JHAS (1979) is mentioned as one of the papers with findings as the basis for OEHHA’s re-evaluation of PHG but it is not discussed in the non-carcinogenic Effects Section under Choosing Appropriate Uncertainty Factors. It should be added to this section, added to the reference list, and the acronym should be defined.”

Editorial Response 2. The acronym has been added to the citation in the “References” section of the PHG document.

Editorial Comment 3: “Figure 13 has no units on the x-axis...Thus, it must be something like “tumor-bearing animals” but the actual title and how the data were calculated should be transparent.”

Editorial Response 3. The mouse tumor data are now presented in Tables 5 and 6 of the PHG document.

Comments from Robert Hollander, The Western Coalition of Arid States

Comment 1: “WESTCAS understands other studies exist and are referenced in the document providing evidence that complete reduction may not always occur, but believes the administered doses in the NTP study are so large they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in the rodents. This is

especially significant as the NTP study did not find excess cancers at the lowered studied doses in both rats and mice.”

Response 1. See Appendix A in the PHG document for a discussion of the data showing that the Cr VI reducing capacity of the rodent GI tract was not saturated over the dose range tested in the NTP (2008) two-year study. The absence of excess tumors at the lower dose levels may have been due to the use of a small number of animals to detect a relatively rare event (tumor formation).

Comment 2: “Equally as important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated and higher level of gastric juices than rodents.”

Response 2. Cr VI is reduced to Cr III in both the rodent and human stomach. This is discussed in detail in the PHG document in the sections “Hexavalent Chromium Reduction by Saliva and Gastric Fluids”, “Absorption” and “Pharmacokinetics of Trivalent versus Hexavalent Chromium.” See also Appendix A. While Cr VI reduction in the GI tract of rodents compared to humans has not been fully described, the U.S. EPA (2010), the New Jersey Department of Environmental Protection (NJDEP, 2009) and OEHHA (this PHG document) have all found that they are similar enough to allow calculation of a human cancer slope factor for Cr VI based on the NTP two-year bioassay.

Comment 3: “The first of these studies was completed in 1968 by Borneff et al...This study has no merit and should not be used to support the subject PHG.”

Response 3. The Borneff et al. (1968) study is not a key study in the derivation of the PHG for Chromium VI and was moved to the Appendix for that reason. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

Comment 4: “In the work completed in 1987 and 1997 by Zhang and Li, the data shows a negative dose-response between chromate exposure in drinking water and cancer rates found in about 10,000 villagers exposed to groundwater contaminated with hexavalent chromium levels as high as 2,600 ppb. The authors concluded there was no association between chromate exposure and any form of cancer in this population. Using a selective re-analysis of this study, the PHG document concludes a statistically significant increase in stomach cancer occurred based on unsupported assumptions about water consumption practices, plume migration and population distributions.”

Response 4. The commenter is in error in saying that the 1987 Zhang and Li paper concluded there was no association; only the 1997 paper, which has since been withdrawn by the journal that published it, concluded that there was no association. Although the names of the second author of the two studies appeared the same, they are actually different individuals. The findings of Beaumont et al. (2008) published in 2008 replicated the findings of the original study (Zhang and Li, 1987): a statistically significant increase in stomach cancers. This is discussed in detail in the “Toxicological Effects in Humans, Carcinogenicity” section of the PHG document. See that discussion

as well as the original publication by Beaumont et al. (2008) for a description of the assumptions and limitations of the OEHHA analysis. Another recent reevaluation of the Zhang and Li (1987) study by Kerger et al. (2009) has been added to the PHG document.

Comments from Andria Ventura, Clean Water Action California

Comment 1: “If anything, OEHHA’s analysis is not adequately conservative in that it actually does not go far enough in considering the impacts on specific vulnerable populations. Their studies do not reflect the department’s guidelines on accounting for early-life susceptibility to carcinogens, putting pregnant women, their fetuses, and young children at greater risk.”

Response 1. The PHG document has been revised to account for increased early-life susceptibility to carcinogens. See “Correction for Early-in-Life Exposures” section of the document.

Comment 2: “Furthermore, we would suggest greater consideration of the large portion of the population whose ability to transform hexavalent chromium into less toxic trivalent chromium may be impaired. One only has to review the wide range of over the counter medications to address common gastrointestinal problems that can impact millions of people’s ability to convert hexavalent chromium to understand the potential threat to the population at large.”

Response 2. These potentially sensitive subpopulations are discussed in the “Sensitive Subpopulations” section of the PHG document. For calculation of the acceptable daily dose (ADD) for noncarcinogenic effects (“Calculation OF The PHG, Noncarcinogenic Effects” section of the PHG), an uncertainty factor of 10 was judged sufficient for protecting potentially sensitive human subpopulations, such as antacid users. Methodology does not currently exist for incorporating such an uncertainty factor into the calculation of the ADD for carcinogenic effects.

Comments from Kristy L Morrison, American Chemistry Council

Comment 1: “In July 2009, Toxicology Excellence for Risk Assessment (TERA) convened a Science Advisory Board (SAB) to provide guidance on research to investigate the potential mode(s) of action (MOA) of hexavalent chromium based on the US EPA Guidelines for Carcinogen Risk Assessment (2005). Based on TERA’s scientific recommendations, The Hamner Institute for Health Sciences was commissioned to conduct research on five key areas integral to assessing the MOA(s) for chromium...”

And “We urge OEHHA to await additional research findings anticipated in 2010 before finalizing the draft PHG.”

And “In a memo dated October 23, 2008, from Dr. David Berry, Senior Toxicologist with the Human and Ecological Risk Division of the Department of Toxic Substances Control, to Dr. Jeff Wong, Chief Scientist of the Department of Toxic Substances Control, the Hamner research program was recognized as critical in addressing the mode of action of chromium and the studies should be ‘prerequisites to any revisions to

the OEHHA public health goal for Cr⁺⁶.’ In issuing the draft PHG prematurely; however, OEHHA has failed to consider the anticipated mode of action research (See Appendix A). We agree with DTSC comments regarding how important it is to use current scientific principles and recent advances such as incorporating mode of action are preferable to using outdated default assumptions.”

Response 1. Neither the August 2009 draft document nor the final PHG document is premature. Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comments from Renee Sharp, Rebecca Sutton and Gina Solomon, Environmental Working Group

Comment 1: “OEHHA’s proposed PHG should be revised to more adequately protect sensitive populations (emphasis in original)...Conversion of hexavalent to trivalent chromium can be impaired in individuals with low-acid stomachs, a condition brought about by several widely used medications, like antacids and proton pump inhibitors, which treat disorders including gastroesophageal reflux disease, peptic ulcer disease, and chronic gastritis. Other health conditions that can result in reduced stomach acid production include pernicious anemia, pancreatic tumors, infection with *Helicobacter pylori*, mucopolidosis type IV, and some autoimmune diseases.”

Response 1. These potentially sensitive subpopulations are discussed in the “Sensitive Subpopulations” section of the PHG document. For calculation of the acceptable daily dose (ADD) for noncarcinogenic effects (“Calculation OF The PHG, Noncarcinogenic Effects” section of the PHG), an uncertainty factor of 10 was judged sufficient for protecting potentially sensitive human subpopulations, such as antacid users.

Comment 2: “One of the peer reviewers (Dr. R. Gwiazda) aptly noted how OEHHA had overlooked some of these concerns in its proposed PHG in the following statement: “There are two sensitive populations that are not included in the estimate of the one in a million lifetime cancer risk: carriers of *Helicobacter pylori* and people with anomalous stomach pH regulation” (Gwiazda 2008).”

Response 2. Methodology does not currently exist for incorporating the potentially heightened sensitivity of these subpopulations into the calculation of the acceptable daily dose (ADD) for carcinogenic effects.

Comment 3: “From the excerpts above, it is clear that OEHHA should revise its proposed hexavalent chromium PHG to reflect the agency’s own recently published guidelines to take into account the special concerns about early-life susceptibility to carcinogens.”

Response 3. The PHG document has been revised to account for the heightened sensitivity of infants and children to carcinogens as described in the OEHHA (2009) guidelines.

Comments from Christy Marani, Central Water District

Comment 1: “According to the Association of California Water Agencies (ACWA), the administered doses in the NTP study are so large that they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in the rodents. This is especially significant as the NTP study did not find excess cancers at lower doses in both rats and mice.”

Response 1. See Appendix A in the PHG document for a discussion of the data showing that the Cr VI reducing capacity of the rodent GI tract was not saturated over the dose range tested in the NTP (2008) two-year study. The absence of excess tumors at the lower dose levels may have been due to the use of too few animals to detect a relatively rare event (tumor formation).

Comment 2: “Equally important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated digestive process.”

Response 2. See the “Metabolism and Pharmacokinetics” section and Appendix A of the PHG document for discussions of human data indicating that Cr VI escapes reduction and is absorbed into the circulation at drinking water concentrations below those used in the NTP (2008) two-year bioassay in rodents.

Comment 3: “Although we recognize all the efforts at research made to date, the NTP study and other referenced studies do not address, for example, the effects of prescription medications and over-the-counter antacids on gastric juices.”

Response 3. These issues are discussed in the PHG document in the section “Toxicological Effects in Humans,” subheading “Sensitive Subpopulations.”

Comments from Gary Buchanan, New Jersey Department of Environmental Protection

Comment 1: “We agree with your conclusion (echoing the NTP conclusion) that decreased water consumption was a contributing factor to decreased body weight compared to controls in the high-dose male and female mice. Additional information supplied to us by NTP provides evidence that for the high dose female mice there was also a systemic component to decreased body weight.”

Response 1. We have added text to the discussion of Figures 9-14 suggesting that the approximate 20 percent decrement in female mouse bodyweight in high dose animals may indicate that the MTD was exceeded in that dose group (NJDEP, 2009).

Comment 2: “In addition, since the issue of possible dehydration and the possibility of its contribution to the neoplasia was raised in the initial peer review of the NTP study, the NJDEP document addresses this question.”

Response 2. We have added text to the discussion of NTP (2008) stating that there were no indications that the rats or mice became dehydrated during the study.

Comment 3: “There are some small and essentially non-significant differences between the values you identified for the denominator of the incidence ratio and those identified in the NJDEP analysis.”

Response 3. The denominators in the tumor incidence values shown in Tables 5 and 6 of the PHG document now correspond to the animals alive at the time of the first occurrence of tumor (day 451 for male mice and day 625 for female mice; OEHHA, 2009).

Comment 4: “You may want to include the observations in our discussion that support self-restriction of water intake in high dose males, but not high dose females, and the related conclusion that the significant decrease in body weight in the high-dose females was a systemic effect indicating a possible exceedance of the MTD rather than a result of palatability issues.”

Response 4. We have added text to the “Maximum Tolerated Dose – Mice” section of the PHG document citing the NJDEP (2009) suggestion that the MTD may have been exceeded in the high dose females.

Comments from Thomas LaHue, Soquel Creek Water District

Comment 1: “We are concerned that the human carcinogenicity of low levels of chromium 6 in drinking water has not yet been clearly established with a significant body of solid scientific evidence.”

Response 1. In the absence of conclusive data in humans, carcinogenicity in rodents is sufficient justification for developing a human protective dose (U.S. EPA, 2005; OEHHA, 2009).

Comments from Anthony Zampello, Raymond Basin Management Board

Comment 1: “The California Health and Safety Code 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)(l). OEHHA did not comply with its own and EPA's procedures for calculating the PHG. As pointed out by the Department of Toxic Substances Control (DTSC) in an October 23, 2008 memo on the PHG, the method employed by OEHHA to calculate the PHG ignored recent advances in assessing carcinogenesis. EPA guidance specifically requires alternate means of assessing the results of cancer bioassays where appropriate scientific data is available. In contrast, OEHHA ignored all other options for calculation of cancer potency and simply adopted the EPA's default "linear extrapolation" procedure for this PHG. In fact, the DTSC and scientific peer reviewers from the University of California suggested that an analysis of alternative approaches should have been included in the draft PHG documents.”

Response 1: OEHHA employed currently accepted procedures for calculating the PHG for Cr VI (U.S. EPA, 2005; OEHHA, 2009; Davis et al., 2010). Multiple means for calculating the cancer potency were considered including choice of animal species (rat versus mouse), sex, tumor site (oral cavity versus small intestine) and mathematical model (such as linear multistage, logistic, probit, Weibull). An alternative approach was also tested based on the most sensitive change detected in any drinking water study: that of mild chronic inflammation in the livers of female rats (NTP, 2008) (see “Calculation Of The PHG, Noncarcinogenic Effects” section). Other alternative approaches were suggested by the peer reviewers, some of which were discussed in OEHHA’s Response to Major Comments on Technical Support Document (OEHHA, 2009b).

Comment 2: “However, the OEHHA has used exactly the kind of overly speculative theories that it was warned not to use by both the Risk Assessment Advisory Committee and the prior peer reviewers. DTSC has indicated this so-called Helicobacter Hypothesis is speculative, lacks relevance to developing the PHG and it should be eliminated from the document as it is speculation. However, OEHHA with absolutely no scientific basis, use this as the primary basis for linking tumor findings in animal studies to the possible occurrence of stomach cancer in humans ingesting chromium in water.”

Response 2: The PHG for Cr VI in drinking water is based on tumors in rodents (NTP, 2008). The Helicobacter hypothesis plays no role in the derivation of the PHG. Note that the hypothesis is not discussed in the technical document but only in the Appendix. The hypothesis was formulated by OEHHA in order to obtain a better understanding of the findings of diverse studies. Some unexplained findings such as the occurrence of tumors in the first generation of the Borneff et al. (1968) study could be explained by the presence of Helicobacter bacteria. Also the hypothesis may explain why stomach tumors occurred following a relatively short term exposure to Cr VI in rural China. It is a scientific resource to keep these discussions attached in the Appendix as records of the

issues that have been addressed in the research for and preparation of this PHG document.

Comment 3: "OEHHA only relied on studies that have been superseded by more recent findings. It also chose to reinterpret other studies that do not fit its own conclusions while also ignoring data that did not support its conclusion. For example, OEHHA's evaluation of the 1987 Zhang J and Li X assessment of chromium pollution of water supplies in China and in 1997, the lead co-author of the 1987 study expanded the assessment of the data found no statistically relevant link between stomach cancer in humans and consumption of water containing chromium 6. There are other examples where OEHHA similarly reevaluated published data and studies to support OEHHA's hypothesis which the 2008 Peer Reviewers noted as "overreaching" and DTSC's memo concluded inadequately addressed the with of (sic) evidence. This subjective process of picking and choosing data regardless if there is a scientific basis to obtain a predetermined answer should not be the process to develop the PHG giving the importance of this task."

Response 3: The findings of Beaumont et al. (2008) published in 2008 (well after the original studies, Zhang and Li, 1987) replicated the findings of the original study and found a statistically significant increase in stomach cancers. The referenced 1997 study was withdrawn in 2006 by the publisher, The Journal of Occupational and Environmental Medicine. The second authors of the 1987 and 1997 studies were different individuals although they showed the same name. Another recent reevaluation of the Zhang and Li (1987) study by Kerger et al. (2009) has been added to the PHG document.

Comment 4: "In fact, DTSC recognized the importance of the Hamner Research program in addressing the "mode of action" (MOA) of chromium and said that the studies should be 'prerequisites to any revisions to the OEHHA public health goal for chromium 6.' By issuing a PHG without waiting for this information, OEHHA is not taking account of the most up-to-date science."

Response 4: Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: "(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data". OEHHA acknowledges that new studies may alter a revised PHG.

From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comments from J. Eric Tynan, Castroville Community Services District

Comment 1: “According to the Association of California Water Agencies (ACWA), the administered doses in the NTP study are so large that they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in rodents. This is especially significant as the NTP study did not find excess cancers at the lowered studied doses in both rats and mice.”

Response 1. See Appendix A in the PHG document for a discussion of the data showing that the Cr VI reducing capacity of the rodent GI tract was not saturated over the dose range tested in the NTP (2008) two-year study. The absence of excess tumors at the lower dose levels may have been due to the use of too few animals to detect a relatively rare event (tumor formation).

Comment 2: “Equally as important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated and higher level of gastric juices than rodents.”

Response 2. See the “Metabolism and Pharmacokinetics” section and Appendix A of the PHG document for discussions of human data indicating that Cr VI escapes reduction and is absorbed into the circulation at drinking water concentrations below those used in the NTP (2008) two-year bioassay in rodents.

Comment 3: “It is our understanding that the Borneff et al study is seriously flawed and should not be considered in the development of the PHG. In the work completed by Zhang and Li, it is our understanding that not all factors were considered when the authors reached their conclusions, including the extremely high levels of hexavalent chromium and the presence of a particular bacterial infection potentially affecting the results.”

Response 3. The Borneff et al. (1968) study is not a key study in the derivation of the PHG for Chromium VI and was moved to the Appendix for that reason. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

The Zhang and Li (1987) study was thoroughly analyzed (see Beaumont et al., 2008). Although the magnitude of the exposure to Cr VI in drinking water is unclear, the population did appear to be exposed to high levels of chromium VI. A statistically

significant increase in stomach tumors was detected when compared to a nearby unexposed population and when compared to the province. The high levels of chromium VI in the wells is what triggered the study (lower levels probably would have gone undetected). Lower levels of chromium VI may still cause cancer but at a rate that would have been undetected in a population of several thousand. The possible infection of the study population by *Helicobacter pylori* is discussed in Appendix B of the PHG document.

Comments from David Koch, City of Watsonville

Comment 1: “The City understands other studies exist and are referenced in the document providing evidence that complete reduction may not always occur, but believes the administration doses in the NTP study are so large they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in the rodents. This is especially significant as the NTP study did not find excess cancers at the lowered studied doses in both rats and mice.”

Response 1. See Appendix A in the PHG document for a discussion of the data showing that the Cr VI reducing capacity of the rodent GI tract was not saturated over the dose range tested in the NTP (2008) two-year study. The absence of excess tumors at the lower dose levels may have been due to the use of a small number of animals to detect a relatively rare event (tumor formation).

Comment 2: “Equally as important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated and higher level of gastric juices than rodents.”

Response 2. Cr VI is reduced to Cr III in both the rodent and human stomach. This is discussed in detail in the PHG document in the sections “Hexavalent Chromium Reduction by Saliva and Gastric Fluids”, “Absorption” and “Pharmacokinetics of Trivalent versus Hexavalent Chromium.” See also Appendix A. While Cr VI reduction in the GI tract of rodents compared to humans has not been fully described, the U.S. EPA (2010), the New Jersey Department of Environmental Protection (NJDEP, 2009) and OEHHA (this PHG) have all found that they are similar enough to allow calculation of a human cancer slope factor for Cr VI based on the NTP two-year bioassay.

Comment 3: “The Borneff et al. study is seriously flawed and should not be considered in the development of the PHG. In the work completed by Zhang and Li, not all factors were considered when the authors reached their conclusions including the extremely high levels of hexavalent chromium and the presence of a particular bacterial infection potentially affecting the results.”

Response 3. The Borneff et al. (1968) study is not a key study in the derivation of the PHG for Chromium VI and was moved to the Appendix for that reason. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

The Zhang and Li (1987) study was thoroughly analyzed (and published, see Beaumont et al., 2008). Although the magnitude of the exposure to Cr VI in drinking water is unclear, the population did appear to be exposed to high levels of chromium VI. A statistically significant increase in stomach tumors was detected when compared to a nearby unexposed population. The high levels of chromium VI in the wells is what triggered the study (lower levels probably would have gone undetected). Lower levels of chromium VI may still cause cancer but at a rate that would have been undetected in a population of several thousand. There was no indication that the study population was infected by bacteria that influenced its sensitivity to Cr VI.

Comments from Danielle Blacet, Association of California Water Agencies

Comment 1: “The Office of Environmental Health Hazard Assessment’s (OEHHA) draft PHG of 60 parts per trillion (ppt) was based largely on the findings of a recent National Toxicology Program (NTP) study that concluded there is sufficient data to classify hexavalent chromium as a carcinogen through the oral route of exposure. The researchers reached this conclusion through selected evidence that hexavalent chromium, when ingested in very high doses, causes cancer of the oral cavity and small intestine in rats and mice.”

Response 1: OEHHA used a weight of the evidence approach, based on toxicokinetic studies, genotoxicity and mechanism studies and animal and human studies to evaluate the carcinogenic risk associated with exposure to hexavalent chromium in drinking water. The evidence was internally consistent and compelling that oral exposure to Cr VI results in cancer. The NTP study provided acceptable data for a quantitative cancer risk assessment.

Comment 2: “As indicated in the draft PHG document, several studies previously estimated that saliva and stomach fluids have the capacity to reduce hexavalent chromium to trivalent chromium in amounts much larger than the ‘maximum plausible levels of hexavalent chromium in water that would likely be ingested by humans...’ The document further asserts that ‘...exhaustion of the capacity of saliva and gastric fluids to reduce hexavalent chromium appears unlikely.’ ACWA understands other studies exist and are referenced in the document providing evidence that complete reduction may not always occur, but believes the administered doses in the NTP study are so large they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in the rodents. This is especially significant as the NTP study did not find excess cancers at the lowered studied doses in both rats and mice. Equally as important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated and higher level of gastric juices than rodents.”

Response 2: All available evidence indicates that the stomach reduction capacity is not overwhelmed (see Appendix A of the PHG document). The lack of tumors at lower doses in the NTP bioassay is not surprising and is typical of many bioassays where tumors were not detected at lower doses. The absence of tumors at lower doses

indicates a good study design. The need for higher doses in carcinogenic bioassays is primarily to offset the statistical limitations of using small numbers of animals (50/sex/dose level) in experimental studies to measure a relatively rare event (e.g., tumor occurrence), and it has been discussed in detail (U.S. EPA, 2005; OEHHA, 2009).

Comment 3: “In addition, we have concerns with the interpretation and use of data from two key studies submitted as evidence that hexavalent chromium in drinking water is a human carcinogen. The Borneff *et al* study is seriously flawed due to the fact there was only a single-dose level examined and an ectromelia epidemic affected both control and treated groups with significant loss of mice. This study should not be considered in the development of the PHG. In the work completed by Zhang and Li, not all factors were considered when the authors reached their conclusions including the extremely high levels of hexavalent chromium.”

Response 3: The Borneff *et al.* (1968) study is not a key study in the derivation of the PHG for Chromium VI and was moved to the Appendix for information purposes. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff *et al.* (1968).

The Zhang and Li (1987) study was thoroughly analyzed (see Beaumont *et al.*, 2008) and was not used in the final derivation of the PHG. Although the magnitude of the exposure to Cr VI in drinking water is unclear, the population did appear to be exposed to high levels of chromium VI. A statistically significant increase in stomach tumors was detected when compared to a nearby unexposed population. The high levels of chromium VI in the wells is what triggered the study (lower levels probably would have gone undetected). Lower levels of chromium VI may still cause cancer but at a rate that would have been undetected in a population of several thousand.

Comment 4: “An internal Department of Toxic Substances Control (DTSC) memo recently obtained by our members titled ‘Hexavalent Chromium Public Health Goal’ also expressed some concerns with the conclusions reached in the OEHHA document. ACWA would like to know how those comments have been or will be taken into consideration by OEHHA staff prior to finalizing a draft PHG for hexavalent chromium.”

Response 4: OEHHA does not include internal memoranda within the Agency in public comments. However, OEHHA did consider the information in the memorandum and has responded to all specific scientific issues relevant to the PHG document in the revised final document. The same scientific issues are also included in the discussions in this response document.

Comments from Ronald Gastelum, Southern California Water Committee.

