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August 23, 2010

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1001 I Street
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Re: Review of the Public Health Goal for Hexavalent Chromium in Drinking Water (Aug. 2009) draft

Dear Dr. Bowes:

Enclosed please find my review of the *Public Health Goal for Hexavalent Chromium in Drinking Water* (Aug. 2009) draft. In accordance with your letter of July 20, 2010, and that of Dr. George Alexeeff of March 22, 2010, I have reviewed the Draft document and provided - for each of the four topics subject to review (according to the Attachment #2 of Dr. Alexeeff) - determinations as to whether the scientific portions of the proposed [PHG] were based on sound scientific knowledge, methods, and practices.

I thank you for the opportunity to review the 2009 Draft document, as well as all related 2008 Reviewers' comments, the in-turn Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) responses, and the comments from the general public (generated in response to the PHG Draft posting on OEHHA website). All of these materials were very carefully scrutinized prior to my making any determinations about whether any individual point-of-science was (or was not) based on sound scientific knowledge, methods, and practices.

Please feel free to contact me should you have any further questions or require more information with respect to the materials I have attached herein.

Respectfully,

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August 19, 2010

Re: Review of Public Health Goal for Hexavalent Chromium in Drinking Water (Aug. 2009) draft

Having performed a through review of the 2009 Public Health Goal (PHG) Draft and evaluating the comments from the 2008 Reviewers, the in-turn Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) responses, and the comments from the general public (generated in response to the PHG Draft posting on OEHHA website), determinations have been made as to whether the scientific portion(s) of the PHG corresponding to each point-of-science below is based on sound scientific knowledge, methods, and practices.

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

OEHHA finds that the preponderance of evidence indicates that Cr^{6+} is absorbed by the oral route, is genotoxic, is carcinogenic by multiple exposure routes, in multiple species, and requires the assumption that environmental exposures to Cr^{6+} pose a cancer risk to humans.

For this particular point-of-science, the section of the Draft dealing with the <u>metabolism</u> of hexavalent chromium (Cr^{6+}) agents **appears accurate**. This determination was made based upon the fact that the revised text has taken into account the major concern cited in the earlier scientific and Public sector comments, i.e., that previous PHGs did not seem to properly consider the reduction capacity of saliva and gastric fluids during estimations of protective levels of Cr^{6+} in drinking water. 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 Cr^{6+} 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 Cr^{6+} to Cr^{3+} 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 Cr^{6+} in this version of the Draft.

This revised portion of the Draft, in citing the Finley et al. (1997) study showing that administration of Cr^{6+} (over a range of 0.1 - 10 mg Cr^{6+}/d, for 4 d) did not cause dose-related changes in the percentage of Cr^{6+} in the urine of human subjects, concludes that "results of these studies do not indicate that oral absorption of administered Cr^{6+} 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 Cr^{6+} that will pass into the GI tract intact rather than only occurring if/when the local ability to reduce ingested Cr^{6+} is overwhelmed, an outcome with its own toxicologic ramifications. (Editorial note: the Finley

results are in 'total Cr present in urine', not Cr^{6+} as could be inferred from the corresponding sentence on Page 12).

The portions of the Draft document that discusses the various non-genetic toxicities reported following ingestion/inhalation of Cr^{6+}-bearing water (or atmospheres) **appear accurate** as presented. While the Developmental and Reproductive Toxicity portion of the Animal Toxicology section is substantive, the Immunotoxicity portion is relatively sparse (and deals primarily with effects on lymphoycte proliferation). There clearly are more studies on the immunotoxicologic impact of Cr^{6+} 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.

The sections of the Draft covering the genetic toxicities induced by exposure to Cr^{6+}-bearing agents also **appear accurate** as presented. Nevertheless, as noted in some of the comments from the Public sector, the 'lack' of negative results could be disconcerting. This Reviewer understands that in "illustrating" how a given agent could be toxic, it is obviously necessary to report toxic outcomes. 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 Cr^{6+}. Clearly, non-toxic outcomes have been included in other portions of the Draft; for example, LOAEL and NOAEL values are reported and used for critical calculations of several endpoints (e.g., health-protective dose [HPD], health-protective concentration [C]). As such, an expansion of this portion of the document to include non-toxic outcomes would have greatly strengthened the overall accuracy and completeness of the Draft.

The section of the Draft dealing with potential means of exposure to Cr^{6+} agents, though a bit short overall and relying on basically three review sources (e.g., ATSDR, US EPA, CDHS), **appears accurate**. The information (and calculations) provided in the text to facilitate the understanding of how exposure during bathing/showering and via dermal contact can lead to deposition of Cr^{6+} in a host is quite helpful.

Though not provided as a formal section in the Draft, the concept of modes of action (MOA) for Cr^{6+}, both with respect to toxicity overall and carcinogenicity in particular, is addressed throughout various portions of the text (e.g., Pages 36-42, 73-74, and portions of Appendix B). Nonetheless, it is apparent from several of the Public sector comments that only a full explanation of *all* MOA for Cr^{6+} should be presented before *any* PHG can be derived and accepted as being based upon sound scientific knowledge, methods, and practices. While no determination as to the accuracy of an MOA 'section' can be rendered (as there is no formal MOA portion in the document), the information provided (albeit scattered about the document), is **scientifically accurate**. (Reviewer comment: The sentiment that only a full explanation of **all** MOA for Cr^{6+} 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]).

2. Selection of the NTP data set and supporting information for extrapolation to humans, particularly regarding interpretations of carcinogenicity data and mechanisms.

