DRAFT

Responses to Major Comments on Technical Support Document

Public Health Goal
For
Hexavalent Chromium
In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Branch
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California Environmental Protection Agency

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TABLE OF CONTENTS

INTRODUCTION

The following are the draft 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. This draft included reference to the new chronic toxicity studies conducted by the National Toxicology Program. Changes have already been made in response to these comments, and were incorporated into the draft posted on the OEHHA website on August 20, 2009. 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. While the comments were often not numbered, this document does number each of the comments and also provides a copy of the comment received and the page where it can be found. Each of the comments is followed by a corresponding numbered response.

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 RECEIVED

Comments from University of California, Santa Cruz (Roberto Gwiazda)

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 ED_{10} 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 uncertainity [sic]. In other words: what is the degree of confidence in the PHG value? Can OEHAA quantify the uncertainity 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 LED_{10}'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 University of California, Berkeley (Leonard Bjeldanes)

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 that 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 University of California, San Diego (Michael Kelner)

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 LED_{10} 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 95^{th} percentile lower confidence limit on the benchmark dose for a 10% tumor response (i.e., LED_{10}) 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/m^3 for male mice, female mice, male rats, and female rats, respectively were derived. The more conservative estimate of 4.4×10^{-6} per·g/m^3 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 LED_{10} value be employed to derive the slope factor. OEHHA presents the ED_{10} values (the "central estimate" referred to above) as well as the LED_{10} values in Tables 10 and 11, but in accordance with the U.S. EPA guidance, the LED_{10} 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 LED_{10} 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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