Cover letter

Comment 1: “California law requires the agency to prepare the risk assessment ‘using the most current principles, practices, and methods used by public health professionals who are experienced practitioners in the fields of epidemiology, risk assessment, and toxicology.’ Cal. Health & Safety Code § 116365(c)(1). Unfortunately, OEHHA has failed to do so in preparing this Draft PHG, as also recognized by the Department of Toxic Substances Control (“DTSC”) in a memorandum dated October 23, 2008, analyzing the pre-release version of the Draft PHG. Furthermore, OEHHA has not rectified past mistakes made in previous draft PHGs for chromium, which were pointed out by past reviewers of these documents. For example, three reviewing bodies - the 1996 Risk Assessment Advisory Committee (made up of 34 nationally renowned scientists), the 2001 external peer review panel (comprising University of California experts), and the 2005 external scientific peer reviews (also consisting of University of California experts) were critical of previous draft PHGs because they contained hypotheses that were too speculative and did not constitute good science.”

Response 1. OEHHA employed the most current, up-to-date procedures in developing the proposed PHG for Cr VI (U.S. EPA, 2005; OEHHA, 2009; Davis et al., 2010). With regard to rectifying past mistakes pointed out by reviewers of PHG documents for chromium, the 1996 Risk Assessment Advisory Committee (RAAC) did not review any PHGs because that program had not yet begun. However, the committee was supportive of OEHHA’s risk assessment procedures in the report’s Executive Summary, stating “Our general finding is that Cal/EPA’s risk assessment products are of good quality, both from the perspective of scientific credibility and professional practice”, “Overall, the best practices of Cal/EPA are equal to, if not better, than those of US EPA” and “Similar approaches are used by Cal/EPA and US EPA programs in evaluating the dose-response relationship of carcinogens and non-carcinogens” (RAAC, 1996). In 2001 the primary recommendation of the Chromate Toxicity Review Committee (CTRC, 2001) that a drinking water standard for Cr VI **not** be based on the study by Borneff et al. (1968) was followed by OEHHA. In 2008 UC reviewers Roberto Gwiazda, Leonard Bjeldanes and Michael Kelner provided comments on the draft PHG which included the recommendation to move discussion of Borneff et al. (1968) and the Helicobacter hypothesis to the Appendix. The draft PHG was revised accordingly.

Comment 2: “These mistakes pointed out by the external peer reviewers, including University of California bodies mentioned above, have been repeated in the current Draft PHG. Although its own procedures and California statutes require it to respond to the issues raised by external peer reviewers, OEHHA has not adequately done so in the Draft PHG. Importantly, by continuing to ignore EPA’s 2005 Guidelines for Cancer Risk Assessment by failing to provide a range of risks associated with the PHG, OEHHA ignores the recommendation of University of California reviewer Dr. Michael Kelner that OEHHA comply with these guidelines by providing a range of risks rather than just one value for risk, which provides a sense of certainty that does not actually exist.”

Response 2. In accordance with the U.S. EPA 2005 Guidelines for Cancer Risk Assessment and other U.S. EPA documents (cited below), the following are some reasons OEHHA developed a single PHG value for Cr VI in drinking water to be protective against cancer rather than a range of PHG values:

- University of California reviewer Dr. Michael Kelner suggested that different rodent data sets from the NTP (2008) study could be used to calculate a range of ED₁₀ values. As discussed in the “Dose-Response Assessment” and “Calculation of the PHG” sections of the PHG document, the rat and mouse data sets for both sexes were considered for dose-response modeling. For reasons discussed in the PHG document and in our Response 1 to Dr. Kelner (in this document, see Table of Contents) the best data set was selected, that of intestinal tumors in the male mouse. This tumor data set was used to calculate a single cancer slope factor and a single PHG value for Cr VI in drinking water. Selection of the best data set for dose-response modeling was done in compliance with the U.S. EPA 2005 Guidelines for Cancer Risk Assessment.
- The phrase in this comment, “providing a range of risks” has been interpreted by some as meaning calculation of cancer risk based on linear extrapolation down to zero dose along with calculation of cancer risk based on a non-linear/threshold model (see DTSC memorandum in Comment 3 below). First, it should be emphasized that none of the three University of California peer reviewers recommended that OEHHA perform a non-linear extrapolation of the cancer risk from the point of departure down to zero dose. Second, the U.S. EPA 2005 Guidelines for Cancer Risk Assessment only recommend development of multiple risk models when data exist constituting “significant biological support” for such alternative models. As discussed in detail in the PHG document, there is an absence of “significant biological support” for threshold models of cancer induction by Cr VI. In contrast, evidence of genotoxicity and mutagenicity by Cr VI supports a linear extrapolation to estimate the cancer risk at low dose levels.
- The U.S. EPA draft Toxicological Review of Hexavalent Chromium (U.S. EPA, 2010) develops a single cancer risk value for ingested Cr VI by linear extrapolation. OEHHA used the identical methodology. The draft U.S. EPA document does not develop a range of cancer risk values based on alternative MOAs for Cr VI. We believe U.S. EPA drafted a Toxicological Review for Cr VI that is in compliance with its own 2005 Guidelines for Cancer Risk Assessment.
- The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires OEHHA to develop a Public Health Goal (PHG) for environmental contaminants in drinking water, not a range of PHGs for each contaminant.

With regard to uncertainty, many issues of uncertainty are discussed throughout the PHG document as they arise. There is also a concentrated discussion of uncertainty in the “Risk Characterization” section. Similar to OEHHA, the U.S. EPA draft Toxicological Review of Hexavalent Chromium (U.S. EPA, 2010) discusses a number of issues of uncertainty associated with the cancer risk assessment. The draft document does not address uncertainty by developing a range of cancer risk values according to different models and MOAs.

Comment 3: “DTSC, in its memorandum, also remarks on OEHHA's non-compliance with EPA guidance in preparing the Draft PHG. EPA guidance requires that where appropriate scientific data is available, an agency use other methodologies to assess carcinogenesis. Both DTSC and University of California peer reviewers recommended that OEHHA include in the Draft PHG an analysis of alternative approaches to calculate cancer risk, as set forth in EPA guidance. OEHHA did not use any other methods to do so. OEHHA instead improperly used a default linear extrapolation procedure, in which the results of a study in which rodents are exposed to high doses are linearly extrapolated across five orders of magnitude of dose to estimate the risk to humans from much lower environmental exposures. Such a linear extrapolation method is extremely conservative, which leads to inappropriate overestimation of the cancer risk of ingested hexavalent chromium, as DTSC points out. OEHHA should have analyzed all available data to determine whether alternatives such as a non-linear analytical approach would have been appropriate.”

Response 3. OEHHA considered a number of varying parameters in estimating the cancer risk. Parameters included choice of data set (mouse versus rat, male versus female, tumor type, tumor site) and choice of mathematical model (multistage, logistic, probit, Weibull and others). Some but not all of these approaches are presented in tables and discussed in the “Dose-Response, Carcinogenic Effects” section of the PHG. Selection of the LED₁₀ and extrapolation to 0 dose were performed according to published U.S. EPA and OEHHA methodology (U.S. EPA, 2005, 2010; OEHHA, 2009; Davis et al., 2010).

Comment 3 suggests that OEHHA's use of linear extrapolation to estimate the cancer risk at low dose levels was contrary to the advice of the UC reviewers and the U.S. EPA 2005 Guidelines for Cancer Risk Assessment. This is incorrect. None of the three UC reviewers suggested that linear extrapolation from the point of departure down to zero dose was inappropriate, and that other models such as non-linear/threshold models should be included. Dr. Bjeldanes did ask for further justification for the use of a linear model, which has been added to the PHG document (see especially the discussion of Table 7 in the PHG document). The U.S. EPA 2005 Guidelines for Cancer Risk Assessment call for inclusion of alternate models when sufficient biological support exists. The PHG document contains ample discussion of why support is lacking (see especially discussion of Table 7) for other than a genotoxic MOA requiring linear extrapolation to zero dose. This comment is correct in citing the DTSC memorandum as recommending non-linear methods for analyzing the tumor data.

Comment 4: “OEHHA's error in defaulting to the linear extrapolation procedure instead of determining whether other alternatives could have been more appropriate is compounded by its failure to push back release of the Draft PHG until the release of currently ongoing studies that will provide additional information. For example, EPA is using its Integrated Risk Information System (‘IRIS’) program to evaluate human health risk from chromium on an expedited basis, and the Hamner Institute is evaluating a non-linear ‘mode of action’ (‘MOA’) approach for the same purposes. These studies, when

available, will provide additional scientific data to OEHHA to help it determine whether the best and most scientifically valid method to analyze risk from chromium is linear extrapolation, as OEHHA prematurely decided, or a non-linear MOA approach. DTSC appreciated the significance of the Hamner Institute's MOA studies, stating in its memorandum that they 'are prerequisites to any revisions to the OEHHA public health goal for [hexavalent chromium.]' By refusing to wait for release of EPA's and the Hamner Institute's information, OEHHA further violates the California Health & Safety Code requirement to 'use the most current principles, practices, and methods' in its risk assessment. This information soon will be readily available, and the short time delay in obtaining it is well outweighed by its value. Furthermore, it is possible, if not probable, that OEHHA may have made decisions that could have led to calculation of a more reasonable standard than 60 parts per trillion, undetectable through standard commercial laboratory procedures, had it used the most current information. A more appropriate PHG that still protects public health is possible, as evidenced by the Agency for Toxic Substances and Disease Registry's recent calculation of a daily dose that is five hundred times the amount calculated in the Draft PHG."

Response 4. Neither the August 2009 draft document nor the final PHG document is premature. Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: "(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data". OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: "When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced."

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

OEHHA's decision to perform linear extrapolation with the tumor incidence data was not a default decision. Rather, linear extrapolation was chosen as the model best supported by the extensive data base for Cr VI, including ample evidence of genotoxicity and mutagenicity.

Comment 5: "In addition to these flaws, OEHHA overlooks the advice of the Risk Assessment Advisory Committee and the two university of California external peer

review panels not to rely on hypotheses that are excessively speculative. One such hypothesis that completely lacks scientific basis regards speculation that the hypothesized presence of bacteria in the digestive tracts of some humans, but not others, may aggravate health effects from chromium. In its memorandum, DTSC stated that this bacterial infection hypothesis "is speculative, lacks relevance to developing the PHG and it should be eliminated from the document as it is speculation."

Response 5. The Helicobacter hypothesis was formulated by OEHHA in order to obtain a better understanding of the findings of diverse studies. It was not used as a basis for developing the PHG. Some unexplained findings such as the occurrence of tumors in the first generation of the Borneff et al. (1968) study could be explained by the presence of Helicobacter bacteria. Also the hypothesis may explain why stomach tumors may have occurred following a relatively short term exposure to Cr VI in rural China. It serves as a scientific resource to keep these discussions attached in the Appendix as records of the issues that have been addressed in the research for and preparation of this PHG document.

Comment 6: "Reliance on this speculative hypothesis causes OEHHA to make improper findings regarding ingestion-caused cancer in humans based on tumor findings in animal studies, as well as to avoid reconciliation of incongruent studies that do not support OEHHA's decision to default to the linear extrapolation method."

Response 6. As stated above in Response 5, the PHG does not rely on the Helicobacter hypothesis in the development of the PHG. The hypothesis is located in Appendix B and clearly indicated as a hypothesis.

Comment 7: "OEHHA's evaluation of the value of the scientific data upon which it relies is faulty. Not only does OEHHA rely on scientific studies that have been superseded by more recent studies, it also reinterprets or ignores other analyses that do not support its own conclusions. As just one example, in the Draft PHG, OEHHA relies heavily upon the 1987 Zhang and Li analysis of the human health effects of chromium in water supplies in China. The lead co-author of this study further assessed the data in a 1997 study, finding no statistically relevant relationship between stomach cancer in humans and consumption of hexavalent chromium-containing water. In addition, in a peer-reviewed study recently published in 2009, Kerger et al, further evaluates the original 1987 data and failed to identify a dose-response relationship or even a rational pattern of association of cancer related mortality with exposure to chromium in the water. Despite this, OEHHA continues to reject this 1997 study, for which it was criticized by the University of California external peer review panel in 2005, and ignores the Kerger study, as neither support its conclusion. OEHHA continues to rely - inappropriately - on the 1987 study to support its position. Multiple other similar examples exist."

Response 7. The findings of Beaumont et al. (2008) replicated the findings of the original study (Zhang and Li, 1987): a statistically significant increase in stomach cancers. The referenced 1997 study has been withdrawn by the publisher. Another

recent reevaluation of the Zhang and Li (1987) study by Kerger et al. (2009) has been added to the PHG document.

From the Attachment –I Executive summary section

Comment 8: “California Health and Safety Code Section 116365(c)(l) specifically requires that OEHHA employ the most current practices and methods used by health science experts when proposing a new PHG. In the past, OEHHA has been criticized for not using sound science in the development of PHGs. Three recent examples are the 1996 Risk Assessment Advisory Committee (comprised of 34 nationally known scientists), the 2001 Scientific Review and 2005 peer review provided by scientists at California universities on earlier draft chromium PHGs. Each of these bodies of scientists and their reviewers criticized OEHHA for using overly speculative hypotheses or for not using sound science as the basis for public health decisions...”

Response 8. OEHHA employed the most current, up-to-date procedures in developing the proposed PHG for Cr VI (U.S. EPA, 2005; OEHHA, 2009; Davis et al., 2010). With regard to rectifying past mistakes pointed out by reviewers of PHG documents for chromium, the 1996 Risk Assessment Advisory Committee (RAAC) did not review any PHGs because that program had not yet begun. However, the committee was supportive of OEHHA’s risk assessment procedures in the report’s Executive Summary, stating “Our general finding is that Cal/EPA’s risk assessment products are of good quality, both from the perspective of scientific credibility and professional practice”, “Overall, the best practices of Cal/EPA are equal to, if not better, than those of US EPA” and “Similar approaches are used by Cal/EPA and US EPA programs in evaluating the dose-response relationship of carcinogens and non-carcinogens” (RAAC, 1996). The objectivity of the “2001 Scientific Review” cited by the commenter came into question after two 2003 legislative hearings concerning allegations that some members of the committee had not properly disclosed their economic interests. Nevertheless, OEHHA carefully reviewed the committee’s report (CTRC, 2001) and followed its primary recommendation that a drinking water standard for Cr VI **not** be based on the study by Borneff et al. (1968). In 2005 UC reviewers Roberto Guizda, Leonard Bjeldanes and Michael Kelner provided comments on the draft PHG which included the recommendation to move discussion of Borneff et al. (1968) and the Helicobacter hypothesis to the Appendix. The draft PHG was revised accordingly.

Comment 9: “First, OEHHA did not comply with its own and the U.S. Environmental Protection Agency’s (EPA) procedures for calculating the draft PHG. As pointed out by the Department of Toxic Substances Control (DTSC) in an October 23, 2008 memorandum on the PHG (Berry, 2008) (the DTSC memorandum), the method employed by OEHHA to calculate the PHG ignored recent advances in assessing carcinogenesis. EPA guidance specifically requires alternate means of assessing the results of cancer bioassays where appropriate scientific data is available. In contrast, OEHHA ignored all other options for calculation of cancer potency and simply adopted the EPA’s default “linear extrapolation” procedure for this draft PHG. This default

procedure linearly extrapolates the results of a high-dose exposure rodent study across five orders of magnitude of dose to estimate the human cancer risk from far lower environmental exposures. According to DTSC, the default methods employed by OEHHA are highly conservative and improperly overestimate the carcinogenic potency of ingested hexavalent chromium. If OEHHA followed the appropriate procedures, it would analyze all the available data to determine whether the weight of evidence favored alternative conclusions such as a nonlinear analytical approach. In fact, DTSC and scientific peer reviewers from the University of California (UC) suggested that an analysis of alternative approaches should have been included in the draft PHG documents. OEHHA improperly refused to do so.

Response 9. OEHHA complied with both U.S. EPA (2005) and OEHHA (2009) guidelines for cancer risk assessment in developing the PHG for Cr VI. Specifically:

- The most up-to-date methods were utilized in developing the PHG. This was substantiated when both the U.S. EPA (2010) and the New Jersey Department of Environmental Protection (NJDEP, 2009) chose the same methodology as OEHHA for calculating the cancer potency of Cr VI.
- The U.S. EPA 2005 Guidelines for Carcinogen Risk Assessment recommend including alternate methods of calculating the cancer risk when significant biological support exists for alternative MOAs. As discussed in the PHG document, this was not the case for Cr VI.
- OEHHA's decision to perform linear extrapolation with the tumor incidence data was not a default decision. Rather, linear extrapolation was chosen as the model best supported by the extensive data base for Cr VI, including ample evidence of genotoxicity and mutagenicity.
- The comment states that OEHHA did not consider all the available data in developing the PHG. This is incorrect. All available data of sufficiently quality were considered. The best data set (intestinal tumors in male mice) from the best long-term cancer study (NTP, 2008) was selected for calculation of the cancer potency. The identical data set was selected by U.S. EPA (2010) and the New Jersey Department of Environmental Protection (NJDEP, 2009).
- Only the DTSC memorandum recommended that OEHHA include a non-linear approach for analyzing the tumor data. None of the three UC reviewers recommended such an approach, although Dr. Bjeldanes asked for more justification for the linear approach. The U.S. EPA (2010) and the New Jersey Department of Environmental Protection (NJDEP, 2009) utilized the same linear approach as OEHHA. Neither group presented alternative, non-linear approaches.
- OEHHA also varied a number of parameters in estimating the cancer risk. Parameters included choice of data set (mouse versus rat, male versus female, tumor type, tumor site) and choice of mathematical model (such as linear multistage, logistic, probit, Weibull and others). Some but not all of these approaches are presented in tables and discussed in the "Dose-Response, Carcinogenic Effects" section of the PHG. Selection of the LED₁₀ and extrapolation to 0 dose were performed according to published U.S. EPA and OEHHA methodology (U.S. EPA, 2005, 2010; OEHHA, 2009; Davis et al., 2010).

Comment 10: “Second, OEHHA did not adequately respond to several important issues raised by the University of California peer reviewers of the draft PHG. One key example regards the comments of Dr. Michael Kelner of UC San Diego's Medical Center. Dr. Kelner strongly recommended that "all the NTP National Toxicology Program] 2007 studies need to be analyzed and slope factors derived for each study by an accepted methodology. Then the mean median (preferably) slope factor is to be utilized for subsequent calculations. NOT the 95% confidence interval." Essentially, Dr. Kelner was urging OEHHA to follow EPA's 2005 Guidelines for Carcinogen Risk Assessment and to provide a range of risks to inform decision makers. By not doing so, OEHHA's work projects a false sense of certainty. The issues raised by the peer reviewers point to fundamental flaws in OEHHA's approach. OEHHA needs to address these important issues. In fact, it is required to so by its own procedures

Response 10. This comment does not interpret Dr. Kelner's peer-review comments correctly. Dr. Kelner suggested calculating different points of departure using a range of animal tumor data sets. He also suggested using a range of ED₁₀ values rather than LED₁₀ values followed by calculation of a mean ED₁₀ value for use as a point of departure. He did **not** recommend that OEHHA “provide a range of risks to inform decision makers.” OEHHA's responses to Dr. Kelner's peer-review comments are provided in this document (see Table of Contents).

Comment 11: “Third, OEHHA has relied on exactly the kind of overly speculative theories that it was warned not to use by both the Risk Assessment Advisory Committee and the prior peer reviewers in the 2005 peer review. With absolutely no scientific basis, OEHHA speculates that adverse effects of chromium may be exacerbated by the hypothesized presence of bacteria in the digestive tracts of some human populations, but not others. DTSC has said this so-called Helicobacter Hypothesis "is speculative, lacks relevance to developing the PHG and it should be eliminated from the document as it is speculation." For OEHHA, this pure speculation is the primary basis for linking tumor findings in animal studies to the possible occurrence of stomach cancer in humans ingesting chromium in water. Further, OEHHA uses this speculation to avoid acknowledging the disparate results of the various studies that would otherwise call into question OEHHA's decision to default to a linear dose-response extrapolation. Without this guess work about bacteria, OEHHA would not have an adequate basis for choosing a 60 ppt PHG. Instead it would have come to the same conclusion as DTSC, i.e., "that ingested doses of Cr⁶⁺ at are insufficient to produce local irritation, tissue damage, inflammation and regenerative hyperplasia are also without additional carcinogenic risk."

Response 11. With regard to warnings about “overly speculative theories,” the 1996 Risk Assessment Advisory Committee (RAAC) did not review any PHGs because that program had not yet begun. However, the committee was supportive of OEHHA's risk assessment procedures in the report's Executive Summary, stating “Our general finding

is that Cal/EPA's risk assessment products are of good quality, both from the perspective of scientific credibility and professional practice", "Overall, the best practices of Cal/EPA are equal to, if not better, than those of US EPA" and "Similar approaches are used by Cal/EPA and US EPA programs in evaluating the dose-response relationship of carcinogens and non-carcinogens" (RAAC, 1996).

In 2005 UC reviewers Roberto Gwiazda, Leonard Bjeldanes and Michael Kelner provided comments on the draft PHG which included the recommendation to move discussion of Borneff et al. (1968) and the Helicobacter hypothesis to the Appendix. The PHG document was revised accordingly.

The PHG does not rely on the Helicobacter hypothesis in the development of the PHG. The hypothesis is located in Appendix B and clearly labeled that it is a hypothesis. The Helicobacter hypothesis was formulated by OEHHA in order to obtain a better understanding of the findings of diverse studies. Some unexplained findings such as the occurrence of tumors in the first generation of the Borneff et al. (1968) study could be explained by the presence of Helicobacter bacteria. Also, the hypothesis may explain why stomach tumors may have occurred following a relatively short term exposure to Cr VI in rural China. We prefer to keep these discussions attached in the Appendix as records of the issues that have been addressed in the research for and preparation of this PHG document.

Comment 12: "Fourth, for this draft PHG, OEHHA erred in its scientific evaluation of the data in published studies in several ways. OEHHA relied on studies that have been superseded by more recent findings. It also chose to reinterpret other studies that do not fit its own conclusions. And OEHHA ignored data that did not support its conclusion. A good example of all three of these problems is OEHHA's evaluation of the 1987 Zhang and Li assessment of chromium pollution of water supplies in China. This was one of the major studies relied upon by OEHHA in developing the draft PHG. In 1997, the lead co-author of the 1987 study expanded the assessment of the data and found no statistically relevant link between stomach cancer in humans and consumption of water containing Cr(VI) (Zhang and Li, 1997). OEHHA did an internal reevaluation of the 1987 study data (which was not peer reviewed). The 2005 PHG scientific peer reviewers criticized OEHHA's rejection of the 1997 study, noting OEHHA's effort to explain the comparative decrease in cancers in areas in the closest proximity to the plant as 'the subject of speculation.' Since the re-analysis of the 1987 Zhang and Li study was a cornerstone of the OEHHA case for the carcinogenic activity of oral Cr(VI) in humans, their 'analysis too, must be subjected to full peer review by specialists in the field.' OEHHA subsequently published a peer-reviewed internal OEHHA reevaluation (Beaumont *et al.*, 2008), and while this evaluation has been cited for its 'serious limitations in the data and the methods of analysis' (Smith, 2009), OEHHA cites its own study and continues to rely on the original 1987 brief report. A recent peer-reviewed and published study further evaluating the original 1987 data for the exposed villages and comparing the cancer rates to nearby areas with no Cr(VI) in groundwater did not find a dose-response relationship or a coherent pattern of association of lung-, stomach-, or all-cancer mortality with exposure to Cr(VI)-contaminated groundwater (Kerger *et*

al., 2009). Thus, OEHHA apparently disregards the more recent studies - both of which did not support OEHHA's hypothesis on an association of stomach cancer in humans drinking Cr(VI)-impacted water. There are other examples where OEHHA similarly reevaluated published data and studies to support OEHHA's hypothesis that the 2008 Peer Reviewers noted as 'overreaching' and that the DTSC memorandum concluded inadequately addressed the weight of evidence.

Response 12. The findings of Beaumont et al. (2008) published in 2008 (well after the original studies, Zhang and Li, 1987) replicated the findings of the original study and found a statistically significant increase in stomach cancers. The second authors of the 1987 and 1997 studies were different individuals although they shared the same surname. The referred to 1997 study was withdrawn in 2006 by the publisher, the Journal of Occupational and Environmental Medicine. Another recent reevaluation of the Zhang and Li (1987) study by Kerger et al. (2009) has been added to the PHG document.

Comment 13: "Fifth, OEHHA has ignored the fact that analyses and studies are underway that could call into question their adoption of the default linear extrapolation procedure. EPA is evaluating chromium risk on an expedited basis through its Integrated Risk Information System (IRIS) program. In addition, OEHHA is monitoring studies by the Hamner Institutes that will help determine whether the linear extrapolation method it chose or a more scientifically valid nonlinear "mode of action" (MOA) approach is the more appropriate risk analysis method for chromium. DTSC recognized the importance of the Hamner Institutes program in addressing the mode of action of chromium and said that the studies should be "prerequisites to any revisions to the OEHHA public health goal for Cr⁶⁺. By issuing a draft PHG without waiting for this information, OEHHA is not taking account of the most up-to-date science."

Response 13. Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: "(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data". OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: "When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced."

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comment 14: "OEHHA has drafted a PHG that is not scientifically reliable and therefore is not helpful to public health and water agencies trying to protect the public. These flaws are not without cost. As DTSC stated, "there are serious consequences associated with overly conservative analysis that fail to account for a carcinogenic MOA." As discussed by EPA's Dellarco and Baetcke (2005), application of an MOA framework to data generated from appropriate studies can also be very informative to risk assessors and policy makers. OEHHA's failure to use the latest risk assessment methods accepted by health science experts can dangerously skew future decisions regarding water supply, water quality treatment technology, and testing and monitoring methodology. By proposing a draft PHG that is so far below currently detectable levels, OEHHA has unnecessarily called into question the safety of California's water supply. Given the potentially enormous consequences to the State of California, it is essential that OEHHA be required to rigorously follow the most current procedures and apply the most up-to-date science before adopting a PHG for chromium. Accordingly, OEHHA should re-evaluate its draft PHG, consistent with its processes, "using the most current principles, practices, and methods used by public health professionals" and the absolute best science. Once that is done, a new and scientifically valid draft PHG should be reissued and peer reviewed."

Response 14. OEHHA used the best and most up-to-date science and methodology available to calculate the cancer potency for ingested Cr VI. Thus, it is not surprising that the U.S. EPA (2010 draft document) and the New Jersey Department of Environmental Protection (Stern, 2010) recently developed cancer potencies for Cr VI by the oral route that are identical to that developed in the PHG document. A discussion of the mutagenic MOA proposed by McCarroll et al. (2010) has been added to the document. The proposed MOA supports our approach.

From the Attachment –II. Background

Comment 15: "The National Toxicology Program (NTP) conducted a carcinogenic and toxicological study of Cr(VI) in response to requests from members of the California Congressional delegation. California health and regulatory agencies also supported NTP conducting this study. California officials were concerned that they lacked information on the oral route of exposure for Cr(VI), as what information was available was insufficient to set a safe drinking water standard. The NTP study was aimed at determining carcinogenic impacts from high-dose chronic exposures to rats and mice. The NTP study, completed in July 2008, was not intended to, and did not, recommend a particular dose or regulatory exposure level. Going beyond risk assessment of oral chromium exposures to management of the risk of chromium in drinking water, OEHHA, in the draft PHG, applied certain key assumptions about dose-response relationships

and other factors and then extrapolated the NTP results to calculate a draft PHG of 60 ppt for Cr(VI) that would give a theoretical risk level of 1×10^{-6} (one in a million).”

Response 15. We agree that the NTP did not recommend a particular dose or regulatory exposure level. OEHHA employed the result of this state of the art cancer bioassay and standard procedure to derive a dose associated with 10^{-6} risk, a level of risk that is protective of public health. The use of high doses in cancer bioassay to estimate low levels of risk has been discussed above and in related documents (U.S. EPA, 2005; OEHHA, 2009).

Note that OEHHA was one of the entities that petitioned the NTP to perform these studies precisely to provide guidance in developing a PHG for Cr VI.

From the Attachment - III. OEHHA Did Not Apply State-of-the-Art Principles and Practices for Assessing Potential Carcinogenic Risk To Humans, Nor Did It Follow Current National and International Regulatory Program Guidelines.

Comment 16: “In summary, prolonged exposure to Cr(VI) above 14.3 mg/L sodium dichromate induces sustained cytotoxicity and cell proliferation that, as described by NTP, is regenerative hyperplasia secondary to epithelial injury. In the 2008 peer review comments of Dr. Bjeldanes, he noted his concerns about the high level of Cr(VI) in the drinking water in the NTP study and recognized that the lesions identified in the small intestine of the mouse are often considered to be pre-cancerous.”

And,

“The genetic changes are postulated to be secondary to the cytotoxicity, metaplasia, and hyperplasia that are clearly induced by Cr(VI). Cr(VI) has been found to be genotoxic in some *in vitro* and *in vivo* test systems but was not acting as a direct mutagen.”

“This postulated MOA for Cr(VI) is mainly based on observations of consistent, nonlinear dose-response relationships for all three key events (sustained cell injury, cell proliferation, and tumors) and concordance of incidence of diffuse hyperplasia in other regions of the intestinal tract (NTP, 2007)”.

Response 16. Neither sustained cytotoxicity nor inflammation was observed in the small intestine of mice during the two-year bioassay (NTP, 2008). Preceding the two-year study, a subchronic toxicity study in mice (NTP, 2007) reported similar findings; i.e., the absence of cytotoxicity and inflammation in the small intestine of mice. Therefore, this paradigm of cell injury leading to cell proliferation and tumorigenesis is not indicated by the findings of both NTP studies. These and related issues are discussed in detail in the section of the PHG document entitled “Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” located in the “Carcinogenicity” section of the document.

Comment 17: “Oral exposure of animals to Cr(VI) but not Cr(III) results in irritation and histopathological changes to tissues including cell injury, death, and regeneration (NTP, 2007; NTP, 2008). Following three-month exposures to Cr(VI), dose-responses in duodenal histiocytic infiltration of the duodenum in rats and epithelial hyperplasia and histiocytic cellular infiltration of the duodenum in mice were observed (NTP, 2007). After two years of exposure, dose-responses in duodenal histiocytic infiltration in rats and duodenal epithelial hyperplasia and histiocytic cellular infiltration in mice were observed.”

Response 17. NTP did not report oral exposure to Cr VI resulted in irritation or histopathological changes to tissue such as cell injury, death and regeneration. Histiocytic infiltration in the small intestine of rats and mice was reported and tumors (adenomas and carcinomas) were only detected in the mouse small intestine. From NTP (2008): “In the 3-month toxicity study (NTP, 2007a) and in the current 2-year studies of sodium dichromate dehydrate, histiocytic cellular infiltration was consistently observed in several tissues including the liver, duodenum and mesenteric and pancreatic lymph nodes of rats and mice. The severities of these lesions were generally minimal to moderate and were characterized by the presence of individual small clusters, and sometimes syncytia of macrophages. The significance of these lesions is not known.”

Comment 18: “Appendix A - Carcinogenic Threshold? [note: there is no discussion of threshold in Appendix A. This is a discussion of the reducing capacity of the stomach documenting Cr(VI) absorption into the body. As questioned by the DTSC memorandum, it ‘is unclear how this discussion contributes to the understanding of a threshold-based dose-response relationship for ingested chromate.’ It is DTSC’s position that ‘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.’]”

Response 18. DeFlora proposed a threshold of carcinogenic effect based on the reducing capacity of the stomach. OEHHA agrees that the ability to reduce CrVI to Cr III is not infinite. However, there appears to be sufficient gastric reducing capacity (84 mg/day according to the estimates of DeFlora and coworkers) to adequately reduce the amount of chromium VI that was administered to humans in several pharmacokinetic studies. Therefore, absorption of hexavalent chromium in these studies was not due to the exceedance of the reducing capacity of the GI tract. In a recent study of rats and mice exposed to Cr VI via their drinking water, there was no threshold for its accumulation in a variety of tissue (Collins *et al.*, *Tox Sci* 118: 368-379, 2010). Rather, its accumulation was either linearly related to its concentration in the drinking water over the entire concentration range tested, or linearly related at low concentrations with indications of a plateau at higher concentrations. These data are discussed in Appendix A of the PHG. As discussed in Response 16 above, intestinal tissue damage was not observed in the two-year bioassay in mice (NTP, 2008).

Comment 19: "Contrary to current cancer risk assessment guidance, no specific mode of action was identified or discussed to support the dose-response model used by OEHHA for the draft PHG. OEHHA states that taken together, 'the toxicity and cancer studies in humans and animals, plus the mechanistic, toxicokinetic and genotoxicity studies, provide sufficient reason for concern regarding the carcinogenic potential of this toxicant in humans' (p. 97). Based on this, OEHHA assumed the default model to be a linear dose-response.

Response 19. It is correct that the mechanism of action of Cr VI in the etiology of cancer in the small intestine in mouse and the oral cavity in the rat is currently not known. However, when evaluating the evidence of carcinogenicity, hexavalent chromium displayed genotoxic activity in *in vitro* and *in vivo* bioassays. Mechanistic studies yielded evidence of the generation of reactive species that are associated with oxidative damage of DNA. Thus, the use of a linear dose response model was appropriate.

Comment 20: "It should be noted that OEHHA did not differentiate between genotoxicity and mutagenicity - which is a very important distinction. If OEHHA had utilized the concepts in EPA's Framework for Determining a Mutagenic Mode of Action for Carcinogenicity, it would have helped them determine whether or not the data support a finding of a mutagenic mode of action for carcinogenicity. The Framework also addresses the adverse endpoints of mutagenicity. OEHHA does not make one reference to Cr(VI)'s mutagenicity in the entire document - with the exception of Appendix A, where it was noted that mutagenicity tests "have revealed that hexavalent chromium is cytotoxic to *E. coli* at concentrations of 10 to 15 ppm (Lantzsich and Gebel, 1997) or 100 to 150 ppm (Olivier and Marzin, 1987)."

Response 20. Mutagenicity is included under the section entitled "Genetic Toxicity." Search of the PHG document indeed revealed that the term mutagenicity was not used until Appendix A. In the first paragraph of the "Genetic Toxicity" section it is noted that Cr VI induced gene mutations in multiple species. References to that work are provided. Discussion of mutagenicity has been added to other parts of the PHG document including where MOA is discussed. The mutagenic mode of action described by McCarroll et al. (2010) has been added to the document.

Comment 21: "While not discussed by OEHHA, the finding of cytotoxicity is also important when considering different modes of action that may be operating over different dose ranges, as stated in EPA's 2005 risk assessment guidelines and referenced in the draft PHG. Such cytotoxicity supports application of a nonlinear dose-response model per EPA's 2005 risk assessment guidelines. Specifically, the guidelines state that 'depending on the strength of the suggestion of mutagenicity, the assessment may justify a conclusion that mutagenicity is not operative at low doses and focus on a nonlinear approach, or alternatively, the assessment may use both linear and nonlinear approaches.'"

Response 21. Given there is no report of cytotoxicity in the oral cavity of rats nor the intestine of mice in the NTP bioassay for Cr VI, it would be difficult to justify including cytotoxicity in a discussion of cancer mechanism.

Comment 22: *In vivo* genotoxicity studies indicate that there are exposures below which DNA damage would not be produced locally or systemically following ingestion of Cr(VI). Daily administration of Cr(VI) as chromate for up to 20 mg/L for nine months did not increase the frequency of DNA-protein crosslinks or produce oxidative DNA damage in mouse forestomach, glandular stomach, or duodenum (De Flora *et al.*, 2008). Micronucleus formation in bone marrow or peripheral blood in mice administered up to 500 mg/L (chromate) in drinking water for up to 210 days was not increased. No genotoxic effects in fetal liver or peripheral blood were observed in treated pregnant mice receiving up to 10 mg/L (chromate) in drinking water (De Flora *et al.*, 2006). The results of incidences of four micronucleus tests conducted in the three strains of mice from 2007 NTP were predominately negative. In Study 1 (up to 1000 mg/L dichromate in drinking water for three months), no significant increases were seen in micronucleated normochromatic erythrocytes in peripheral blood samples from male or female B6C3F1 mice. In Study 2 (up to 250 mg/L chromate in drinking water for three months), a significant exposure concentration-related increase ($P < .001$) in micronucleated normochromatic erythrocytes was seen in am3-C57BL/6 male mice (transgenic for PhiX17am3). An equivocal increase in micronucleated erythrocytes was noted in male B6C3F1 based on a small increase in micronucleated normochromatic erythrocytes that did not reach statistical significance. No increase in micronucleated changes normochromatic erythrocytes was observed in male BALB/c mice. No significant effect of sodium dichromate dihydrate exposure on the percentage of and polychromatic erythrocytes was observed in any of the three micronucleus tests conducted in Study 2 (Bucher, 2007). None of this information is discussed in the draft PHG.”

Response 22. The PHG “Genotoxicity” section has been updated.

Comment 23: “Clearly, OEHHA recognized the important role of irritation/inflammation, cytotoxicity, hyperplasia in tumor formation (pp. 42, 134), yet it failed to develop the logical and well established hypothesis for Cr(VI) mode of carcinogenic action, *ie.*, sustained cell injury, death, and repair (Figure 1). OEHHA mentioned the NTP’s findings of a significant and dose-related increase in diffuse hyperplasia in mice duodenum. OEHHA cited the NTP’s findings “that collectively, these lesions are considered consistent with regenerative hyperplasia secondary to previous epithelial cell injury.”

Response 23. No irritation/inflammation or evidence of cytotoxicity was reported in the oral cavity of rats or intestine of mice in the 2-year NTP bioassay. NTP noted that the stomach irritation (not a tissue where an increase in tumors was observed) seen in the 3 month study was not evident in the 2 year bioassay (see discussion of NTP, 2008 in “Toxicological Effects in Animals, Carcinogenicity” section of the PHG document). Note

that the stomach irritation observed in the 3-month study occurred only in the high dose animals. This dose (1000 ppm sodium dichromate dihydrate) exceeded all the dose levels used in the 2 year bioassay to measure tumor induction.

Comment 24: “While not stated, if OEHHA’s evaluation of the weight of evidence of ‘all available data were insufficient to establish the mode of action’ (EPA, 2005), then OEHHA should have presented alternative analyses. Specifically, OEHHA should have presented results based on both a linear and nonlinear approach as part of its risk characterization process. Such an analysis would help provide risk managers and decision-makers with a perspective on the uncertainty inherent in the numerical value of OEHHA’s draft PHG. A calculation based solely on the linear dose-response model presents the draft PHG as if it were ‘the number’ that would be protective of human health. Specifically, OEHHA should have followed the 2005 EPA guidance, i.e., ‘where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach, an assessment may present results based on more than one approach.’”

Response 24. After reviewing all the data relating to Cr VI’s mode of action, OEHHA made the determination that a linear extrapolation was the correct approach for predicting tumor response in the low dose region of the dose- response curve. The well-documented ability of Cr VI to cause genotoxicity (including mutation induction) in test animals, cultured mammalian cells, insects, yeast and bacteria was an important factor in that determination. Other groups including the New Jersey Department of Environmental Protection (Stern, 2010) and the U.S. EPA (2010) have come to similar conclusions, supporting a scientific consensus. Presumably, U.S. EPA followed their own guidelines for cancer risk assessment when they made the decision to base the cancer slope factor on a linear model and not on a non-linear/threshold model. Various sources of uncertainty associated with development of the PHG for Cr VI are discussed throughout the document, with a more concentrated discussion in the “Risk Characterization” section.

Comment 25: “Applying the benchmark dose (BMD) approach (a nonlinear dose extrapolation) to the NTP mouse duodenal hyperplasia data, as was done by ATSDR (2008) and as provided for in EPA’s 2005 guidelines, results in BMDL10 values of 0.09 to 0.13 mg Cr VI/kg/day. Consistent with EPA practices, an uncertainty factor of 100-fold could be applied to account for extrapolation from animals to humans (10x) and for intra-human sensitivity (10X). The resulting reference dose would be approximately 0.001 mg/kg/day. The results of applying the linear and nonlinear dose-response models yield values with more than a 500-fold difference in daily doses, with proportional differences in the corresponding drinking water criteria, e.g., OEHHA’s draft PHG of 60 ppt (using the linear model) and ATSDR’s Minimum Risk Level of 35,000 ppt (using the BMD approach).”

Response 25. ATSDR’s Minimum Risk Level for Cr VI referenced above was based on non-cancer effects, to be protective against such effects. It should not be compared to the value calculated in the PHG that is also protective against cancer (20 ppt in the current draft).

Comment 26: “OEHHA did not use the most current principles and practices in determining the non-cancer health-protective dose (HPD). Rather than using the benchmark dose/nonlinear approach on the mouse data for the noncancer risk assessment, OEHHA identified the lowest adverse effect level (LOAEL) from the rat study (female liver – mild chronic inflammation, fatty changes) and applied a 1,000-fold uncertainty factor that included 10x to account for the lack of a no observed adverse effect level (NOAEL). OEHHA guidance calls for the use of BMD over NOAEL/LOAEL. The DTSC memorandum on the draft PHG found that the NTP subchronic data incorrectly identified the NOAEL as an LOAEL, and DTSC criticized OEHHA for applying 1,000-fold uncertainty factors in developing the HPD.”

Response 26. At present the Cr VI PHG based on cancer effects is 100-fold lower than if it were based on non-cancer effects (see “Calculation Of The PHG” section of the document). OEHHA will be applying the BMD approach in future analyses of the non-cancer data. Our preliminary analysis applying the BMD approach to the non-cancer data followed by an uncertainty factor of 100 yields a final value that is more than 100-fold **higher** than the proposed PHG based on cancer effects. Thus, the proposed PHG (0.02 ppb) for protecting against both cancer and non-cancer effects would not change.

Comment 27: “In particular, Dr. Kelner strongly recommended that ‘all the NTP 2007 studies need to be analyzed and slope factors derived for each study by an accepted methodology. Then the mean median (preferably) slope factor is to be utilized for subsequent calculations. NOT the 95% confidence interval.’ Dr. Kelner was urging OEHHA to use the mean or median ED10 as described in EPA’s 2005 guidelines, e.g., ‘risk assessors should calculate, to the extent practicable, and present the central estimate and the corresponding upper and lower statistical bounds (such as confidence limits) to inform decision makers.’”

Response 27. Current methodology followed by both the U.S. EPA (2005; Davis et al., 2010) and OEHHA (2009) is to use the LED₁₀ to derive the cancer slope factor.

Comment 28: “OEHHA states that it acknowledges the ‘various uncertainties inherent in cancer risk assessment’ in the Risk Characterization section of the draft PHG document (pp. 96-98), but there is no quantitative assessment of uncertainty in the value of the draft PHG, nor is there any discussion or quantitative estimate of the large ‘uncertainty factor’ in the equation used to calculate the PHG (pp. 95-96).”

Response 28. OEHHA is not aware of an established methodology for quantifying the uncertainty of uncertainty factors or the uncertainty associated with cancer risk extrapolation.

Comment 29: “Contrary to the recommendations in this report and peer reviewers’ comments on the 2005 draft PHG, OEHHA has developed a widely speculative hypotheses that inflammation caused by bacteria may be additive to, or synergistic with, adverse effects of hexavalent chromium-produced irritation on the stomach such that inflammation may “help push an individual along the path to stomach tumors” (OEHHA, Comments for the NTP Cr(VI) Public Meeting, July 24, 2002). Furthermore, OEHHA’s approach is far from valid or conventional and dismisses valid scientific data (see Section IV). Although OEHHA’s Bacterial Infection Hypothesis is overly speculative, it serves as the basis for developing the draft PHG for Cr(VI) in drinking water of 60 ppt.

Nevertheless, in the draft PHG documentation, OEHHA included the 2007 NTP study results and revived their Bacterial Infection Hypothesis to ultimately tie three Itey [sic] studies together to support OEHHA's preconception that Cr(VI) is carcinogenic to humans at environmentally relevant doses."

Response 29. The PHG does not rely on the Helicobacter hypothesis in the development of the PHG. The hypothesis is located in Appendix B and clearly labeled that it is a hypothesis. The Helicobacter hypothesis was formulated by OEHHA as part of an effort to obtain a better understanding of the findings of diverse studies, such as the occurrence of tumors in the first generation of the Borneff et al. (1968) study and stomach tumors following a relatively short term exposure to Cr VI in rural China. These discussions serve as a scientific resource and are attached in the Appendix as records of the issues that have been addressed in the research for and preparation of this PHG document.

Comment 30: "OEHHA's 2005 PHG peer reviewers discounted the use of the Borneff et al. (1968) study for cancer risk assessment purposes for multiple reasons, including the high mortality associated with the mouse pox outbreak in the study animals... However, OEHHA discounts the authors' explanation of the study findings and promotes their own speculative hypothesis that an unidentified bacterial infection in the parental generation (F₀) was in part responsible for stomach tumor formation. Stomach cancer was not produced in their first generation (F₁) because the bacterial infection was not passed to offspring due to Cr(VI) bactericide activity (p. 126)."

Response 30. The Borneff et al. (1968) study is not a key study in the derivation of the PHG for Chromium VI and is now placed in the Appendix for information purposes. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

Comment 31: "OEHHA relies on the original publication regarding the Chinese population associated with drinking water contaminated with Cr(VI) (Zhang and Li, 1987)... 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 (Kerger et al., 2009). Kerger et al. is not even referenced or discussed."

Response 31. Kerger et al. (2009) is now discussed in detail along with Beaumont et al. (2008) in the "Toxicological Effects in Humans, Carcinogenicity" section of the PHG.

Comment 32: "Furthermore, Dr. Bjeldanes submitted for OEHHA's consideration a study (Bednar and Kies, 1991) where 'no association was found between low levels of Cr(VI) in drinking water (up to 10 ppb) with total cancer mortality.' OEHHA dismissed this study and Dr. Bjeldane's criticism of OEHHA's selectivity stating 'the analysis was not specific to Cr(VI)' and that this makes it 'difficult to compare the findings to those of Beaumont et al. (2008) of a relationship between hexavalent chromium in water and increased risk of stomach cancer.'

Response 32. The study by Bednar and Kies (1991) is discussed in more detail in the final PHG document. An important limitation of this study was that sampling in the study occurred for only two years. Unlike the Zhang and Li (1987) study, no specific source of Cr VI exposure was identified. Also, while overall cancer mortality rates were evaluated, tumors at specific sites were not.

Comment 33: “OEHHA does recognize that the data underlying Zhang and Li (1987) have several important limitations that included lack of exposure data and a short observation time (14 years) after residents first noticed the yellow color of the water. However, OEHHA draws on the Bacterial Infection Hypothesis to overcome some of these limitations in order to continue relying upon the positive association of increased stomach and over all cancer rates with drinking Cr(VI)-tainted water.”

Response 33. Zhang and Li (1987) is discussed in the “Toxicological Effects in Humans, Carcinogenicity” section of the PHG. This detailed analysis of the study, much of it taken from Beaumont et al. (2008), stands on its own, without any reference to the Helicobacter Hypothesis. That hypothesis, and its **possible** relation to the 14 year observation time cited above, is only discussed in Appendix B.

Comment 34: “When confronted with lack of concordance in tumor locations between NTP (2007), Borneff et al. (1968), and Zhang and Li (1987) (mouse intestine, mouse forestomach and human stomach, respectively), OEHHA evokes the Bacterial Infection Hypothesis... In addition to noting that the NTP mice that developed intestinal cancer were bacteria-free, OEHHA ties the intestinal tumor location to the Helicobacter infection since it is characterized by the occurrence of metaplasia in the stomach – ‘a transformation of the stomach into a tissue that resembles intestine’ (p. 136).”

Response 34. The PHG does not rely on the Helicobacter hypothesis in the development of the PHG. The hypothesis is located in Appendix B and clearly indicated as such. The Helicobacter hypothesis was formulated by OEHHA as part of an effort to obtain a better understanding of the findings of diverse studies such as the occurrence of tumors in the first generation of the Borneff et al. (1968) study and stomach tumors following a relatively short term exposure to Cr VI in rural China. These discussions serve as a scientific resource and are attached in the Appendix as records of the issues that have been addressed in the research for and preparation of this PHG document.

Comment 35: “It should be noted that all OEHHA’s speculation on tumor formation is focused on the occurrence of tumors in mice and humans but does not mention or attempt to explain the tumors produced in the oral cavity of the rat in the NTP study.”

Response 35. The rat tumor data from NTP (2008) are discussed in detail in the “Toxicological Effects in Animals, Carcinogenicity” section of the PHG.

Comment 36: “OEHHA states that the International Agency for Research on Cancer (IARC) (1990) concluded that CR(VI) is a ‘strong’ carcinogen for the respiratory tract, while the document concluded that ‘there is sufficient evidence in humans for the carcinogenicity of Cr(VI) compounds as encountered in the chromate production, chromate pigment industry and chromium plating industries.’”

Response 36. The word “strong” has been deleted.

Comment 37: “Based on Dr. Gwiazda’s 2008 peer review comments on the peer review version of the draft PHG document, OEHHA ‘ignored’ the confidence intervals of the epidemiological rate ratios in reaching its (OEHHA’s) conclusion that most occupational studies showed an increase risk of stomach cancer. Dr. Gwiazda commented that if OEHHA chose to include the analysis, it should be “consistent and address the contradictory observation that on the basis of the rate ratios alone, e.g., 25% of the studies would support a protective role of Cr(VI) exposure against stomach cancer! But this logical conclusion was ignored.”

Response 37. We have added more discussion of Table 8 that includes the suggestions of Dr. Gwiazda to: 1) not compare the rate ratios to 1.00, and 2) conclude that the results are consistent with an association between occupational exposure to Cr VI (via inhalation) and stomach cancer.

Comment 38: “As pointed out in the DTSC memorandum, analyses of these same data by Cole and Rodu (2005) indicated there were no significant increases in stomach or gastrointestinal tumors associated with Cr(VI) exposure.”

Response 38. The study by Cole and Rodu (2005), along with some of its shortcomings, is discussed in the PHG document.

Comment 39: “As discussed above, OEHHA relies on the original publication on the Chinese population associated with drinking water contaminated with Cr(VI) (Zhang and Li, 1987) and OEAA’s reassessment of the Chinese data (Beaumont et al., 2008) to draw the connection between exposure to Cr(VI) and stomach cancer in humans and various cancer sites in experimental laboratory animals. In doing so, OEHHA ignores other publications that do not support OEHHA’s contention of the causal link between oral exposure to Cr(VI) and cancer in humans, including the recent publication on the study population by Kerger et al. (2009). Furthermore, in his 2008 peer review of the draft PHG, Dr. Bjeldanes brought the Bednar and Kies (1991) drinking water study to OEHHA’s attention. In this study of 453 communities in Nebraska, no association was found between low levels of chromium in drinking water and total cancer mortality. OEHHA affirmed the finding and agreed that the data could be examined but cast doubts on the results. OEHHA believes the analytical method likely did not measure Cr(VI) but rather total chromium (Cr(VI) and Cr(III)). OEHHA ignores similar problems with the exposure assessment of the Chinese study population.”

Response 39. Kerger et al. (2009) is now discussed in the PHG document. With regard to the study by Bednar and Kies (1991), a number of its limitations are now discussed in the PHG document including that sampling in the study occurred for only two years. Unlike the Zhang and Li (1987) study, no specific source of Cr VI exposure was identified. Also, while overall cancer mortality rates were evaluated, tumors at specific sites were not.

Comment 40: “Another example of OEHHA’s selective interpretation of the literature can be found in its description of the role of Cr(VI) reduction to Cr(III) in the stomach and in cells – the subject of Appendix A, ‘Carcinogenic Threshold?’ to OEHHA’s draft PHG document. Appendix A is intended to provide support of OEHHA’s default to a linear extrapolation model because a fraction of ingested Cr(VI) is absorbed into the body – escaping the body’s first line of defense, i.e., gastrointestinal reduction of Cr(VI)

to Cr(III). OEHHA points to the 2007 NTP study showing the dose-related systemic absorption of orally administered Cr(VI) in mice being inconsistent with the research of De Flora and others that OEHHA characterizes as the ‘assertion that hexavalent chromium absorption occurs only when the reducing capacity of the GI tract is exhausted.’ Contrary to OEHHA’s interpretation of the literature, the studies published by researchers such as De Flora and others do not suggest that the detoxification pathways are 100% efficient or unsaturable. These researchers’ contributions to the literature indicate that the reduction of Cr(VI) to Cr(III) in the gastrointestinal tract limits the bioavailability and attenuates the potential for adverse effects of Cr(VI) compounds *in vivo*. Apparently, OEHHA takes the position that since Cr(VI) can be absorbed into the body, inferring that there is no threshold for Cr(VI) carcinogenicity via ingestion.” This is a critical OEHHA determination that ignores other mechanisms that attenuate the bioavailability and potential adverse effects of Cr(VI), including DNA damage (Sedman et al., 2006). The high rate of reduction of very low concentrations of Cr(VI) to Cr(III) effectively detoxifies Cr(VI) since Cr(III) is not readily taken up by cells, i.e., it is not bioavailable. This markedly changes the shape of the dose-response curve at low doses because the reduced Cr(VI) is no longer bioavailable.”

Response 40. Appendix A addresses the Cr VI concentration range used in the NTP studies. Appendix A states, “The absorption at the doses that were tested does not appear to be due to the exhaustion of the reducing capacity of the GI tract.” This can be inferred by the absence of thresholds in Figures A1 through A6. Thus, the original title of Appendix A, “Carcinogenic Threshold?” This title was not meant to rule out the possibility that there is a threshold for carcinogenesis at much lower concentrations of Cr VI. We do not know the answer to this, since we do not have dose response data for either Cr VI absorption or tumorigenesis at low concentrations of Cr VI. We have modified the title of Appendix A to “Carcinogenic Threshold: Was the reductive capacity of the rodent GI tract exceeded in the NTP (2008) two-year bioassay?”

Comment 41: “OEHHA overlooked relevant *in vivo* genotoxicity data published in peer-reviewed journals during the development of the draft PHG... Curiously, the results of the four genotoxicity tests (micronucleus) conducted by NTP on three strains of mice receiving Cr(VI) in the drinking water at chromate concentrations up to 1,000 mg/L for three months were not considered by OEHHA (Bucher, 2007).”

Response 41. The results of both De Flora et al. (2006) and De Flora et al. (2008) are presented in Table 2. The mouse erythrocyte micronuclei data from NTP (2007) have been added to Table 2.

Comment 42: “VII. Rather than Applying ‘Uncertainty Factors’ Ranging Over Five Orders of Magnitude in Developing the Draft PHG, OEHHA Should Identify the Key Data Gaps and Acknowledge Ongoing Studies That Would Reduce the Uncertainty in OEHHA’s Risk Assessment. VIII. OEHHA Should Take No Action to Finalize the PHG Until It Can Review the Results of the Ongoing Research, Including the Hamner Institute’s Research Into the MOA.”

Response 42. First, the PHG for Cr VI in drinking water is based on tumor induction. No uncertainty factors were used to develop this number (0.02 ppb).

Second, Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

RESPONSES TO MAJOR COMMENTS RECEIVED ON DECEMBER 2010 DRAFT, SECOND COMMENT PERIOD (2011)

Comments from Ann Mason and Laura Brust, American Chemistry Council

Cover Letter

Comment 1: “The most important point in the ACC comments is that OEHHA improperly applies age sensitivity factors, without consideration of mode of action (MOA), to reduce the PHG from 0.06 ppb to 0.02 ppb.”

Response 1. See “Correction for Early-in-Life Exposures” section of the PHG document. The Age Sensitivity Factor (ASF) for modifying cancer potency was used as described (OEHHA, 2009). This approach applies to all carcinogens, regardless of purported mechanism of action, unless chemical-specific data exist that could be used to make more specific adjustments to risk. Such chemical-specific data are not available for Cr VI. A mutagenic mode of action described by McCarroll et al. (2010) has been added to the document.

Comment 2: “OEHHA also fails to support significant changes from the 2009 draft PHG and provide the documentation and rationale for some of its calculations and assumptions used to support the revised draft PHG.”

Response 2. The revised PHG document has provided additional support for calculations and assumptions used.

Comment 3: “Moreover, in many cases, OEHHA does not adequately consider the comments of peer reviewers in the revised draft PHG.”

Response 3. The PHG document has been revised to address additional comments of the peer reviewers. Note that the peer reviewers do not always agree with each other so that a revision in response to comments from one reviewer may not appear to respond to comments from another peer reviewer. The critical point is that all comments have been considered by OEHHA.

Comment 4: “Finally, OEHHA should use the best available science, including MOA data, fully present both linear and nonlinear approaches, present the rationale and justification for its calculations and assumptions, and fully address and incorporate the comments from its own invited experts who provided peer review comments.”

Response 4. See the following sections of the PHG document for discussion of the MOA issues for which data are available: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” Table 7 in the section entitled “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.”

Executive Summary

Comment 1: “OEHHA also proposes a PHG of 2 ppb for non-cancer effects based on liver toxicity in female rats in the NTP study (2008).”

Response. The PHG document develops a single PHG value to protect against all toxic effects of Cr VI in drinking water: that of 0.02 ppb. The drinking water concentration of 2 ppb is protective from only non-cancer effects. It is not a PHG.

Comment 2: “While purporting to meet the requirements to use the best science in decisions that relate to protecting public health, OEHHA continues to use default assumptions rather than chemical-specific information and sound science to inform risk assessment.”

Response 2. OEHHA’s decision to perform linear extrapolation from the point of departure to the zero dose level was not a default decision. It was based on the extensive data base of studies covering the toxicity of Cr VI. That data base includes multiple studies indicating that Cr VI is both genotoxic and mutagenic (see “Genotoxicity” section of the PHG document). The data base also contains little support for an MOA other than genotoxicity/mutagenicity; for example, no cytotoxicity was observed at dose levels producing tumors in rodents (NTP, 2008). These were the primary considerations for choosing an MOA and analytical model. The U.S. EPA recently came to similar conclusions in their draft Toxicological Review of Hexavalent Chromium (2010), Presumably, this review was performed using “sound science.”

Comment 3: “Data about the mode of action (MOA) or Cr(VI) currently are being developed as part of a major research initiative that began in early 2009, and these data will be presented in March at the 2011 meeting of the Society of Toxicology.”

Response 3. OEHHA continues to use all available data collected through sound science in its development of the Cr VI PHG.

Comment 4: “OEHHA fails to address comments from peer reviewers of the draft August 2009 PHG document and the Draft Dec. 2010 PHG document, and expert panel comments on the draft 1999 PHG document.”

Response 4. The PHG document has been revised to address additional comments of peer reviewers. This document contains OEHHA’s responses to the 2008 and 2009 peer reviews (see Table of Contents). Note that the peer reviewers do not always agree with each other so that a revision in response to comments from one reviewer may not appear to respond to comments from another peer reviewer. The critical point is that all comments have been considered by OEHHA.

Comment 5: “OEHHA inadequately responds to public comments on earlier PHG document, including lack of any MOA consideration, especially when MOA forms the overarching conceptual framework for cancer risk assessment (EPA, 2005a).”

Response 5. See the following sections of the PHG document for discussion of the MOA issues for which data are available: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.”

Comment 6: “Regarding the MOA, lack of consideration of interspecies differences in toxicokinetics of Cr(VI) and the failure to recognize that pathologies seen in rodents are likely portal-of-entry effects.”

Response 6. The rodent tumors observed in the two-year bioassay (NTP, 2008) may well be site-of-contact effects. However, given the available data, calculation of the cancer potency would be the same whether a site-of-contact effect or a systemic effect were assumed.

Comment 7: “Instead, the Draft Dec. 2010 PHG document correctly assumes that the metabolic products of Cr(VI) are DNA-reactive and wrongly assumes that DNA-reactivity equates to mutagenicity.”

Response 7. OEHHA does not equate DNA reactivity with mutagenicity. A specific citation within the PHG document would be most helpful. In cultured mammalian cells, there are a number of published studies which report robust (in excess of 3-fold increases) mutagenic responses to Cr VI (see Paschin et al. (1983) *Mut Res* 103(3-6):345-347; Mitchell et al. (1988) *Environ Mol Mutagen* 12(Suppl 13):37-101; Myhr and Caspary (1988) *Environ Mol Mutagen* 13(12):103-194; McGregor et al. (1987) *Environ Mutagen* 9(2):143-160; Oberly et al (1982) *J Toxicol Environ Health* 9(3):367-376). Reviews discussing these studies are cited in the first paragraph of the “Genetic Toxicity” section of the PHG document. Cr VI also caused mutations in bacteria, yeast, *D. melanogaster* and mice (see reviews mentioned above and U.S. EPA, 2010).

Comment 8: “Lack of consideration of nonlinearity and the presence of a threshold. Although Appendix A, titled ‘Carcinogenic Threshold?,’ (in the Draft Dec. 2010 PHG document) discusses the idea of a threshold, this appendix considers only reductive capacity and absorption, and because of the lack of any consideration of MOA, fails to take into account epigenetic changes (such as those mentioned in the previous bullet) that underlie the tumor responses and that likely do have thresholds. The lack of

consideration of MOA also prevents exploration of the use of precursor effects as recommended in the EPA's *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a)."

Response 8. The title of Appendix A has been revised to read, "Carcinogenic Threshold?: Was the reductive capacity of the rodent GI tract exceeded in the NTP (2008) bioassay?" Discussion has been added to the PHG document concerning the MOA data that support the use of a low dose linear extrapolation to calculate cancer potency. For example, see the "Mechanism of Genotoxicity and Carcinogenicity" section for studies demonstrating a genotoxic, and possibly mutagenic MOA for Cr VI. See also the discussion of Table 7 that presents tissue and cellular findings from NTP studies that do not support an MOA based on cytotoxicity and compensatory cellular proliferation.

Comment 9: "Regarding the water consumption to calculate life-stage exposures, use of an atypical calculation method that expresses life-stage as a unit less fraction of a lifespan. In addition, the water consumption rates used in the non-substantive change document released by OEHHA on January 25, 2011 cannot be verified from the original sources and appear to be incorrect for some age groups (EPA, 2008; Kahn and Stralka, 2009)."

Response 9. For the methodology used to correct for early-in-life exposures (life-stage calculations) to carcinogens, see OEHHA (2009). The methodology for calculating water consumption rates using the data from U.S. EPA (2008) and Kahn and Stralka (2009) is now presented in the footnote to Table 17 and in the discussion of Table 17.

Comment 10: "OEHHA inappropriately uses the age-sensitivity adjustment detailed in OEHHA (2009) because of lack of consideration of MOA. The age sensitivity adjustment was derived from data using solely statistical methods without consideration of biology or MOA other than a single paragraph classifying the chemical as genotoxic or non-genotoxic (p.4 of OEHHA, 2009). In addition, it is difficult to validate the calculations that employ this adjustment because the necessary data are scattered throughout the document."

Response 10. It is difficult to know if this comment refers to OEHHA (2009) or to the Cr VI PHG document. The "Calculation of The PHG," subheading "Carcinogenic Effects" section of the PHG document illustrates how the age sensitivity factors are incorporated into the PHG calculation.

Comment 11: "OEHHA uses scientific literature in a biased or inappropriate manner, including: The use of two highly flawed studies in mice and humans, respectively (Borneff et al., 1968; Zhang and Li, 1987), to attempt to establish a link between Cr(VI) exposure and gastrointestinal cancer in humans. The use of these studies is in direct contradiction of the advice of an expert panel convened by the University of California in 2001 to review the 1999 PHG document."

Response 11. The primary recommendation of the Chromate Toxicity Review Committee (CTRC, 2001) that a drinking water standard for Cr VI **not** be based on the study by Borneff et al. (1968) was followed by OEHHA. In 2005 UC reviewers Roberto Gwiazda, Leonard Bjeldanes and Michael Kelner provided comments on the draft PHG document which included the recommendation to move discussion of Borneff et al.

(1968) and the Helicobacter hypothesis to the Appendix. The PHG document was revised accordingly. With regard to the two studies by Zhang and Li (1987; 1997), the 1997 report was retracted by the journal in which it was published. Although the names of the second authors for the two studies appeared the same, they actually are two different individuals. The Zhang and Li (1987) study was thoroughly analyzed (see Beaumont et al., 2008). Although the magnitude of the exposure to Cr VI in drinking water is unclear, the population did appear to be exposed to high levels of chromium VI. A statistically significant increase in stomach tumors was detected when compared to a nearby unexposed population. The high levels of chromium VI in the wells is what triggered the study (lower levels probably would have gone undetected). Lower levels of chromium VI may still cause cancer but at a rate that would have been undetected in a population of several thousand. Another recent reevaluation of the Zhang and Li (1987) study by Kerger et al. (2009) has been added to the PHG document.

Comment 12: “OEHHA uses scientific literature in a biased or inappropriate manner, including: An attempt to impeach the results of the Gatto et al. (2010) meta-analysis that found no associations between occupational exposure to Cr(VI) and gastrointestinal cancer in humans. Although the Draft Dec. 2010 PHG document makes several suggestions to ‘improve’ the Gatto et al., meta-analysis, it is unlikely that any of these suggestions would alter the results published in Gatto et al., 2010.”

Response 12. Our discussion of Gatto et al. (2010) is a straightforward identification of some possible limitations of the study.

Comment 13: “OEHHA fails to explore the uncertainty associated with dose-response modeling. The narrative and tables describing the modeling are very brief and difficult to follow. The number of animals at risk for the various dose groups in NTP (2008) was changed from those in the Draft August 2009 PHG document without explanation, and neither set of values are the results of the commonly used poly-3 survival adjustment (Portier and Bailer, 1989).”

Response 13. The numbers of animals at risk are shown in Table 5 and Table 6. As indicated in the footnotes to both tables, these are the mice alive at the time of the first occurrence of tumor (day 451 for males and day 625 for females) and if the tissue was available for analysis. This is a standard method for determining the number of animals at risk for tumors (U.S. EPA, 2005; OEHHA, 2009).

Specific Comments and Responses

Comment 1-1: “In early 2009, ACC’s Cr(VI) Panel initiated the Cr(VI) MOA Framework Research Program (Appendix A) designed to elucidate details of the carcinogenic mode of action (MOA) of Cr(VI) in rodents from oral exposures...Hence, OEHHA personnel knew that the study was in progress but nonetheless released the Draft August 2009 PHG document and the Draft Dec. 2010 PHG document, neither of which considers the MOA.”

Response 1-1. The carcinogenic mode of action (MOA) of Cr VI is discussed in detail in the PHG document (see especially sections “Pharmacokinetics of Trivalent versus

Hexavalent Chromium, Genetic Toxicity, Mechanism of Genotoxicity and Carcinogenicity, and Examination of Evidence for Carcinogenicity”). OEHHA will consider new data as they become final and available.

Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comment 2-1: “Some of the bioassay data from which OEHHA (2009) developed these age sensitivity ratios was found to be flawed by the National Toxicology Program (NTP) and EPA...Given these problems with data from the Ramazzini Institute, codifying this idea in guidance such as OEHHA (2009) or EPA (2005b) may have been premature.”

Response 2-1. OEHHA’s derivation of Age Sensitivity Factors (AFSs) in OEHHA (2009) was based on data from 23 carcinogenic chemicals. One of these, vinyl chloride, is on the list of six chemicals to be re-reviewed by U.S. EPA. This re-review was deemed necessary to resolve possible differences of opinion between pathologists at NTP and at the Ramazzini Institute. The comment suggests that OEHHA’s (2009) document on early-in-life susceptibility to carcinogens is unreliable due to its use of vinyl chloride data from the laboratory of Maltoni, who later founded Ramazzini. Should the Maltoni et al. (1981) data be found to be unreliable, OEHHA will revise its document (2009) accordingly. However, given that vinyl chloride is only one of twenty-three chemicals comprising the data base for OEHHA (2009), it is likely that the ASFs would change very little.

Comment 2-2: “The ASF values on page 86 of the Draft Dec. 2010 PHG document are:

Prenatal (in utero) ASF 10
Postnatal (Birth-2 yr.) ASF 10

Juvenile (2-16 yr.) ASF	3
Adult (>16 yr.) ASF	1

OEHHA does not explain why these [ASF] values are different from the values presented in OEHHA (2009)."

Response 2-2. The ASF values used in the Cr VI PHG are the same values presented in OEHHA (2009). See the Technical Support Document, page 3.

Comment 2-3: "In addition, the method of calculating drinking water intake *in utero* is not provided. We can only assume that OEHHA is referring to exposure *in utero* through maternal water consumption."

Response 2-3. The section "Correction for Early-in-Life Exposures" states that for the third trimester of pregnancy the drinking water consumption rate is assumed to be that of an adult (i.e., maternal consumption). We have added this information to the "Calculation Of The PHG," subheading "Carcinogenic Effects" section.

Comment 2-4: "The equation for calculating individual life-stage exposures for water consumption is $Exposure_j = ASF_j \times d_j \times cons^o_j$. However, life-stage exposure duration is not the appropriate multiplier."

Response 2-4. Because the four life-stages are of different durations, calculating the lifetime exposure requires a weighted mean calculation. This is achieved by including a duration adjustment for each life-stage.

Comment 2-5: "Because the slope factors are in units of $(mg/kg-d)^{-1}$, the exposure term should remain in units of L/kg-d. The unit kg-d will cancel to leave a water concentration in mg/L. OEHHA does not explain why it expresses life-stage as a unit less fraction of a 70-year lifespan in the Draft Dec. 2010 PHG document."

Response 2-5. The correct units have been added to the equation that immediately follows Table 17. See "Correction for Early-in-Life Exposures" section of the PHG document for a definition of the duration adjustment term.

Comment 2-6: "The tap water ingestion rates used to derive the water consumption rates are hidden...OEHHA should use the correct values for adults' and children's drinking water ingestion rates when revising this Draft PHG document."

Response 2-6. The **per capita** drinking water values from Kahn and Stralka (2009) were mistakenly used in the previous draft PHG document. Instead, the **consumers only** drinking water values from the same publication have been used to revise the PHG document. This resulted in the same final PHG value of 0.02 ppb (rounded). The protocol OEHHA followed to calculate the time-weighted mean drinking water ingestion rates using the data from Kahn and Stralka (2009) and U.S. EPA (2008) is now given in the "Calculation Of The PHG" section of the document.

Comment 2-7: “In the Draft Dec. 2010 PHG document, there is absolutely no discussion about the form in which this tap water is consumed. This is an important issue for Cr(VI), as it is well known to be rapidly reduced to Cr(III) in some beverages that are made from tap water in the home (e.g., orange juice, lemonade, coffee, tea). It appears that OEHHA assumes that all water consumed by the adult is from the same source, despite the fact that most people go to work or school and move several times in a 70-year lifetime. Such compounded conservative assumptions in exposure assessment overestimate the true risk.”

Response 2-7. We have added to the “Calculation of The PHG” section of the document that the water intake data cover pure water consumed as a beverage or used in the home or local establishments to prepare food or drink (Kahn and Stralka, 2009). The PHG document does not attempt to determine how often the average American adult relocates during a lifetime. The document makes the health-protective assumption that some adults will live most of their lives in the region they were born. We believe this is a reasonable assumption for the purposes of this risk assessment.

Comment 3-1: “Neither the Draft Dec. 2010 PHG document nor the Draft August 2009 PHG document provides the information needed for dose-response modeling in a single place.”

Response 3-1. The “Dose-Response Modeling” section of the PHG document now states the places in the document where the tumor incidence data and the lifetime time-weighted average doses in rodents are located.

Comment 3-2: “Why did the number of animals at risk increase from the 2009 document to the 2010 document?”

Response 3-2. In the 2009 draft an animal was excluded from the analysis if it died more than 40 days prior to the appearance of the first tumor of the small intestine. In the 2010 document an animal was excluded from the analysis if it died at any time prior to the appearance of the first tumor of the small intestine. The latter methodology is in keeping with OEHHA (2009) and U.S. EPA (2005) guidance.

Comment 3-3: “By using only a single model in the Draft Dec. 2010 PHG document, and by not exploring a range of PODs, OEHHA thwarts the intent of U.S. EPA’s Cancer Guidelines (EPA, 2005a)...As pointed out by Dr. Michael Kelner, the cancer potency slope can be highly dependent on which POD (10%, 5%, or 1%) is selected for its determination. Prof. Mitchell Cohen, in his 2010 comments, points out that the set of values of 1%, 5%, and 10% excess cancer risk could be used as points of departure. Dr. Cohen reminds OEHHA of U.S. EPA’s recommendation to “routinely calculate and present the point estimate of the ED_x (a central tendency estimate) and the corresponding upper and lower 95% statistical bounds.” It is not clear why OEHHA disregards these peer reviewers’ comments.”

Response 3-3. Current standard methodology followed by both the U.S. EPA (2005; Davis et al., 2010) and OEHHA (2009) is to use the LED₁₀ to derive the cancer slope factor.

Contrary to what is stated in this comment from the American Chemistry Council, OEHHA has not disregarded the comments of the two peer reviewers mentioned here. We are aware of Dr. Kelner's point that the cancer slope factor depends on which point of departure is selected. See OEHHA's responses 5 and 6 to Dr. Kelner's comments on this particular point (see Table of Contents, this document). While it is true that Dr. Cohen discussed using the 1, 5 and 10 percent effect levels as points of departure, after further consideration he went on to conclude that, "the use of the LED₁₀ was appropriate for generating the PHG for human exposures to Cr⁶⁺ in drinking water." Both the ED₁₀ values and the LED₁₀ values for tumor incidence in male and female mice are presented in Tables 10 and 11 of the PHG document.

Comment 3-4: "As currently written, the Draft Dec. 2010 PHG document suggests there is only one possible value for the PHG when, in fact, consideration of uncertainty suggests a range of values and that the value depends on the choices made in the course of data evaluation, calculations and modeling...An example of the type of modeling that is indicated in EPA (2005a) is shown in the tables below...OEHHA did not choose the best-fitting model based on Chi-square or the model that provides the best fit and most parsimony based on the Akaike information criterion, as is indicated in EPA's *Benchmark dose Technical Guidance Document* (EPA, 2000)...The empirical fits discussed here were conducted using the number of animals at risk in the Draft Dec. 2010 PHG document and thus, OEHHA should have conducted a full exploration of the uncertainty in empirical dose response modeling. Had OEHHA done so, it is likely that the probit model rather than the multistage model would have been chosen."

Response 3-4. The PHG document develops two health-protective concentrations for Cr VI in drinking water; one to protect against non-carcinogenic effects and one to protect against carcinogenic effects. The lower concentration is designated the PHG to be protective against all adverse health effects. OEHHA does not develop a range of PHG values. Such an approach was considered when the PHG program was established and judged not to be helpful, given the role of PHGs as non-regulatory guidelines that the Department of Public Health uses in developing regulatory drinking water standards. In addition, the California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires OEHHA to develop a Public Health Goal (PHG) for environmental contaminants in drinking water, not a range of PHGs for each contaminant.

Modeling the dose-response data using a variety of different models, as suggested in the comment, is not an uncertainty analysis. As stated in the "Dose-Response Assessment," subheading "Carcinogenic Effects," subheading "Dose-Response Modeling" section of the PHG document, the multistage model was used to model the tumor incidence data because this is the model preferred by OEHHA (2009) and U.S. EPA (2010) for conducting cancer dose-response assessments. This is primarily due to

the multistage model's generally good fit of the data in the relatively high dose range used in rodent bioassays (Armitage and Doll, 1961). With regard to the criteria U.S. EPA recommends for choosing between models when using its benchmark dose software, when the benchmark dose 95% lower bound confidence limit (BMDL) is different for models with adequate fits, the model yielding the lowest BMDL should be selected (Davis et al., 2010).

Comment 3-5: "Hence, the 2% POD is within the range of observation for male mice and the 1% POD is within the range of observation for female mice and, according to EPA (2005a), should be the preferred value from which to extrapolate to lower doses."

Response 3-5. Recent guidance from U.S. EPA (Davis et al., 2010) recommends using a benchmark response of 10 percent when dealing with dichotomous data from cancer bioassays performed with 50 animals per dose group.

Comment 3-6: "To calculate a slope factor, one would need a means for species extrapolation. EPA's Cancer Guidelines and the Agency guidance on the use of physiologically-based pharmacokinetic (PBPK) modeling in risk assessment indicate that a PBPK model is the preferred means of species extrapolation (EPA, 2005a, 2006). However, because the effects observed in mice are likely portal-of-entry effects (as discussed below), the current generation PBPK model for Cr(VI) developed by O'Flaherty et al. (2001) cannot be used because it does not include intestinal segmentation and therefore is structurally unable to address portal-of-entry effects in the intestinal epithelium. Instead, a next-generation PBPK model that extends the model of O'Flaherty et al. (2001) and incorporates the toxicokinetic features of polarity along the small intestine and partial reduction of ingested Cr(VI) while in the stomach is under development (Summit Toxicology, 2010). This report on this next-generation model is provided as Appendix D."

Response 3-6. The Cr VI cancer slope factor in the PHG document was calculated using the best data and methods available at this time, in accordance with the cancer risk assessment guidelines of the U.S. EPA (2005) and OEHHA (2009). OEHHA will consider the completed, next-generation PBPK model when it is published in final form in a peer-reviewed journal.

Comment 4-1: "As discussed in detail below, the Draft Dec. 2010 document relies on a single analysis of very uncertain epidemiological data from China (Zhang and Li, 1987, 1997; Beaumont et al., 2008) and supports this reliance with an equally uncertain animal study (Borneff et al., 1968). The use of these data was criticized by an expert panel convened by the University of California under contract to the California EPA (OEHHA, 2001b)."

Response 4-1. The PHG for Cr VI in drinking water is developed using a two-year bioassay performed in rats and mice (NTP, 2008), not the human study cited in this comment. The study by Borneff et al. (1968) is only discussed in the Appendix of the PHG document, and is not used to develop the PHG.

With regard to the two studies by Zhang and Li (1987; 1997), the 1997 report was retracted by the journal in which it was published. The Zhang and Li (1987) study was thoroughly analyzed (see Beaumont et al., 2008). Although the magnitude of the exposure to Cr VI in drinking water is unclear, the population did appear to be exposed to high levels of chromium VI. A statistically significant increase in stomach tumors was detected when compared to a nearby unexposed population. The high levels of chromium VI in the wells is what triggered the study (lower levels probably would have gone undetected). Lower levels of chromium VI may still cause cancer but at a rate that would have been undetected in a population of several thousand. Another recent reevaluation of the Zhang and Li (1987) study by Kerger et al. (2009) has been added to the PHG document.

Comment 4-2: "Five peer reviewers designated by the University of California, several public water agencies, other governmental agencies, and non-governmental institutions provided extensive comments on the Draft August 2009 PHG document. These comments have been largely unaddressed in the current document."

Response 4-2. All substantive comments by all these reviewers have been addressed in our "Responses to Major Comments" and the PHG document revised accordingly.

Comment 5-1: "Despite comments submitted by ACC and others in response to the Draft August 2009 PHG document, OEHHA does not consider MOA in the Draft Dec. 2010 PHG document."

Response 5-1 (repeat of Response 5). See the following sections of the PHG document for discussion of the MOA issues for which data are available: "Pharmacokinetics of Trivalent versus Hexavalent Chromium," "Mechanism of Genotoxicity and Carcinogenicity," "Examination of Evidence for Chromium Carcinogenicity," and "Risk Characterization."

Comment 5-2: "With regard to the MOA, OEHHA did not consider several key questions about the NTP study results, including:

1. Why did mice get tumors in the small intestine, but rats did not?
2. Why do fewer tumors occur in mice in distal parts of the small intestine (jejunum, ileum) than in the duodenum as a function of dose?
3. If Cr(VI) were acting as a mutagen, then why were no tumors present in the stomach or forestomach of either mice or rats; why not in multiple tissues?
4. Why were intestinal tumors only observed in animals experiencing prolonged hyperplasia of the intestinal epithelium?
5. Is there a no effect level (NOEL) for intestinal hyperplasia in the mouse?
6. Is there a dose at which Cr(VI) reduction in the stomach is sufficient to lower the dose to the intestinal epithelium such that key events in the carcinogenic MOA do not occur?
7. Are cancer observations in mice relevant to humans who are exposed at much lower levels?
8. And finally, what is the MOA in mice and is it relevant to humans?"

Response 5-2.

1. Interspecies differences in tumor location are not uncommon.
2. This finding is stated in the “Toxicological Effects in Animals,” subheading “Carcinogenicity,” subheading “Mouse,” subheading “Neoplasms” section of the PHG document. The biological basis for this finding is not known.
3. Ingested Cr VI is a multi-site carcinogen in rodents (NTP, 2008).
4. In discussing hyperplasia in NTP (2008), one should also address why there were tumors of the oral cavity in rats in the absence of hyperplasia. Both of these issues are discussed in the “Toxicological Effects in Humans,” subheading “Carcinogenicity,” subheading “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice” section of the PHG document. The intestinal epithelial hyperplasia observed in NTP (2008) was **not** cellular proliferation in response to tissue damage, as discussed in this section of the PHG document.
5. We do not know the answer to this question.
6. We do not know the answer to this question.
7. Observations in mice are relevant to humans and this is one of the basic principles of animal testing. OEHHA and other regulatory agencies have established a method for low dose extrapolation. Experiments at lower doses in animals are not feasible due to the much larger numbers of animals needed to detect an effect.
8. See the section of the PHG document entitled “Examination of Evidence for Chromium Carcinogenicity” for a discussion of the evidence for Cr VI carcinogenicity in animals and humans, including aspects of its MOA.

Comment 5-3: “The results of the research will be reported at the March 2011 Society of Toxicology Conference, and manuscripts for peer review and publications are expected to be complete by June 2011. By not considering the results of the Cr(VI) MOA Framework Research Program, OEHHA has taken a position that is inconsistent with its own mission and stated requirements to use the best available science in public health determinations.”

Response 5-3. Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. OEHHA acknowledges that new studies may alter a revised PHG.

From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comment 5-4: “The risk analyses conducted in the Draft Dec. 2010 PHG document assume that humans and mice are equally susceptible, even though mice and rats are not equally susceptible. The findings in NTP (2008) indicate the need for a careful deliberative consideration of MOA rather than simply choosing the most sensitive response upon which to base a toxicity criterion.”

Response 5-4. The PHG document does not assume that humans and mice are equally susceptible to ingested Cr VI. Choosing data from the most sensitive species for dose-response modeling when adequate human data are not available does not imply that the two species are equally sensitive. We assume that humans are at least as sensitive as the most sensitive species to be health protective. This conforms to standard risk assessment practice used by both the U.S. EPA (2005) and OEHHA (2009). Further, the inhalation risk estimates in humans versus the oral potency in animals indicates that Cr VI was approximately 1000 times more potent in humans by the inhalation route compared to the animal potency from the drinking water studies.

Comment 5-5: “Because the effects of ingested Cr(VI) observed in rats and mice in NTP (2008) are portal-of-entry effects, the use of allometric scaling (e.g., $BW^{0.25}$) is not an appropriate method for species extrapolation.”

Response 5-5. Given the inadequate toxicokinetic data for ingested Cr VI in mice and humans, allometric scaling has been judged to be an appropriate method for extrapolating dose between the two species (Stern, 2010; U.S. EPA, 2010; OEHHA, this PHG document).

Comment 5-6: “The Draft Dec. 2010 PHG document provides a lengthy discussion of reduction by saliva and gastric fluids and the effect of this reduction on absorption and subsequent tissue concentrations of chromium (pp. 9-12). However, OEHHA has not carefully examined tissue levels in the study used as the basis of OEHHA’s cancer slope factor. NTP (2008) provides tissue chromium concentrations in both male rats and female mice in the forestomach, glandular stomach and liver (Appendix J in NTP, 2008).”

Response 5-6. The chromium tissue levels from NTP (2008) are presented in Figures A3 to A6 and discussed in Appendix A of the PHG document.

Comment 5-7: “On page 72 of the Draft Dec. 2010 PHG document, OEHHA states that Cr(VI) is genotoxic both in vivo and in vitro. It would be more correct, however, to state that Cr(VI) is DNA-reactive both in vivo and in vitro.”

Response 5-7. The “Genetic Toxicity” section of the PHG document discusses a number of studies where Cr VI was genotoxic following administration to animals (Table 2). The first paragraph of that section cites review articles that themselves cite a large number of studies showing that Cr VI is genotoxic in cultured mammalian cells and bacteria.

Comment 5-8: “The papers cited above show evidence of DNA-reactivity but not necessarily genotoxicity and definitely not mutagenicity. Neither DNA-reactivity nor genotoxicity can be equated with mutagenicity. As peer reviewer Prof. Toby Rossman comments on page 2 of his 2009 review, ‘DNA damage per se does not inform us about eventual heritable change (i.e., a mutation), which is the true issue.’ Prof. Rossman went on to say ‘the description of an agent as ‘genotoxic carcinogen’ is out of date. What we really need to know is whether an agent has a mutagenic mode of action (MOA).’ ‘Genotoxicity’ is not a specific finding, and the term ‘DNA-reactivity’ should be used instead. More importantly, OEHHA must make a determination that Cr(VI) has a mutagenic MOA to justify the use of linear extrapolation from the point of departure to zero.”

Response 5-8. Genotoxicity has been and continues to be an important concept in toxicology and risk assessment. As illustrated in Table 2 of the PHG document, ingested Cr VI was genotoxic in short-term tests performed in vivo. As demonstrated by the review articles cited in the first paragraph of the “Genetic Toxicity” section of the PHG document, Cr VI was also mutagenic in bacteria, cultured mammalian cells, *D. melanogaster* and mice.

Comment 5-9: “Assuming that Cr(VI) acts by a mutagenic MOA ignores the existence of repair mechanisms, the production of reactive oxygen species (ROS) from reduction of Cr(VI), and resulting alterations in control of the cell cycle and apoptosis. Peer reviewer Prof. Elizabeth Snow in her 2009 comments remarks: “a low dose, linear response (based on mutagenicity) also assumes a lack of DNA repair and other protective mechanisms with an expected maximum protective effect at low dose (cf. comment #4 on p. 3).”

Response 5-9. A linear cancer response at low dose levels is consistent with DNA repair. Consider radiation induced carcinogenesis, the best data set we have covering cancer induction by low dose levels of any genotoxic carcinogen (radiation-induced cancer in human A-bomb survivors). The cancer incidence responds linearly at low doses of radiation despite the well-characterized ability of mammalian cells to repair potentially lethal DNA damage (PLD repair).

Comment 5-10: “It is clear the tumor development [in NTP (2008)] is related to local inflammation and hyperplasia in the target tissue...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.”

Response 5-10. The non-neoplastic findings of NTP (2008) are presented in Table 7 of the PHG document. The discussion accompanying Table 7 stresses that tissue damage was not observed. Also, inflammation was not observed in the tissue where tumors developed. Thus, it is incorrect to conclude that the cellular changes listed in Comment 5-10 are required for tumor induction.

Comment 5-11: “The NTP drinking water studies provide strong evidence that epithelial proliferation is likely to be an early and necessary key event underlying Cr(VI)-induced carcinogenesis of the mouse small intestine (NTP, 2007, 2008). These bioassay results also provide evidence for the temporal sequencing of subsequent key events. If Cr(VI) were acting by a mutagenic MOA, the early hyperplasia, evident by 90 days, should result in a short time-to-tumor. However, the time-to-tumor formation was extended (>451 days), and treatment did not affect survival (i.e., animals were not dying as would be expected if tumors developed early in life) in the NTP drinking water study.”

Response 5-11. Hyperplasia was not observed in the rat oral cavity (NTP, 2008) suggesting that a non-genotoxic MOA is unlikely. Given the propensity of some carcinogens to act as both initiators and promoters, we believe it is premature to conclude that the diffuse hyperplasia observed in the duodenum of mice in NTP (2008) is the initiating event in the MOA of Cr VI, rather than a promoting event for cells already initiated via a genotoxic alteration.

Comment 5-12: “The temporal progression of responses observed in the NTP bioassays indicates that histiocytic infiltration occurs in mice by 90 days; hyperplasia occurs in mice at both non-tumorigenic and tumorigenic doses by 90 days; and tumors occur at two years at doses above 1 mg/kg/d, corresponding to a concentration of 28.6 mg/L in drinking water (NTP, 2007, 2008). These data indicate a multi-step progression that is more consistent with the rarity of these tumors and their long latency. Hence, the implicit assumption of a mutagenic MOA is unfounded. Indeed, data from the same study upon which the draft PHG is based contradict this assumption. For these reasons, the choice of linear low dose extrapolation cannot be supported.”

Response 5-12. The PHG document’s section “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice” presents the inconsistencies that accompany the hypothesis that histiocytic infiltration and hyperplasia are required for tumor induction by Cr VI. The finding that these two endpoints were observed at 90 days in some tissue is not sufficient for a determination that a threshold MOA is operative. OEHHA did not assume a genotoxic MOA. Rather, the data presented in the PHG are consistent with a genotoxic or mutagenic MOA and do not support an alternative MOA. See also Response 5-10 for a discussion of why inflammation and tissue damage are unlikely to be key events in tumor induction by Cr VI, and Response 5-11 for a discussion of why the observed hyperplasia is also not likely to be an initiating event.

Comment 5-13: “Had OEHHA considered MOA, or had MOA been the overarching principle of the Cr(VI) PHG risk assessment, as suggested in EPA’s Cancer Guidelines (EPA, 2005a), then the idea of nonlinearity and the possibility of a threshold might have received proper consideration. OEHHA should fully discuss its rationale for choosing a linear approach over a non-linear approach by fully demonstrating both to just its choice.”

Response 5-13. The MOA for tumor induction by ingested Cr VI is discussed in detail in the following sections of the PHG document: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” Table 7 in the section entitled “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.” To more fully respond to Comment 5-13 we have added the following statement in two of these sections, “Therefore, an MOA other than that of genotoxicity or mutagenicity is not supported by these findings. The standard approach for carcinogens operating via a genotoxic or mutagenic MOA is to apply a linearized multistage model to calculate the cancer potency (U.S. EPA, 2005, 2010; OEHHA, 2009).”

Comment 5-14: “The default assumption of linearity has also been questioned in reviews of the Draft August 2009 PHG for Cr(VI).”

Response 5-14. OEHHA did not assume linearity. The linear approach was chosen based on the positive findings for genotoxicity by Cr VI and the inconsistent data in support of any alternative mechanism.

Comment 5-15: “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.”

Response 5-15. See Response 5-14 above.

Comment 5-16: “The Draft Dec. 2010 PHG document dismisses Bednar and Kies (1991) because the analysis was for total chromium and the sampling occurred for two years only. Nonetheless, Dr. Bjeldanes is correct that Bednar and Kies (1991) could provide a rough estimate of a no effect level in humans as a means to ‘groundtruth’ the PHG value.”

Response 5-16. The PHG document discusses a number of limitations of the Bednar and Kies (1991) study including that sampling in the study occurred for only two years. Unlike the Zhang and Li (1987) study, no specific source of Cr VI exposure was

identified. Also, while overall cancer mortality rates were evaluated, tumors at specific sites were not.

Comment 5-17: “Prof. Elizabeth Snow comments on the use of the 2007 NTP data saying that ‘a linear fit to the NTP data is the default protocol as defined by the U.S. EPA and OEHHA and that the data could equally well be fitted to a nonlinear, supralinear (concave) or ‘hockey stick’ response model (cf. p. 3).’ She further states that ‘based on this study (NTP, 2007), along with very limited evidence for tumor response at the lower levels of Cr6, there is very limited evidence for a linear dose response (cf. p. 3).”

Response 5-17. This is the case with most carcinogens. Dose-response data are not available in the low dose region where human exposures are expected. Under these circumstances, where data support a genotoxic/mutagenic MOA but do not provide substantial support for an alternative MOA, use of a linear model is recommended by both U.S. EPA (2005) and OEHHA (2009).

Comment 5-18: “The 2009 peer review comments of Prof. Mitchell Cohen are even more explicit ‘it is clear that the data presented in the Draft (PHG) document shows that the tumor formation in the mice (NTP data) as a function of Cr⁶⁺ [Cr(VI)] level in drinking water is not linear (cf. p. 6). Unfortunately, OEHHA decided to remove Figure 13 from the 2010 revised PHG. This figure would have allowed the reader to visualize the actual shape of the dose-response curves for both male and female mice in the NTP studies.”

Response 5-18. The absence of statistically significant increases in tumors at the two lowest drinking water concentrations should not be interpreted as a threshold (i.e., nonlinear response) for tumorigenicity, since the number of animals may have been too low to detect tumors at the two lowest drinking water concentrations. The use of high doses in cancer bioassays is by design to offset the statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors). The mouse tumor incidence data for NTP (2008) are presented in Tables 5 and 6 of the PHG document. Therefore, the Figure 13 cited in this comment was thought to be unnecessary and was not included in the final PHG document.

Comment 5-19: “One study that was not considered in the Draft August 2010 PHG document was Armienta-Hernandez and Rodriguez-Castillo (1995).”

Response 5-19. This study is not included in Table 8 of the PHG document because it is not an epidemiological study of cancer. However, a paragraph has been added to the PHG document about the 1995 study. Please see Response 6-1 below.

Comment 5-20: “OEHHA also did not consider the population of Hinkley, California, a small desert town in San Bernadino county.”

Response 5-20. A paragraph describing the March 2011 report on rates of all cancers combined in Hinkley, California (Morgan 2011) along with the paper by Fryzek et al. (2001) are discussed in the “Toxicological Effects in Humans,” subheading “Carcinogenicity” section of the PHG document.

Comment 5-21: “Consideration of the MOA of Cr(VI) tumorigenesis using mechanistic knowledge of *H. pylori* infection in humans would likely enable the understanding of why Armienta-Hernandez and Rodriguez-Castillo (1995) observed a NOEL orders of magnitude higher than the proposed PHG value.”

Response 5-21. The cited study did not report data for cancers of the GI tract.

Comment 6-1. “One study that was not considered in the Draft August 2010 {sic} PHG document was Armienta-Hernandez and Rodriguez-Castillo (1995) ... {in which} no adverse health effects, including cancer, were observed.”

Response 6-1. Armienta-Hernandez and Rodriguez-Castillo (1995) was not an epidemiologic study of cancer. For example, the Methods section of the article contains no methods related to health effects. The study was helpful, however, with respect to the possibility of self-limited exposure at high concentrations. The investigators reported that residents near a chromate production facility did not want to consume water with Cr VI concentrations above 0.5 mg/L because of its yellowish color. OEHHA has added a paragraph to the PHG document about this study.

Comment 6-2. “OEHHA also did not consider the population of Hinkley, California... Dr. John Morgan examined cancer rates...The rate for all cancers was not elevated in Hinkley.”

Response 6-2. OEHHA has added a paragraph to the PHG about the Morgan (2011) cancer incidence rate study. The paragraph notes that fewer cases of all types of cancer occurred (196) than were expected (224.2) and that results were not presented for specific types of cancer.

Comment 7-1: “With regard to inhalation exposure from showering, there is a mismatch between the exposures used to develop the inhalation slope factor and showering. The inhalation slope factor was derived for a chromate processing facility. A domestic shower with a temperature of 38°C is not a reasonable target of extrapolation from metal fumes generated at temperatures over 1000°C. This issue was also raised by Dr. David Berry in his comments on an early draft of the Draft August 2009 PHG document. OEHHA should respond to Dr. Berry’s comments and provide the justification for its application of an industrial inhalation slope factor to residential exposures.”

Response 7-1. Classification of Cr VI by OEHHA, U.S. EPA, ATSDR and IARC as an inhalation carcinogen does not specify nor differentiate between the possible airborne forms (particulate, mist or vapor). The inhalation cancer potency estimate is based on measured levels of chromium in air in the relevant studies. The OEHHA estimate of

potential exposure to Cr VI in air from domestic tap water was based on a study by Keating and McKone (1993) that showed that droplet production in showering was highly variable, depending on the shower head type; the shower head used by Paustenbach et al. (2003) was apparently one of the lower droplet-production types. This has no effect on the proposed PHG because the inhalation exposure from showering is so small (less than one percent of the total).

Comment 8-1: “In the very last paragraph on page 96 of the August 2009 draft PHG document, under the subheading ‘Risk Characterization,’ OEHHA states ‘[t]here are many sources of uncertainty in the calculation of the proposed PHG.’ This statement is the only discussion of uncertainty. No further discussion of the sources of uncertainty and how they might impact the calculation of the PHG is provided. Risk managers cannot determine the level of uncertainty in the PHG. The sentence that follows the one quoted above reads: ‘The NTP carcinogenicity studies provide robust data for the assessment of oral cancer risk attributed to Cr VI (cf. p. 96).’ This is an accurate statement; yet, OEHHA deleted seven of the eight dose-response analyses it conducted using the NTP data set, the results of which were shown in Tables 10 and 11 of the Draft August 2009 PHG. In addition, OEHHA did not choose the most appropriate model based on EPA guidance (EPA, 2000, 2005a). OEHHA should fully document and provide the justification for deleting data and selecting a model that does not provide the best fit the data and violates the EPA guidance.”

Response 8-1. As stated in the “Dose-Response Assessment,” subheading “Carcinogenic Effects,” subheading “Dose-Response Modeling” section of the PHG document, the multistage model was used to model the tumor incidence data because this is the model preferred by OEHHA (2009) and U.S. EPA (2010) for conducting cancer dose-response assessments unless the data suggest otherwise. This is primarily due to the multistage model’s generally good fit of the data in the relatively high dose range used in rodent bioassays (Armitage and Doll, 1961). This is the reason the other seven models are no longer presented in the PHG document. Modeling the data according to eight different formulas is not an uncertainty analysis. It should be noted that recent EPA guidance, for situations in which different BMD models of adequate fit yield different BMDLs, is to choose the lowest BMDL, not necessarily the model that provides the best fit (Davis et al., 2010).

Comment 8-2: “There is no discussion of the uncertainty in water consumption rates or that these revised water consumption rates would likely produce an overly health-protective PHG value even if the ASFs were not used. In addition, the calculation of age-specific drinking water rates presented in the Jan. 25, 2011, corrections appear incorrect. OEHHA should clarify the rationale for this choice of drinking water rates and provide details of how they were calculated...The Draft Dec. 2010 PHG document does not make clear whether the water ingested consists of all water or tap water.”

Response 8-2. The **per capita** drinking water values from Kahn and Stralka (2009) were mistakenly used in the previous draft PHG document. Instead, the **consumers only** drinking water values from the same publication have been used to revise the

PHG document. This resulted in the same final PHG value of 0.02 ppb (rounded). The protocol OEHHA followed to calculate the time-weighted mean drinking water ingestion rates using the data from Kahn and Stralka (2009) and U.S. EPA (2008) is now given in the “Calculation Of The PHG” section of the document. We have added to the “Calculation Of The PHG” section of the document that the water intake data cover pure water consumed as a beverage or used in the home or local establishments to prepare food or drink (Kahn and Stralka, 2009).

Comment 8-3: “Several peer reviewers commented on the absence of analyses of the data that would show a range of results that better reflect the uncertainty and inconsistency in the shape of the dose-response curves in rats and mice. OEHHA has not responded to these comments and should do so prior to making any final decision related to its draft PHG.”

Response 8-3 (repeat of Response 3-4). The PHG document develops two health-protective concentrations for Cr VI in drinking water; one to protect against non-carcinogenic effects and one to protect against carcinogenic effects. The lower concentration is designated the PHG to be protective against all adverse health effects. OEHHA does not develop a range of PHG values. Such an approach was considered when the PHG program was established and judged not to be helpful, given that the purpose of the PHG is to provide guidance to the Department of Public Health in setting regulatory drinking water standards. Modeling the dose-response data using a variety of different models, as suggested in the comment, is not an uncertainty analysis. As stated in the “Dose-Response Assessment,” subheading “Carcinogenic Effects,” subheading “Dose-Response Modeling” section of the PHG document, the multistage model was used to model the tumor incidence data because this is the model preferred by OEHHA (2009) and U.S. EPA (2010) for conducting cancer dose-response assessments. This is primarily due to the multistage model’s generally good fit of the data in the relatively high dose range used in rodent bioassays (Armitage and Doll, 1961).

Conclusions: All conclusions, except the one shown below, are recapitulations of points raised earlier.

Comment 10-2: “The documents lacks consideration of the ubiquitous and widespread presence of Cr(VI) in both groundwater and drinking water supplies. To date, no human cancers or other adverse health effects have been attributed to natural background levels of Cr(VI) in drinking water.”

Response 10-2. It is doubtful that any study has ever attempted to measure the fraction of human cancers attributable to background levels of Cr VI, since this is probably logistically impossible.

Comments from Michael Rogge and Janet Kester, Ph.D, D.A.B.T., California Manufacturers & Technology Association

Transmittal Letter

Comment TL-1: “Because the vast majority of chrome 6 in groundwater in California is naturally occurring, adoption of the proposed PHG at 0.02 ppb will likely compel drinking water rate payers to fund the high costs of construction and operation of a new treatment technology and the purchase of expensive alternative drinking water supplies...However, when one considers the cumulative effect of the various PHGs recently adopted or proposed by OEHHA, including the proposed PHG for chrome 6, as well as a number of additional pending PHGs, it is reasonable to expect substantial additional future reductions in water allocations to agricultural operations, new residential and business development projects, and potentially, to future environmental restoration and management projects.”

Response TL-1. The PHG is a non-regulatory guideline that the Department of Public Health (DPH) uses to set regulatory drinking water standards. DPH can consider the kinds of economic impacts cited by the commenter when setting drinking water standards. State law prohibits OEHHA from considering economic factors when developing PHGs.

Comment TL-2: “Numerous external scientific peer reviewers, including Cal/EPA’s Department of Toxic Substances Control and members of the public, have criticized OEHHA for its failure to comprehensively evaluate the applicability of alternative MOAs as a basis for identification of the MOA most pertinent to test animals and its extrapolation to humans at relevant doses.”

Response TL-2. The mechanism by which ingested Cr VI causes cancer in animals and humans is discussed in a number of places in the PHG document. The acronym MOA has been added to the document to help readers locate these discussions. The sections with concentrated discussions of mechanisms are: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” Table 7 and the section entitled “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.” The DTSC comments were contained in an internal memorandum, not a formal scientific peer review.

Comment TL-3: “This issue is the subject of the Hexavalent Chromium Mode of Action Research Project (the Research Project), a multi-year research project being undertaken by a select group of scientists with substantial expertise in risk assessment, toxicology and other appropriate scientific specialties...The overall goal of the Research Project is to provide critical information to address gaps inherent in the scientific database used to support the assessment of human health risks posed by oral exposures to chrome 6. Although highly germane to the proposed PHG for chrome 6 in California, OEHHA’s current schedule for adoption of a final PHG does not appear to allow the time necessary for consideration of the imminent release of the scientific data that will be generated in the MOA study noted above.”

Response TL-3. Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Specific Comments

Comment 1: “In particular, OEHHA should provide a detailed evaluation of the oral carcinogenic MOA for Cr(VI) and human relevance of the National Toxicology Program (NTP) two-year bioassay data (NTP 2008) used as the basis for oral cancer potency factor development.”

Response 1. The mechanism by which ingested Cr VI causes cancer in animals and humans is discussed in a number of places in the PHG document. The acronym MOA has been added to the document to help readers locate these discussions. The sections with concentrated discussions of mechanisms are: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” Table 7 and the section entitled “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.”

Comment 2: “A Cr(VI) MOA Research Project designed in accordance with current EPA guidance to elucidate critical questions and data gaps inherent in the existing data base concerning the nature and sequence of key events in oral Cr(VI) carcinogenesis is currently underway...OEHHA should use the soon-to-be published results of the Cr(VI) MOA Research Project to fill data gaps in the MOA and inform extrapolation across doses and species using refined physiologically-based pharmacokinetic (PBPK) models for mice, rats, and humans.”

Response 2. OEHHA will review papers and material relating to this study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comment 3: “Using BMD analysis of the same NTP data set (chronic inflammation of the liver in female rats), the Agency for Toxic Substances and Disease Control calculated a Minimal Risk Level for Cr(VI) (0.001 mg/kg-day) that is five times higher than the Health Protective Dose (HPD) developed by OEHHA for the non-cancer PHG (0.0002 mg/kg-day) (ATSDR 2008).”

Response 3. At present the Cr VI PHG based on cancer effects is 100-fold lower than if it were based on non-cancer effects (see “Calculation Of The PHG” section of the document). OEHHA will be applying the BMD approach in future analyses of the non-cancer data. Our preliminary analysis applying the BMD approach to the non-cancer data followed by an uncertainty factor of 100 yields a final value that is more than 100-fold **higher** than the proposed PHG based on cancer effects. Thus, the proposed PHG (0.02 ppb) for protecting against both cancer and non-cancer effects would not change.

Comment 4: “Further, the derivation of the non-cancer PHG did not adequately consider questions, highlighted by the NTP, about the biological significance of non-neoplastic 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.”

Response 4. The PHG document now contains additional discussion of the liver changes observed in female rats in NTP (2008). See section “Toxicological Effects in Animals,” subheading “Chronic Toxicity,” subheading NTP, 2008. It is true that liver changes were observed in treated females and in aged, control animals. However, when a concurrent control population is available, as was the case here, OEHHA would not discount an effect that was significant relative to the concurrent control, even if the values fell within the historical control range.

Comment 5: “The literature review performed by OEHHA is incomplete, and in some cases misquotes or misrepresents the results of key studies. Of particular concern is the discussion of epidemiological evidence for cancer of the gastrointestinal (GI) tract.”

Response 5. OEHHA has attempted to include all studies in the PHG document containing data that are important for development of the PHG for Cr VI. Additional epidemiological studies have been added since the December 2010 draft PHG document. Misquotes and misrepresentations should be specified so that they can be corrected.

Comment 6: “OEHHA should include a quantitative uncertainty analysis along with an expanded qualitative uncertainty analysis. This should include OEHHA’s rationale for making specific science policy choices, including the scientific support for alternatives, and evaluation of their quantitative impact on the PHG calculation.”

Response 6. OEHHA is not aware of an established methodology for quantifying the uncertainty associated with cancer risk extrapolation.

Comment 7: “95th percentile drinking water intake rates are overly conservative and insufficiently documented. These intake rates are based on self-reported rather than measured body weights (Kahn and Stralka 2009), and the sample sizes for young

infants, who have the highest estimated daily water intake rates of all age groups, did not meet minimum reporting requirements, rendering the 95th percentile artificially high. Moreover, the intake rates for infancy and childhood age groups (0.114 and 0.041 L/kg-day) could not be verified based on the references provided. Based on these shortcomings, OEHHA should replace the water consumption values used in the 2010 draft with more appropriate (and transparently derived) values.”

Response 7. The methodology for calculating water consumption rates using the data from U.S. EPA (2008) and Kahn and Stralka (2009) is now presented in the footnote to Table 17 and in the discussion of Table 18 in the PHG document. In the previous draft of the PHG document the **per capita** water consumption rates were mistakenly used. The revised PHG document uses the **consumers only** rates. The final PHG value of 0.02 ppb (rounded) was unaffected. The drinking water consumption rates reported by Kahn and Stralka (2009) are the same values recommended by U.S. EPA (2008) for use in human health risk assessments. They came out of the largest survey of its kind: the United States Department of Agriculture’s (USDA’s) 1994-1996 and 1998 Continuing Survey of Food Intake by Individuals (CSFII). With regard to the 95th percentile drinking water rate being overly conservative, OEHHA has traditionally sought to protect this large fraction of the at risk population.

Comment 8: “Application of generic sensitivity factors (ASFs) is inappropriate for Cr(VI) and insufficiently documented. Whereas EPA has determined that children may be more susceptible than adults to carcinogens known to act via a mutagenic MOA (EPA 2005b), OEHHA’s new policy will be applied to all carcinogens, regardless of the theorized MOA (OEHHA 2009c).”

Response 8. The Age Sensitivity Factor (ASF) for modifying cancer potency was used as described (OEHHA, 2009). This approach applies to all carcinogens, regardless of purported mechanism of action, unless chemical-specific data exist that could be used to make more specific adjustments to risk. Such chemical-specific data are not available for Cr VI.

Comment 9: “Regardless of MOA, there is no basis for applying ASFs in the particular case of oral exposure to Cr(VI), because it causes tumors only at the portal of entry at extremely high doses, and as noted by OEHHA, ‘little...would be expected to get to the conceptus because of all the reduction in the intervening maternal organs’ (OEHHA 2010, page 128).”

Response 9. First, application of an ASF to infants and children is not counter-indicated by a “portal of entry” MOA (OEHHA, 2009). Second, chromium accumulation in a number of tissues indicates that the hexavalent form enters the body and becomes distributed systemically (see “Distribution” section and Appendix A of the PHG document). Thus, it is premature to conclude that Cr VI does not reach the conceptus. The quoted text from Appendix B of the PHG document has been revised accordingly.

Comment 10: “The multifaceted Cr(VI) MOA Research Project is designed to directly address critical questions and data gaps concerning the MOA of Cr(VI) administered via drinking water...Considering the imminent availability and direct relevance of Cr(VI) MOA Research Project studies for elucidating the carcinogenic MOA of orally administered Cr(VI), CMTA emphatically reiterates the opinion, also expressed by

DTSC in its review of a previous draft, that OEHHA should suspend finalization of the Cr(VI) PHGs for both carcinogenic and non-carcinogenic effects until it has thoroughly reviewed these data and incorporated them into its quantitative analyses.”

Response 10. OEHHA acknowledges that new research is on-going and looks forward to the new data when available for consideration. The Safe Drinking Water Act of 1996, amended 1999 (Health and Safety Code [H&SC], Section 116365) contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. When new research data become available, OEHHA will consider them in the development of a revised PHG for hexavalent chromium. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Comment 11: “EPA currently uses a body weight-normalized drinking water intake rate of 0.032 L/kg-day for calculating Regional Screening Levels for tap water based on carcinogenic effects, assuming residential exposure from birth through age 30 (EPA 2010). This value corresponds to approximately the 88th percentile of ‘all ages’ intake by the U.S. population. In the 2010 draft PHG, OEHHA departed from this current regulatory practice by using 95th percentile age-specific body weight-normalized drinking water intake rates for (1) the third trimester of pregnancy, (2) infancy (0-2 years), childhood (2-16 years), and adulthood (16-70 years), based on an unpublished 2010 OEHHA guidance document...The values used by OEHHA are therefore not only overly conservative (as a result of using the 95th percentile versus the already conservative 85th – 88th percentiles), but their validity is also questionable. Based on these shortcomings, the water consumption values used in the 2010 draft should be replaced with more appropriate (and transparently derived) values.”

Response 11 (repeat of Response 7). The methodology for calculating water consumption rates using the data from U.S. EPA (2008) and Kahn and Stralka (2009) is now presented in the footnote to Table 17 and in the discussion of Table 18 in the PHG document. In the Announcement of Non-substantive Reference Change for the December 31, 2010 Draft Chromium VI PHG Document the **per capita** water consumption rates were mistakenly used. The final PHG document uses the **consumers only** rates. The final PHG value of 0.02 ppb (rounded) was unaffected. The drinking water consumption rates (Kahn and Stralka, 2009) utilized in the PHG

document are the same values recommended by U.S. EPA (2008) for use in human health risk assessments. They came out of the largest survey of its kind: the United States Department of Agriculture's (USDA's) 1994-1996 and 1998 Continuing Survey of Food Intake by Individuals (CSFII). With regard to the 95th percentile drinking water rate being overly conservative, OEHHA has traditionally sought to protect this large fraction of the at risk population.

Comment 12: "In contrast with EPA guidance, OEHHA's new policy '...will be applied to all carcinogens, regardless of the theorized mode of action' (OEHHA 2009, page 51). Also unlike EPA, OEHHA included the third trimester of pregnancy as a 10-fold more sensitive life stage. This significant deviation from current EPA guidance and policy, and the significant extrapolation beyond the existing database that it constitutes, warrants careful examination by the scientific community. Although OEHHA's document provides general information about the methodology used, detail is insufficient to allow thorough review. None of the studies examined involved Cr(VI), nor did they include carcinogenesis occurring at the portal of entry."

Response 12. Both OEHHA and U.S. EPA have found it to be scientifically necessary to apply age susceptibility factors (ASFs) to account for potential early-in-life increased susceptibility to Cr VI (OEHHA, "Correction for Early-in-Life Exposures" section of this PHG document; U.S. EPA, 2010). It is correct that the PHG document for Cr VI, unlike U.S. EPA (2010), includes a ten-fold ASF for calculating the fraction of the lifetime cancer risk due to exposure to Cr VI during the third trimester. The detailed rationale for correcting for exposure during the third trimester is presented in OEHHA (2008), available as Appendix J online at http://www.oehha.ca.gov/air/hot_spots/tsd052909.html. Note that in the final PHG document, exposure to Cr VI during the third trimester contributed only one percent of the total lifetime risk of cancer due to Cr VI in drinking water. Thus, if the third trimester were excluded from the lifetime cancer calculation, the final PHG value of 0.02 ppb (rounded) would not change. It is also correct that Cr VI was not one of the carcinogens analyzed for age-related increased susceptibility (OEHHA, 2008). The reason was the insufficiency of the database for Cr VI. Lastly, a "portal of entry" mode of action does not preclude increased susceptibility in infants and children.

Comment 13: "It is especially noteworthy that OEHHA's application of ASFs to Cr(VI) is not supported by the only relevant data currently available, the Borneff et al. (1968) multigenerational study, and conflicts with its own discussion of this issue in Appendix B of the 2010 draft PHG document (OEHHA 2010, page 128):

'The Borneff study used a multigenerational protocol, which resulted in two generations exposed in utero and during weaning (F1 and F2) and one generation that was not (F0)...For Cr VI, perinatal exposure would not be expected to make much of a difference because of the reducing ability of the dam's stomach, blood and the placenta. Little Cr VI would be expected to get to the conceptus because of all the reduction in the intervening maternal organs.'"

Response 13. Chromium accumulation in a number of tissues indicates that the hexavalent form enters the body and becomes distributed systemically (see "Distribution" section and Appendix A of the PHG document). Thus, it is premature to

conclude that Cr VI does not reach the conceptus. The quoted text from Appendix B of the PHG document has been revised accordingly.

Comment 14: “OEHHA’s new policy of applying ASFs to all carcinogens regardless of MOA should be thoroughly explicated and peer-reviewed before it is used in risk assessments. Because OEHHA has not identified a mutagenic (or any) MOA for Cr(VI), its application of ASFs to Cr(VI) is inconsistent with current EPA guidance. Regardless of MOA, there is no basis for applying ASFs in the particular case of oral exposure to Cr(VI), because it causes tumors only at the portal of entry at extremely high doses, and “little... would be expected to get to the conceptus because of all the reduction in the intervening maternal organs” (OEHHA 2010).”

Response 14. The Age Sensitivity Factor (ASF) for modifying cancer potency was used as described (OEHHA, 2009). This approach applies to all carcinogens, regardless of purported mechanism of action, unless chemical-specific data exist that could be used to make more specific adjustments to risk. Such chemical-specific data are not available for Cr VI. Application of an ASF to infants and children is not counter-indicated by a “portal of entry” MOA (OEHHA, 2009). In addition, chromium accumulation in a number of tissues indicates that the hexavalent form enters the body and becomes distributed systemically (see “Distribution” section and Appendix A of the PHG document). Thus, it is premature to conclude that Cr VI does not reach the conceptus. The text that was quoted in Comment 13 above has been revised accordingly.

Both OEHHA and U.S. EPA have found it to be scientifically necessary to apply age susceptibility factors (ASFs) to account for potential early-in-life increased susceptibility to Cr VI (OEHHA, “Correction for Early-in-Life Exposures” section of this PHG document; U.S. EPA, 2010). It is correct that the PHG document for Cr VI, unlike U.S. EPA (2010), includes a ten-fold ASF for calculating the fraction of the lifetime cancer risk due to exposure to Cr VI during the third trimester. The detailed rationale for correcting for exposure during the third trimester is presented in OEHHA (2008), available as Appendix J online at http://www.oehha.ca.gov/air/hot_spots/tsd052909.html. Note that in the final PHG document, exposure to Cr VI during the third trimester contributed only one percent of the total lifetime risk of cancer due to Cr VI in drinking water. Thus, if the third trimester were excluded from the lifetime cancer calculation, the final PHG value of 0.02 ppb (rounded) would not change. It is also correct that Cr VI was not one of the carcinogens analyzed for age-related increased susceptibility (OEHHA, 2008). The reason was the insufficiency of the database for Cr VI.

Comment 15: “In view of the inherent shortcomings of the NTP two-year bioassay protocol, it must be recognized that “clear evidence of carcinogenicity” from long-term exposure to extremely high concentrations of Cr(VI) does not constitute proof that humans exposed to much lower concentrations are at increased risk.”

Response 15. Two-year bioassays in rodents, traditionally performed at high dose levels, have been used for many years to estimate cancer risks to humans. The scientific justification for this has been discussed previously (U.S. EPA, 2005; OEHHA, 2009).

Comment 16: “As mentioned previously, OEHHA did not provide coherent evaluations of (1) animal MOA, and (2) human relevance to support its selection of an LNT low-dose extrapolation method in the 2009 or 2010 drafts, notwithstanding extensive criticism of previous drafts by DTSC, peer reviewers, and members of the public. Indeed, the term “mode of action” does not appear anywhere in the text, and EPA’s 2005 Carcinogen Risk Assessment Guidance was not cited in the context of MOA, although OEHHA purportedly adhered to this guidance.”

Response 16. Discussion has been added to the following sections of the PHG document concerning the MOA data that support the use of a low dose linear extrapolation to calculate cancer potency: “Mechanism of Genotoxicity and Carcinogenicity” (large number of studies demonstrating a genotoxic, and possibly mutagenic, MOA for Cr VI); “Toxicological Effects in Animals,” subheading “Carcinogenicity,” subheading “Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice” (that the tissue and cellular findings shown in Table 7 do not support an alternative MOA for tumor induction by Cr VI). The acronym MOA has been added to the document to help readers locate these discussions. The sections with concentrated discussions of mechanisms are: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” Table 7 and the section entitled “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.”

Comment 17: “Dr. Bjeldanes commented,

‘The proposed PHG for Cr(VI), which is fully six orders of magnitude lower than the active concentrations in mice, is well below current safety standards, appears to be lower than levels in uncontaminated waters, is near the limits of detection with currently available analytical methods, and apparently does not consider the likelihood of a threshold for Cr(VI) biological activity, requires further justification.’

OEHHA’s response to Dr. Bjeldanes was, ‘for this risk assessment, OEHHA has followed the most recent carcinogen guidelines of the U.S. EPA (2005) and OEHHA’s own principles (OEHHA, 2005). Basically, if there is evidence that an agent acts through a genotoxic mechanism (as there is for Cr VI), no threshold for effect is assumed’ (OEHHA 2009b, page 9). This interpretation of current scientific thought and EPA and international guidance is clearly out of date and incorrect.”

Response 17. The OEHHA quotation cited here by the CMTA is incomplete. OEHHA’s response to Dr. Bjeldanes went on two sentences later to say, ‘An inability to absorb Cr VI could be considered a pharmacokinetic threshold (independent of genotoxicity considerations). However, all the available pharmacokinetic studies indicate that a portion of the Cr VI is orally absorbed, at the doses studied, with results far too variable to indicate or estimate a threshold.’ Dr. Bjeldanes’ comment, along with those of other reviewers, has prompted OEHHA to expand its discussion of MOA in the final PHG document. The PHG document now emphasizes that the two primary considerations driving the decision to perform a linear low-dose extrapolation are the genotoxicity of Cr VI and insufficient support for an alternative threshold MOA. Text covering these

issues has been added at two places in the PHG document: “Mechanism of Genotoxicity and Carcinogenicity” section and “Toxicological Effects in Animals,” subheading “Carcinogenicity,” subheading “Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice.”

Comment 18: “The fallacy of uncritically assuming that positive tests in genotoxicity tests necessarily imply a mutagenic MOA is evidenced by (1) the high incidence of positive results in genotoxicity testing with many common chemicals (including sugar and salt) that do not appear to pose a carcinogenic risk under conceivable human exposure conditions (e.g., Dearfield and Moore, 2005; Pottenger et al., 2007); and (2) the now well-established fact that cancer is the end result of a multi-step process by which a normal cell is transformed into a cancerous one exhibiting the six “hallmarks” of cancer (Hanahan and Weinberg, 2000)...”

Response 18. Data presented or cited in the PHG document demonstrate that Cr VI is both genotoxic and mutagenic. There is no assumption of a mutagenic MOA.

Comment 19: “The only peer reviewer who critically addressed the charge question regarding MOA was Dr. Toby Rossman, who stated,...’These events generally show thresholds.’”

Response 19. See Responses to Dr. Rossman’s comments.

Comment 20: “OEHHA should use the soon-to-be published results of the Cr(VI) MOA Research Project to support a robust evaluation of carcinogenic MOA in animals, and use the refined PBPK model to inform extrapolation across doses and species for development of Cr(VI) PHGs for both carcinogenic and non-carcinogenic effects.”

Response 20. OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comment 21: “Yet, as addressed in detail in previous comments, OEHHA’s conclusion that reductive capacity is exceeded was based primarily on high-dose studies involving non-oral routes of exposure that are not relevant to potential human exposure conditions.”

Response 21. The “Metabolism and Pharmacokinetics” section of the PHG document contains extensive discussion of Cr VI reduction to Cr III. The general conclusion is that the reductive capacity of the GI tract of rodents and humans was rarely if ever exceeded.

Comment 22: “As discussed by Thompson et al. (2011) and illustrated in Figure 2 taken from that publication, depicting toxicokinetic data collected by the NTP (2007), gastrointestinal reduction of Cr(VI) undergoes a transition in mice at concentrations above 3 to 10 mg/L in drinking water. Such data clearly indicate that (1) a dispositional threshold exists for systemic Cr(VI) uptake, and (2) even the lowest concentration of Cr(VI) in the NTP bioassay probably exceeded the animals’ gastrointestinal reductive capacity, resulting in systemic uptake and increased chromium concentrations in liver and kidney.”

Response 22. With regard to (1), the methodology used in NTP (2007) to measure chromium accumulation in tissue and blood may have lacked the sensitivity to measure the small increases that may occur at the lower drinking water concentrations. This same reservation applies to the data in Sutherland et al. (2000). Note that ingestion studies with radioactive Cr VI have reported absorption at dose levels below those shown in Figure 2 from Thompson et al. (2011). With regard to (2), Collins et al. (2010) analyzed chromium accumulation in tissue of mice and rats given drinking water containing from 5 to 180 mg/L of Cr VI for two years. These data were collected during the NTP bioassay, performed at the same drinking water concentrations tested for tumor induction. The chromium accumulation data indicated that the gastric reduction capacity was not saturated in these animals. Issue (1) is discussed in the “Metabolism and Pharmacokinetics” section of the PHG document while issue (2) is discussed in Appendix A of the PHG document.

Comment 23: “The target tissues in the NTP bioassay demonstrated a readily apparent dose-response gradient (duodenum>jejunum>ileum), both anatomical and temporal. Dose-related increases in lesions associated with tissue damage (degeneration, edema, inflammation, hemorrhage, erosion, ulceration, infiltration, and hyperplasia), observed after 90 days of treatment, occurred along this gradient. These observations are consistent with tumorigenesis secondary to cellular injury, oxidative stress, inflammation, and necrosis due to direct contact of Cr(VI) with the small intestine epithelium, followed by cell regeneration and inhibition of apoptosis.”

Response 23. The PHG document contains a section entitled “Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice.” This section presents data from the two-year bioassay (NTP, 2008) in Table 7 of the PHG document. This section also discusses data from the 90 day study by NTP (2007). These data do **not** support an MOA of tumorigenesis secondary to tissue damage.

Comment 24: “OEHHA’s approach to developing Cr(VI) PHGs for carcinogenic and non-carcinogenic effects does not comport with current EPA and international guidelines for human cancer risk assessment.”

Response 24. The PHG document develops a **single** PHG value that is protective of both carcinogenic and non-carcinogenic effects. The PHG document follows U.S. EPA (2005) risk assessment guidelines and OEHHA guidelines (2009). Both entities utilized linear extrapolation to develop essentially identical cancer slope factors for oral exposure to Cr VI (U.S. EPA, 2010; final PHG for Cr VI in drinking water). It is not clear what “international guidelines” are being referenced here.

Comment 25: “Based on overly conservative and insufficiently documented exposure and toxicity assumptions, and lacking coherent evaluations of (1) animal MOA, and (2) human relevance, both the 2009 and 2010 draft PHGs are fatally flawed. The weight of experimental and epidemiological evidence and exercise of best risk assessment practices under current regulatory guidance support development of a health-protective PHG that is orders of magnitude higher. “

Response 25. OEHHA disagrees with this comment for a number of reasons:

- The human relevance of exposure to Cr VI in drinking water is demonstrated by the only two epidemiology studies to measure organ-specific cancer in exposed human populations: Zhang and Li (1987) and Linos et al. (2011). See the section in the final PHG document entitled “Toxicological Effects in Humans” for data demonstrating a statistically significant increase in stomach cancer (Zhang and Li, 1987) and liver cancer (Linos et al., 2011) in exposed populations.
- Note also that the Peer Reviewers of the August 2009 draft PHG document were generally supportive of OEHHA’s approach. See the General Comments and Responses provided at the beginning of each 2009 Peer Reviewer’s Comments in this document (see Table of Contents).
- U.S. EPA (2010) and the New Jersey Department of Environmental Protection (2009) took similar approaches to that taken by OEHHA in developing essentially identical cancer slope factors for Cr VI in drinking water. The commonality of the approach suggests it is not fatally flawed.
- The mechanism by which ingested Cr VI causes cancer in animals and humans is discussed in a number of places in the PHG document. The acronym MOA has been added to the document to help readers locate these discussions. The sections with concentrated discussions of mechanisms are: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” Table 7 and the section entitled “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.”

Comments from Timothy Quinn, Association of California Water Agencies

Comment 1: “ACWA understands other studies exist and are referenced in the document providing evidence that complete reduction may not always occur, but we believe the administered doses in the NTP study are so large they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in the rodents. This is especially significant as the NTP study did not find excess cancers at the lowered studied doses in both rats and mice.”

Response 1. See Appendix A in the PHG document for a discussion of the data showing that the Cr VI reducing capacity of the rodent GI tract was not saturated over the dose range tested in the NTP (2008) two-year study. The absence of excess tumors at the lower dose levels may have been due to the use of a small number of animals to detect a relatively rare event (tumor formation).

Comment 2: “Equally as important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated and higher level of gastric juices than rodents.”

Response 2. Cr VI is reduced to Cr III in both the rodent and human stomach. This is discussed in detail in the PHG document in the sections “Hexavalent Chromium Reduction by Saliva and Gastric Fluids”, “Absorption” and “Pharmacokinetics of

Trivalent versus Hexavalent Chromium.” See also Appendix A. While Cr VI reduction in the GI tract of rodents compared to humans has not been fully described, the U.S. EPA (2010), the New Jersey Department of Environmental Protection (NJDEP, 2009) and OEHHA (this PHG) have all found that they are similar enough to allow calculation of a human cancer slope factor for Cr VI based on the NTP two-year bioassay.

Comment 3: “The Borneff et al study is seriously flawed due to the fact there was only a single-dose level examined and an ectromelia epidemic affected both control and treated groups with significant loss of mice. ACWA still feels this study should not be considered in the development of the PHG.”

Response 4. The Borneff et al. (1968) study is not a key study in the derivation of the PHG for Chromium VI and was moved to the Appendix for that reason. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

Comment 5: “The organs exposed to the largest concentrations of chromium and that were in most immediate contact with the chromium were the forestomach, glandular stomach, serum, and red blood cells. In examining the results provided it is clear that after a year of exposure to 5 mg/L of hexavalent chromium, none of the mice or rats showed any higher concentrations of chromium in these four tissues than did the mice or rats in the control population exposed to no hexavalent chromium. Further, none of the rodents exposed to 5 mg/L hexavalent chromium for two years in the histopathology showed any excess cancers. The NTP data supports the well-established observation that the reductive capacity of the mammalian stomach can convert hexavalent chromium to the non-toxic reduced chromium at even very high concentrations.”

Response 5. Tables 2 and 3 from Collins et al. (2010) show that statistically significant increases in chromium occurred in a number of tissues from both mice and rats receiving 5 mg/L of Cr VI in their drinking water during the two-year bioassay. The absence of excess tumors at 5 mg/L Cr VI may have been due to the use of a small number of animals to detect a relatively rare event (tumor formation).

Comment 6: “In addition, we believe this point would be made clearer if the public had access to the results of the full study...The complete set of 10 results per organ would have been very helpful to ACWA in its effort to assess OEHHA’s draft PHG document.”

Response 6. These data have been published in a peer-reviewed scientific journal by Collins et al. (2010). Our understanding from reading this paper is that while up to ten animals per exposure group were put into individual metabolism cages for collection of urine and feces, measurements of tissue chromium were performed on three animals per exposure group. Those are the values presented in Tables 2 and 3 of that paper and in Tables J1 and J2 of the original NTP study report.

Comment 7: “Dr Cohen states, ‘It is clear the data presented in the Draft document (c.f. Figure 13; Editorial note: abscissa needs the addition of units as the values shown do not correspond to any of the reported doses in Tables 5 and 6) shows that tumor formation in the mice as a function of Cr6+ level in drinking water is not linear.’”

Response 7. In the 2008 NTP study statistically significant increases in tumors of the small intestine were observed for both male and female mice at the two highest drinking water concentrations. Exact trend tests were positive for both sexes. The absence of statistically significant increases in tumors at the two lowest drinking water concentrations should not be interpreted as a threshold for tumorigenicity (i.e., should not be construed as a nonlinear dose-response curve), since the number of animals may have been too low to detect tumors at the two lowest drinking water concentrations.

Comment 8: “Dr. Rossman provides several reasons objecting to the use of a linear dose response model for the draft PHG and supporting his statement, ‘The assumption is that Cr(VI) in drinking water has a mutagenic MOA with no threshold. This is not valid for the following reasons.’”

Response 8. OEHHA does not know the mechanism by which Cr VI causes cancer in humans or animals. It is both genotoxic and mutagenic as described in the PHG document. Since there are insufficient data to support an MOA other than that via genotoxicity/mutagenicity, the PHG document models the tumor data according to a linear multistage model as recommended (U.S. EPA, 2005; OEHHA, 2009; McCarroll et al., 2010).

Comment 9: “Dr. Snow states, “Based on this study, along with very limited evidence of tumor response at lower levels of Cr6, there is very limited evidence for a linear dose response. It is more likely, due to the high probability of extracellular conversion of the Cr6 to the much less toxic Cr3, that uptake and bioavailability of the Cr6, in itself, will exhibit a non-linear (threshold) dose response.”

Response 9. It is the case with most carcinogens that dose-response data are not available in the low dose region where human exposures are expected. With regard to a high probability that extracellular Cr VI will be converted to Cr III, this may or may not be true. The PHG document contains examples of Cr VI absorption at dose levels that are far below the calculated capacity of the GI tract of humans and rodents to reduce all ingested Cr VI to Cr III. The PHG document also discusses examples where Cr VI absorption was not concentration dependent.

Comment 10: “By using a default linear dose response model, when the data supports a non-linear dose response, OEHHA is justifying an overly conservative PHG based on an assumption that represents the most critical driver for the PHG calculation.”

Response 10. The linear dose response model was chosen for two reasons. First, Cr VI is genotoxic and mutagenic (see “Genetic Toxicity” section of the PHG document). Second, there are insufficient data to support a threshold MOA in which tissue damage (or other type of cellular effect) is the primary carcinogenic event (see “Toxicological Effects in Animals,” subheading “Carcinogenicity,” subheading “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice” section of the PHG document).

Comment 11: “We are aware of some significant new studies addressing the health effects of hexavalent chromium...ACWA urges OEHHA to follow the progress of this work and consider the results of this study and others that might emerge as soon as

they are completed in order to ensure the subsequent hexavalent chromium MCL is based on the best available science.”

Response 11. OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comments from David Chang, California-Nevada Section, American Water Works Association

Comment 1: “In the calculation of the PHG for hexavalent chromium, an aggregate uncertainty factor of 3000 is applied, the maximum recommended by the California’s Risk Assessment Advisory Committee and the U.S. Environmental Protection Agency.”

Response. The proposed PHG for Cr VI in drinking water is 0.02 ppb. No uncertainty factor was used in its calculation. Ingesting drinking water containing Cr VI at this concentration for seventy years is associated with a one in one million extra risk of developing cancer.

Comments from Elliott Rothman, City of Pomona

Comment 1: “As indicated in the draft PHG document, several studies previously estimated that saliva and stomach fluids have the capacity to reduce hexavalent chromium to trivalent chromium in amounts much larger than the “maximum plausible levels of hexavalent chromium in water that would likely be ingested by humans...” The document further asserts that “...exhaustion of the capacity of saliva and gastric fluids to reduce hexavalent chromium appears unlikely.” We understand that other studies exist and are referenced in the document providing evidence that complete reduction may not always occur, but we believe the administered doses in the National Toxicology Program (NTP) study are so large they easily overwhelmed the reductive capacity of both the oral cavity and the stomach in the rodents. This is especially significant as the NTP study did not find excess cancers at the lowered studied doses in both rats and mice. Equally as important, the stomach composition of humans and rodents is very different, with humans having a much more sophisticated and higher level of gastric juices than rodents.”

Response 1. See Appendix A in the PHG document for a discussion of the data showing that the Cr VI reducing capacity of the rodent GI tract was not saturated over the dose range tested in the NTP (2008) two-year study. The absence of excess tumors at the lower dose levels may have been due to the use of too few animals to detect a relatively rare event (tumor formation). Cr VI is reduced to Cr III in both the rodent and human stomach. This is discussed in detail in the PHG document in the sections “Hexavalent Chromium Reduction by Saliva and Gastric Fluids”, “Absorption” and “Pharmacokinetics of Trivalent versus Hexavalent Chromium.” See also Appendix A. While Cr VI reduction in the GI tract of rodents compared to humans has not been fully described, the U.S. EPA (2010), the New Jersey Department of Environmental Protection (NJDEP, 2009) and OEHHA (this PHG) have all found that they are similar enough to allow calculation of a human cancer slope factor for Cr VI based on the NTP two-year bioassay.

Comment 2: “The Borneff et al study is seriously flawed due to the fact there was only a single-dose level examined and an ectromelia epidemic affected both control and treated groups with significant loss of mice. The City of Pomona feels this study should not be considered in the development of the PHG.”

Response 2. The Borneff et al. (1968) study is not a key study in the derivation of the PHG for Chromium VI and was moved to the Appendix for that reason. OEHHA provided extensive analysis of its findings in its endeavor to consider all available scientific data when evaluating chemicals and developing PHGs aimed at protecting public health. The weight of evidence approach taken by OEHHA necessitated a discussion of Borneff et al. (1968).

Comment 3: “However, in examining the results of the tissue distribution study as presented in Tables J1 and J2 of the above mentioned study, only three results are presented for each exposure group per sample period instead of ten...The complete set of 10 results per organ would have been very helpful to Pomona in our effort to assess OEHHA’s draft PHG document.”

Response 3. These data have been published in a peer-reviewed scientific journal by Collins et al. (2010). Our understanding from reading this paper is that while up to ten animals per exposure group were put into individual metabolism cages for collection of urine and feces, measurements of tissue chromium were performed on three animals per exposure group. Those are the values presented in Tables 2 and 3 of that paper and in Tables J1 and J2 of the original NTP study report.

Comment 4: “We are aware of some significant new studies addressing the health effects of hexavalent chromium. These studies are nearing completion and could potentially provide a more thorough understanding of hexavalent chromium’s mode of action and other critical issues that should be included in a risk assessment. The City of Pomona urges OEHHA to follow the progress of this work and consider the results of this study and others that might emerge as staff must review and revise, if appropriate, all public health goals at least once every five years “...based upon the availability of new scientific data.” [Health and Safety Code §116365(E)(e)(1)].”

Response 4. OEHHA acknowledges that new research is on-going and looks forward to the new data when available for consideration. The Safe Drinking Water Act of 1996, amended 1999 (Health and Safety Code [H&SC], Section 116365) contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. When new research data become available, OEHHA will consider them in the development of a revised PHG for hexavalent chromium. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

Comments from Kevin Milligan, City of Riverside

Comment 1: "OEHHA ultimately issued its current revised draft PHG of 0.02 ppb, citing updated information regarding sensitive sub-populations. Riverside requests clarification on whether the revision was based in response to the peer review and public comments, or if OEHHA was concurrently considering their own 2009 report regarding effects of early in life exposures to hexavalent chromium."

Response 1. The part of the PHG document concerning sensitive sub-populations was revised in response to comments from both the public and peer reviewers. The revisions are in accordance with the OEHHA (2009) report on early-in-life susceptibility to carcinogens.

Comment 2: "Moreover, Riverside understands that there are studies currently in progress, (and scheduled to be completed in the summer of 2011), that may provide critical information on the mode of action and carcinogenicity of orally ingested hexavalent chromium. Accordingly, Riverside requests that OEHHA thoroughly evaluate the findings of these studies before establishing a final PHG that will be used by the California Department of Public Health to set its MCL."

Response 2. Health and Safety Code Section 116365.5 required the Department of Public Health to develop a primary drinking water standard for Cr VI by January 1, 2004. Health and Safety Code Section 116365 requires the development of a PHG by OEHHA before the department can adopt a primary drinking water standard. In light of this statutory mandate, it would be very difficult for OEHHA to justify further delay to finalizing the PHG in order to incorporate any appropriate findings from the Hamner Institutes research program.

Health and Safety Code Section 116365 contains an important provision that addresses new scientific research when it becomes available: "(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data". OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: "When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced."

OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comment 3: "To our knowledge the PHG does not include a risk characterization of the microbial risk related with current disinfection practices compared to the health risk associated with the conversion of trivalent chromium to hexavalent chromium. Has OEHHA considered this risk assessment for the proposed hexavalent chromium PHG? If not, how will these challenges be addressed in the current regulatory framework?"

Response 3. The PHG document addresses the risk of health effects due to Cr VI in drinking water. Related risks due to microbial contamination and the compounds used to treat such contamination are outside the scope of the PHG.

Comments from Steve Bigley, Coachella Valley Water District

Comment 1: “The Office of Environmental Health Hazard Assessment (OEHHA) draft Cr6 PHG of 0.02 parts per billion (ppb) is calculated from cancer observed in the National Toxicology Program rodent study completed in 2007. Specifically, this calculation is based on cancer found in the small intestines of 5 of the 50 male mice exposed to drinking water containing 90,000 ppb of Cr6 for 2-years or the typical life span of a mouse. The male mice in this study that received doses of 5,000 ppb, 10,000 ppb and 30,000 ppb showed no statistically significant increase in cancer when compared to cancer observed in control mice receiving no Cr6 in their drinking water.”

Response 1. The data in Table 5 of the PHG document show that male mice given drinking water containing 30,000 or 90,000 ppb of Cr VI had incidences of intestinal tumors (adenomas or carcinomas) that were significantly greater than controls. In addition, there was a positive trend for increasing intestinal tumors with increasing concentration of Cr VI.

Comment 2: “While this data clearly shows a threshold below which no increased cancer was observed in the rodents, OEHHA is allowed to use a default linear dose response model when there is insufficient data to explain the mode of action by which the 5 male mice developed cancer in their intestines.”

Response 2. There were seven male mice at 30,000 ppb of Cr VI and 20 male mice at 90,000 ppb that developed intestinal tumors (adenomas or carcinomas), compared to one control mouse (both pair-wise comparisons were statistically significant). As mentioned above, there was also a positive trend for increasing intestinal tumors with increasing concentration of Cr VI. At the two lowest dose levels the increases in tumor incidence were not significant compared to the control incidence. This should not be interpreted as a threshold for tumor induction, since it may be due to the use of too few animals to detect a relatively rare event (tumorigenesis).

Comment 3: “Dr. Cohen states, ‘It is clear that the data presented in the Draft document (c.f. Figure 13; Editorial note: abscissa needs the addition of units as the values shown do not correspond to any of the reported doses in Tables 5 and 6) shows that tumor formation in the mice as a function of Cr6+ level in drinking water is not linear.’”

Response 3. In the 2008 NTP study statistically significant increases in tumors of the small intestine were observed for both male and female mice at the two highest drinking water concentrations. Exact trend tests were positive for both sexes. The absence of statistically significant increases in tumors at the two lowest drinking water concentrations should not be interpreted as a threshold for tumorigenicity (i.e., should not be construed as a nonlinear dose-response curve), since the number of animals may have been too low to detect tumors at the two lowest drinking water concentrations. The use of high doses in cancer bioassays is designed to offset the

statistical limitations of using small numbers of animals (50 /sex/dose level) to measure a relatively rare event (tumors).

Comment 4: “Dr. Rossman provides several reasons objecting to the use of a linear dose response model for the draft PHG and supporting his statement, ‘The assumption is that Cr(VI) in drinking water has a mutagenic MOA with no threshold. This is not valid for the following reasons.’”

Response 4. OEHHA does not know the mechanism by which Cr VI causes cancer in humans or animals. It is both genotoxic and mutagenic as described in the PHG document. Since there are insufficient data to support an MOA other than that via genotoxicity/mutagenicity, the PHG document models the tumor data according to a linear multistage model as recommended (U.S. EPA, 2005; OEHHA, 2009; McCarroll et al., 2010).

Comment 5: “Dr. Snow states, “Based on this study, along with very limited evidence of tumor response at lower levels of Cr6, there is very limited evidence for a linear dose response. It is more likely, due to the high probability of extracellular conversion of the Cr6 to the much less toxic Cr3, that uptake and bioavailability of the Cr6, in itself, will exhibit a non-linear (threshold) dose response.”

Response 5. It is the case with most carcinogens that dose-response data are not available in the low dose region where human exposures are expected. With regard to a high probability that extracellular Cr VI will be converted to Cr III, this may or may not be true. The PHG document contains examples of Cr VI absorption at dose levels that are far below the calculated capacity of the GI tract of humans and rodents to reduce all ingested Cr VI to Cr III. The PHG document also discusses examples where Cr VI absorption was not concentration dependent.

Comment 6: “OEHHA has also disregarded and twisted the scientific opinion of one of the most highly respected toxicologists on the subject of Cr6 toxicology. Dr. Silvio De Flora has studied Cr6 toxicity for over 30 years and many of his studies are referenced in the draft PHG...While the study results include statistically significant decreases in certain tumors in the Cr6 exposed rodent test groups, these findings do not support a health benefit from ingestion Cr6 just as the statistically significant increases in cancer observed in male mice at the highest Cr6 dose is not biologically significant and does not bear relevance to human exposures.”

Response 6. First, OEHHA agrees that Cr VI is not likely to protect against cancer. Second, biological significance does not follow from occasional increases or decreases in tumors. Rather, OEHHA looks for a dose-responsive change exhibiting statistical significance. In mice such a pattern was observed for intestinal tumors.

Comment 7: “The NTP study report is actually based on three distinct studies: a clinical study, a histopathology study, and a tissue distribution study. While the clinical study is used to support the PHG, the histopathology and tissue distribution studies are given little consideration by OEHHA. The tissue distribution study clearly showed no increase in Cr6 levels in the tissues studied when rodents ingested 5,000 ppb of Cr6 for one year. Likewise, rodents exposed to 5,000 ppb of Cr6 for 2-years in the histopathology study showed no excess cancers.”

Response 7. See Appendix A of the PHG document for presentation of the tissue chromium levels in the animals comprising the two-year bioassay. As discussed in that section, increases in tissue chromium were detected at all dose levels, including 5,000 ppb. The histopathological findings of the two-year bioassay are discussed in the section entitled “Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” located in the “Carcinogenicity” section of the PHG document.

Comment 8: “This NTP data supports the well-established observation that the reductive capacity of the mammalian stomach can convert Cr6 to the non-toxic reduced form of chromium even at levels 100 times greater than the current California drinking water MCL for chromium.”

Response 8. See the “Metabolism and Pharmacokinetics” section of the PHG document for examples of Cr VI absorption occurring at concentrations estimated to be lower than the reductive capacity of the mammalian stomach. This would be possible if Cr VI absorption and reduction were competing processes occurring in the GI tract, as discussed in the PHG document.

Comment 9: “OEHHA and the peer reviewers also failed to identify some important information missing from the tissue distribution study. The scope of this study included the collection of samples of 4 specific tissues from each of the 10 animals selected from each test group. However, the summary tables (Table J1 and J2) for this study only include results for 3 to 6 animals depending on the tissue. No explanation has been provided for why the additional tissue data has not been made available to the public.”

Response 9. These data have been published in a peer-reviewed scientific journal by Collins et al. (2010). Our understanding from reading this paper is that while up to ten animals per exposure group were put into individual metabolism cages for collection of urine and feces, measurements of tissue chromium were performed on three animals per exposure group. Those are the values presented in Tables 2 and 3 of that paper and in Tables J1 and J2 of the original NTP study report.

Comment 10: “OEHHA takes the position that using a more precautionary linear model assumption when there is a gap in available science is justified and the best way to reduce health risks.”

Response 10. As discussed in the PHG document, the data on hand for Cr VI suggest it acts via a genotoxic mode of action. Carcinogens with genotoxic MOAs are modeled using a linear model by both U.S. EPA (2005) and OEHHA (2009), based in part on the linear dose-response relationship observed for radiation-induced human cancer; the data set covering the lowest dose levels and cancer incidences so far measured (Brenner et al., 2003).

Comment 11: “Studies that focus on exposing rodents to unrealistic levels of an element to illicit an adverse response do not provide the good science needed to properly predict potential health risks at realistic low levels of exposure.”

Response 11. Two-year bioassays with rodents are traditionally performed at high dose levels in order to offset the statistical limitations of using 50 animals per sex per dose level to detect a relatively rare event (tumor formation).

Comment 12: “Studies designed to properly evaluate the mode of action and provide sufficient information to determine if a threshold dose response exists for the subject element is critical to completing an accurate risk assessment.”

Response 12. See the following sections of the PHG document for discussion of the MOA issues for which data are available: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” Table 7 in the section entitled “Non-neoplastic findings – Possible relationship between tissue damage, inflammation, hyperplasia and tumors in rats and mice,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.”

Comment 13: “The obvious gap in science used to support the draft Cr6 PHG has already been identified and studies are ongoing to help determine the mode of action for Cr6 toxicity observed in rodents. These studies are nearing completion and are designed to provide a more thorough understanding of the mode of action and other critical issues that should be included in a Cr6 risk assessment for drinking water.”

Response 13. OEHHA acknowledges that new research is on-going and looks forward to the new data when available for consideration. The Safe Drinking Water Act of 1996, amended 1999 (Health and Safety Code [H&SC], Section 116365) contains an important provision that addresses new scientific research when it becomes available: “(e) (1) Public health goals established by the office shall be reviewed at least once every five years and revised, pursuant to the provisions of subdivision (c), as necessary based upon the availability of new scientific data”. When new research data become available, OEHHA will consider them in the development of a revised PHG for hexavalent chromium. OEHHA acknowledges that new studies may alter a revised PHG. From the risk characterization section of the PHG: “When and if better studies of hexavalent chromium toxicity, dose-response, and exposure become available, the uncertainties associated with the risk assessment can be reduced.”

Comments from David Luker, Desert Water Agency

Comment 1: “Specifically, Desert Water Agency awaits epidemiology study results that demonstrate the affect of hexavalent chromium in humans, as the difference in indigestion processes, stomach composition, and levels of gastric juices between rodents and humans were not taken into account in the referenced study. We are also hopeful that such a study will be based upon realistic concentrations of water with hexavalent chromium present.”

Response 1. See the “Toxicological Effects in Humans” section of the PHG document, subheading “Carcinogenicity,” for a detailed discussion of the study by Zhang and Li (1987). This study detected a statistically significant increase in stomach cancer mortality in persons drinking water contaminated with Cr VI. Also see Beaumont et al. (2008; Cancer mortality in five villages in China with hexavalent chromium-contaminated drinking water. *Epidemiology* 19:12-23).

Comments from Ron Hunsinger, East Bay Municipal Utility District

Comment 1: “The risk characterization section in the draft PHG report should include an assessment of the risk associated with the formation of Chromium 6 following exposure to a disinfectant such as ozone, chlorine, or chloramines. In order to fully characterize the risk posed by Chromium 6, OEHHA should acknowledge this source of Chromium 6 and incorporate a microbiological risk component into the discussion.”

And,

“The draft PHG report does not identify the conversion of Chromium 3 to Chromium 6 following exposure to a disinfectant such as ozone, chlorine, or chloramine as a source of Chromium 6. Pathogenic inactivation and Chromium 6 production occur simultaneously and present different public health threats. However, the draft PHG report addresses only the chemical threat.”

And,

“Risk characterization should enumerate the microbiological risks (USEPA 2009) associated with the current disinfection practices and compare them to the health risk associated with the conversion of Chromium 3 to Chromium 6 via the interaction of a disinfectant and Chromium 3.”

Response 1. While oxidation of Cr III to Cr VI by drinking water disinfectants such as ozone, chlorine or chloramines is theoretically possible, we have been unable to locate any data relating to this specific topic. Were such data to be located, they would be included in the “Environmental Occurrence and Human Exposure” section of the PHG document. However, calculation of the PHG value would not be affected by such data. Consideration of microbial risk is outside the scope of the PHG document.

Comment 2: “We recommend the following references be incorporated into the report to ensure the toxicological literature review is exhaustive...”

Response 2. There is a very large body of published literature on chromium covering its chemistry, environmental occurrence, toxicity, possible human dietary requirement and other characteristics. We have attempted to include in the PHG document those papers most relevant for developing a drinking water value that protects human health. Two of the three papers cited in this comment come from the laboratory of Professor De Flora. The final PHG document discusses five other papers from this laboratory, indicating that this group’s research on chromium has been adequately considered.

Comments from Rebecca Sutton, Environmental Working Group

Comment 1: “EWG and NRDC urged OEHHA to ensure adequate protection of another sensitive population, those with medical conditions or on medications that reduce stomach acidity. Conversion of hexavalent to trivalent chromium can be impaired in individuals with low-acid stomachs, a condition brought about by several widely-used medications, including antacids and proton pump inhibitors, prescribed for gastroesophageal reflux disease, peptic ulcer disease, and chronic gastritis. Other health conditions that can result in reduced stomach acid production include pernicious

anemia, pancreatic tumors, infection with *Helicobacter pylori*, mucopolidosis type IV, and some autoimmune diseases.

A susceptible subpopulation united by a variety of common to rare medical conditions faces an elevated risk from oral exposure to hexavalent chromium. We hope the revised public health goal of 0.02 ppb will protect such individuals from the effects of hexavalent chromium in tap water. We suggest that OEHHA examine this issue further during its periodic review of public health goals.”

Response 1. Some of these potentially sensitive subpopulations are discussed in the “Sensitive Subpopulations” section of the PHG document. For calculation of the acceptable daily dose (ADD) for noncarcinogenic effects (“Calculation OF The PHG, Noncarcinogenic Effects” section of the PHG), an uncertainty factor of 10 was judged sufficient for protecting potentially sensitive human subpopulations, such as antacid users. Methodology does not currently exist for incorporating the potentially heightened sensitivity of these subpopulations into the calculation of the protective dose for carcinogenic effects.

Comments from Dan Askenaizer, Glendale Water and Power

Comment 1: “When OEHHA published the revised draft PHG of 0.02 ppb, the PHG document cited updated information regarding sensitive sub-populations. In the press release for the revised PHG, OEHHA states ‘new research has documented that young children and other sensitive populations are more susceptible than the general population to health risks from exposure to carcinogens. The changes were recommended by the peer review and reflect OEHHA’s new guidelines for early-in-life exposures, which acknowledge this susceptibility.’ The need to incorporate OEHHA’s policy on sensitive subpopulations was clearly stated by one of the peer reviewers of the 2009 draft PHG. However, these statements by OEHHA seem to imply that new research involving CrVI and sensitive sub-populations became available to OEHHA. If there is additional new information regarding CrVI and protecting the health of sub-populations, it would be helpful for OEHHA to make that information public.”

Response 1. The “new research” quoted above refers to the new OEHHA guidelines for early-in-life exposures to carcinogens and the data that are the basis for those guidelines (OEHHA, 2009). No new data on Cr VI were received.

Comment 2: “While Appendix A in the December 31, 2010 draft PHG presents a discussion of the issue of a carcinogenic threshold, the information presented does not appear to directly address the question of a threshold as raised by several of the peer review comments. “

Response 2. We agree with this comment. The title to Appendix A has been modified to the following, “Carcinogenic Threshold: Was the Reductive Capacity of the Rodent GI Tract Exceeded in the NTP (2008) Bioassay?”

Comments from David Chang, Golden State Water Company

Comment 1: “In the calculation of the PHG for hexavalent chromium, an aggregate uncertainty factor of 3000 is applied, the maximum recommended by the California Risk Assessment Advisory Committee and the U.S. Environmental Protection Agency.”

Response 1. The proposed PHG for Cr VI in drinking water is 0.02 ppb. No uncertainty factor was used in its calculation (see “Calculation of the PHG,” subheading “Carcinogenic Effects” section of the PHG document). Ingesting drinking water containing Cr VI at this concentration for seventy years is associated with a one in one million extra risk of developing cancer.

Comments from Mic Steward, The Metropolitan Water District of Southern California

Comment 1: “OEHHA ultimately issued its current revised draft PHG of 0.02 ppb, citing updated information regarding sensitive sub-populations. Metropolitan requests clarification on whether the revision was based in response to the peer review and public comments, or if OEHHA was concurrently considering their own 2009 report regarding effects of early in life exposures to chromium 6.”

Response 1. The part of the PHG document concerning sensitive sub-populations was revised in response to comments from both the public and from peer reviewers. The revisions were in accordance with the OEHHA (2009) report on early-in-life susceptibility to carcinogens.

Comment 2: “Moreover, Metropolitan understands that there are studies currently in progress (and scheduled to be completed in the summer of 2011) that may provide critical information on the mode of action and carcinogenicity of orally ingested chromium 6. Accordingly, Metropolitan requests that OEHHA thoroughly evaluate the findings of these studies as part of establishing a final PHG that will be used by the California Department of Public Health to set its MCL.”

Response 2. OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comments from Richard Atwater, Southern California Water Committee

Comment 1: “While purporting to meet the requirements to use the best science in decisions that relate to protecting public health, OEHHA continues to follow the practice of using default assumptions rather than chemical-specific information and sound science to inform risk assessment.”

Response 1. The PHG document finds that Cr VI is genotoxic and mutagenic (see “Genetic Toxicity” section of the PHG document). It also finds that the available data do **not** support a threshold MOA of tissue damage followed by regenerative cell proliferation (see “Toxicological Effects in Animals,” subheading “Carcinogenicity,” subheading “Non-neoplastic findings – Possible relationships between tissue damage,

inflammation, hyperplasia and tumors in rats and mice” section of the PHG document). Unless there are data suggesting a different approach, both U.S. EPA (2005) and OEHHA (2009) model tumor data for genotoxic/mutagenic carcinogens by linear extrapolation. This is not a default assumption, but a methodological choice driven by the data.

Comment 2: “The Draft December 2010 Public Health Goal document contains the following deficiencies: failure to address comments from peer reviewers of the August 2009 PHG document, the draft December 2010 PHG document and expert panel comments on the draft 1999 PHG document.”

Response 2. This document responds to comments received in response to the August 2009 draft and the December 2010 draft. The findings of the expert panel were disavowed by the California Environmental Protection Agency following legislative hearings on allegations that some panel members had not properly disclosed their economic interests.

Comment 3: “Inadequate response to public comments on earlier PHG documents, including: Lack of any mode of action (MOA) consideration, especially when MOA forms the overarching conceptual framework for cancer risk assessment (EPA, 2005a).”

Response 3. See the following sections of the PHG document for discussion of the MOA issues for which data are available: “Pharmacokinetics of Trivalent versus Hexavalent Chromium,” “Mechanism of Genotoxicity and Carcinogenicity,” “Examination of Evidence for Chromium Carcinogenicity,” and “Risk Characterization.” The mutagenic mode of action described by McCarroll et al. (2010) has been added to the document.

Comment 4: “Inadequate response to public comments on earlier PHG documents, including: Regarding the MOA, lack of consideration of interspecies differences in toxicokinetics of Cr(VI) and the failure to recognize that pathologies seen in rodents are likely portal-of-entry effects.”

Response 4. The rodent tumors observed in the two-year bioassay (NTP, 2008) may well be site-of-contact effects. However, given the available data, calculation of the cancer potency would be the same whether a site-of-contact effect or a systemic effect were assumed.

Comment 5: “Inadequate response to public comments on earlier PHG documents, including: Regarding the MOA, lack of consideration of nonlinear toxicodynamic effects of Cr(VI) that likely underlie the cancer response. These effects include reactions with DNA, oxidative stress, inflammation and disruption of gene networks that regulate the cell cycle. Instead, the draft December 2010 PHG document correctly assumes that its metabolic products of Cr(VI) are DNA-reactive and wrongly assumes that DNA-reactivity equates to mutagenicity.”

Response 5. Potentially “nonlinear toxicodynamic effects of Cr(VI)” are discussed in the PHG document. For reactions with DNA and oxidative stress see the “Genetic Toxicity” section of the document. For discussion of the inflammation caused by Cr VI see the “Toxicological Effects in Animals,” subheading “Carcinogenicity,” subheading “Non-neoplastic findings – Possible relationships between tissue damage, inflammation,

hyperplasia and tumors in rats and mice” section of the PHG document. Disruption of gene networks was not discussed because few data were located on this topic. OEHHA does not equate DNA reactivity with mutagenicity and has not done so in any of the previous drafts or in the final PHG document. There are many ways to damage DNA that do not lead to mutations. Having said that, there are numerous published studies indicating that Cr VI is mutagenic. In cultured mammalian cells, there are a number of published studies which report robust (in excess of 3-fold increases) mutagenic responses to Cr VI (see Paschin et al. (1983) *Mut Res*103(3-6):345-347; Mitchell et al. (1988) *Environ Mol Mutagen* 12(Suppl 13):37-101; Myhr and Caspary (1988) *Environ Mol Mutagen* 13(12):103-194; McGregor et al. (1987) *Environ Mutagen* 9(2):143-160; Oberly et al (1982) *J Toxicol Environ Health* 9(3):367-376). Reviews discussing these studies are cited in the first paragraph of the “Genetic Toxicity” section of the PHG document. Cr VI also caused mutations in bacteria, yeast, *D. melanogaster* and mice (see reviews mentioned above and U.S. EPA, 2010).

Comment 6: “Inadequate response to public comments on earlier PHG documents, including: Lack of consideration of nonlinearity and the presence of a threshold. Although Appendix A, titled ‘Carcinogenic Threshold?’ gives lip service to the idea of a threshold, this appendix considers only reductive capacity and absorption, and because of the lack of any consideration of MOA, fails to take into account epigenetic changes that underlie the tumor response that likely do have thresholds. The lack of consideration of MOA also prevented exploration of the use of precursor effects as recommended in EPA’s Guidelines for Carcinogen Risk Assessment (EPA, 2005a).”

Response 6. The title of Appendix A has been revised to read, “Carcinogenic Threshold?: Was the reductive capacity of the rodent GI tract exceeded in the NTP (2008) bioassay?” Discussion has been added to the following sections of the PHG document concerning the MOA data that support the use of a low dose linear extrapolation to calculate cancer potency: “Mechanism of Genotoxicity and Carcinogenicity” (large number of studies demonstrating a genotoxic, and possibly mutagenic, MOA for Cr VI); “Toxicological Effects in Animals,” subheading “Carcinogenicity,” subheading “Non-neoplastic findings – Possible relationships between tissue damage, inflammation, hyperplasia and tumors in rats and mice” (that the tissue and cellular findings shown in Table 7 do not support an alternative MOA for tumor induction by Cr VI).

Comment 7: “Use of deficient scientific literature, including: The use of two highly flawed studies in mice and humans respectively (Borneff et al., 1968; Zhang and Li, 1987) to attempt to establish a link between Cr(VI) exposure and gastrointestinal cancer in humans. The use of these studies is in direct contradiction of the advice of an expert panel convened at the University of California in 2001 to review the 1999 PHG document.”

Response 7. The findings of the expert panel on the draft 1999 PHG document were disavowed by the California Environmental Protection Agency following legislative hearings on allegations that several members had not properly disclosed their economic interests. The study by Zhang and Li (1987) and its limitations are thoroughly discussed in the final PHG document. The section of the final PHG document entitled “Examination of the Evidence for Chromium Carcinogenicity” emphasizes the

importance of this study's finding of a statistically significant increase in stomach cancer mortality in the exposed population. This is an important finding that must be part of any serious discussion of whether Cr VI is carcinogenic in humans. The study by Borneff et al. (1987) is discussed in the Appendix. While it was not used to develop the PHG, its inclusion serves as a scientific resource and as a record of the issues that have been addressed in the research for and preparation of this PHG document.

Comment 8: "Use of deficient scientific literature, including: Attempt to impeach the results of the Gatto et al. (2010) meta-analysis that found no association between occupational exposure to Cr(VI) and gastrointestinal cancer in humans."

And,

"Although the draft December 2010 PHG document made several suggestions to "improve" the meta-analysis, it is unlikely that any of these suggestions would alter the results."

Response 8. Discussion of Gatto et al. (2010) is a straightforward identification of some possible limitations of the study.

Comment 9: "The Draft December 2010 Public Health Goal document contains the following deficiencies: Inappropriate use of the age-sensitivity adjustment detailed in OEHHA (2009) because of lack of consideration of MOA. In addition, it was difficult to validate the calculations that employed this adjustment because the necessary data were scattered throughout the document."

Response 9. See OEHHA (2008) for a detailed discussion of the relationship between MOA and early-in-life susceptibility to carcinogens. The "Calculation Of The PHG," subheading "Carcinogenic Effects" section of the PHG document illustrates how the age sensitivity factors are incorporated into the PHG calculation.

Comment 10: "The Draft December 2010 Public Health Goal document contains the following deficiencies: Failure to explore the uncertainty associated with dose-response modeling. The narrative and tables describing the modeling were very brief and difficult to follow. The number of animals at risk for the various dose groups in NTP (2008) was changed from those in the draft August 2009 PHG document without explanation, and neither set of values were the results of the commonly used poly-3 survival adjustment (Portier and Bailer, 1989)."

Response 10. The numbers of animals at risk are shown in Table 5 and Table 6. As indicated in the footnotes to both tables, these are the animals alive at the time of the first occurrence of tumor (day 451 for males and day 625 for females) and if the tissue was available for analysis. This is a standard method for determining the number of animals at risk for tumors (U.S. EPA, 2005; OEHHA, 2009).

Comment 11: "The revised drinking water consumption rates have decreased, even though they are said to be 'upper 95th percentile values estimated by OEHHA,' as were the original consumption rates. For example, the original drinking water rate for a 70 kg adult was 3.15 liters/day and it is now 2.66 liters/day. The question arises, will OEHHA go back to the 3.15 liter/day value when the Director adopts their draft document?"

Response 11. The methodology for calculating water consumption rates using the data from U.S. EPA (2008) and Kahn and Stralka (2009) is now presented in the footnote to Table 17 and in the discussion of Table 18 in the PHG document. In the previous draft of the PHG document the **per capita** water consumption rates were mistakenly used. The revised PHG document uses the **consumers only** rates. The final PHG value of 0.02 ppb (rounded) was unaffected. The drinking water consumption rates reported by Kahn and Stralka (2009) are the same values recommended by U.S. EPA (2008) for use in human health risk assessments. They came out of the largest survey of its kind: the United States Department of Agriculture's (USDA's) 1994-1996 and 1998 Continuing Survey of Food Intake by Individuals (CSFII).

Comment 12: "U.S. EPA used the 90th percentile for the drinking water rate in determining an acceptable concentration for fluoride. The 90th percentile is closer to the traditional 2 liters/day drinking water consumption rate."

Response 12. With regard to the 95th percentile drinking water rate being overly conservative, OEHHA has traditionally sought to protect this large fraction of the population.

Comment 13: "OEHHA does not distinguish between direct and indirect consumption of tap water...Yet there is no adjustment for this in OEHHA's tap water consumption rates."

Response 13. We have added to the "Calculation of The PHG" section of the document that the water intake data cover pure water consumed as a beverage or used in the home or local establishments to prepare food or drink (Kahn and Stralka, 2009). The data are not available for correcting for the amount of Cr VI that is reduced to Cr III when tap water is used to prepare beverages such as juice and coffee, just as there are inadequate data for calculating the amount of Cr III that is oxidized to Cr VI when tap water is handled in various other ways.

Comments from Michael Sovich, Three Valleys Municipal Water District

Comment 1: "OEHHA ultimately issued its current revised draft PHG of 0.02 ppb, citing updated information regarding sensitive sub-populations. TVMWD requests clarification on whether the revision was based in response to the peer review and public comments, or if OEHHA was concurrently considering their own 2009 report regarding effects of early in life exposures to hexavalent chromium."

Response 1. The part of the PHG document concerning sensitive sub-populations was revised in response to comments from both the public and from peer reviewers. The revisions were in accordance with the OEHHA (2009) report on early-in-life susceptibility to carcinogens.

Comment 2: "Moreover, TVMWD understands that there are studies currently in progress (and scheduled to be completed in the summer of 2011) that may provide critical information on the mode of action and carcinogenicity of orally ingested hexavalent chromium. Accordingly, TVMWD requests that OEHHA thoroughly evaluate the findings of these studies before establishing a final PHG that will be used by the California Department of Public Health to set its MCL."

Response 2. OEHHA will review papers and materials relating to the Hamner Institutes study when they are published. If the study produces compelling information that should be reflected in the PHG document, OEHHA will take appropriate action.

Comment 3: “To our knowledge, the PHG does not include a risk characterization of the microbial risk related with current disinfection practices compared to the health risk associated with the conversion of trivalent chromium to hexavalent chromium. Has OEHHA considered this risk assessment for the proposed hexavalent chromium PHG? If not, how will these challenges be addressed in the current regulatory framework?”

Response 3. While oxidation of Cr III to Cr VI by drinking water disinfectants such as ozone, chlorine or chloramines is theoretically possible, we have been unable to locate any data relating to this specific topic. Were such data to be located, they would be included in the “Environmental Occurrence and Human Exposure” section of the PHG document. However, calculation of the PHG value would not be affected by such data. Consideration of the microbial risk is outside the scope of the PHG document.

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