OEHHA concluded that the best available tumor data for the risk extrapolation was the significantly increased incidence of tumors of the small intestine in male mice reported in the recent NTP lifetime drinking water studies of Cr^{6+}.

While it would seem that rendering a determination as to whether this particular point-of-science was based on sound scientific knowledge, methods, and practices would be fairly straight-forward, the pathway involved in reaching a final conclusion was actually difficult. For example, the clause **"for extrapolation to humans**" already indicates preclusion of human data (i.e., due to occupational/environmental exposures) regarding interpretation of carcinogenic potentials, etc. That determination by the OEHHA appears to have not been made lightly. As noted on Page 60 of the document, "over a thousand articles related to human exposure to hexavalent chromium and cancer were identified". Appropriately, the screening methods used for identification and selection of studies for further analyses as well as the specific criteria to be applied for data abstraction from the selected studies have been spelled out in great detail (leading to the Table 7 compilation of 30 occupational studies dealing with cancers of ingestion- and digestion-related organs).

Unfortunately, the same Page 60 statement does not readily apply to that form of exposure of greatest concern here, i.e., ingestion via drinking water. In fact, only one study that had any potential applicability (i.e., Zhang and Li, 1987) is reported in any detail. Regrettably, this study was found to be fraught with problems (e.g., exposure characterization issues, bad study design, faulty interpretation of data, etc.) and ultimately deemed - in the context of stomach/GI cancers - "unsuitable for deriving a dose-response relationship for hexavalent chromium" (Page 95) as well as unusable for an "estimation of a health-protective level for hexavalent chromium …" (Page 76). While the re-analyses of the data from these 1987 studies (Beaumont et al., 2008) indicated a significant relationship between exposure to Cr^{6+}-contaminated drinking water and increases in rates of stomach cancers, the original problems in the experimental design and exposure characterization did not allow for this human data to be used for deriving any relationships that could be incorporated into the final PHG.

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 "Cr^{6+} in drinking water" and total cancer mortality. The OEHHA noted problems in Cr speciation as a main reason for not utilizing the results of that study and went on to state that "these data could be examined regarding statistical power to detect an effect at the reported chromium levels, but the lack of identification of the chromium species 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". 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 Cr^{6+}-induced effects and thereby mitigate any perceived "selective bias") would have greatly strengthened the overall accuracy and completeness of this Draft.

Based on a lack of scientifically sound human exposure-based data, it was **deemed appropriate that animal study data instead be utilized to generate the PHG**. The question that remains still is whether the NTP data is the most appropriate for that purpose. Issues pertaining to suitability of animal models for extrapolation to human health endpoints are beyond the scope of this particular review; however, it is this Reviewer's opinion that any uncertainty about the validity of inter-species extrapolation itself is properly dealt with in each of the various calculations found in latter portions of the Draft document (Pages 89-98).

With respect to the non-carcinogenic health endpoints, the Draft provides six studies that allowed for assessment of effects from sub-chronic/chronic exposure to Cr^{6+} in the drinking water of rodents (c.f. listing of study parameters and results on Pages 75-76). Derivations of health-protective doses (HPD) for each study were appropriately performed and the outcomes (in terms of potential mg Cr^{6+}/kg-day) listed in Table 17 (Page 94). Because the NTP data consistently yielded the lowest HPD values for children, adult females, and adult males among

the six studies, and in the absence of any outward concerns with study design or performance, **the use of the NTP data set to generate a final HPD of 0.002 mg Cr/L (for non-cancer health endpoints) was both appropriate and accurate**.

With respect to carcinogenic endpoints, the Draft noted on Page 43 that "until the recent publication of the results of the NTP bioassay for sodium dichromate (NTP 2007b), only one long-term animal cancer bioassay where hexavalent chromium was administered by the oral route was identified, i.e., Borneff et al. (1968)". However, as with the Zhang and Li study, there were factors in the 1968 study (i.e., an outbreak of ectromelia [mousepox] virus) that rendered the data unsuitable for use in developing dose-response relationships; other problems with the Borneff study that were equally "lethal" are provided in Appendix B of the Draft document. Thus, the only chronic Cr^{6+} drinking water study that remained for extrapolation was the 2007 NTP study. As such, **selection of the NTP data set as a source of animal model-derived data was both appropriate and accurate.**

As indicated by the 2008 Reviewers and in some of the Public sector comments, there are issues regarding Cr^{6+} intake by the rodents at the highest doses tested. Appropriate criticisms were made as to whether such exposures would ever have the chance to occur among the general population-at-large. However, in dealing with the issue of Maximum Tolerated Dose (MTD), the OEHHA indicates in the Draft that: (A) any observed changes in body weight among rodents in the highest dose groups were likely "attributed, in part, to a decrease in water intake" as opposed to from the Cr^{6+} itself (i.e., "no clinical findings were attributed to sodium dichromate dihydrate exposure"); and, (B) "by the end of the study, the mean body weight of male mice (high dose) was not substantially different from control" even though their water intake was still substantively lower (Pages 53-55, Figures 9-15), suggesting the animals became "tolerant" to the physical characteristics of the Cr^{6+}-bearing water (i.e., taste, etc.). While this issue of changes in water intake could lead to a determination that the NTP study design (and, thus, the resultant data) cannot be declared completely sound, this judgment is countered by the fact that there is no practical means by which to determine from the NTP study the temporal relationship between exposure dose and development of tumors in these hosts. That is, without knowing *when* in the 2-year exposure continuum the tumors were initiated, it would be improper to place too much weight on changes in Cr^{6+}-intake patterns that evolve later in the exposure period. To do so would be to assume that some threshold (cumulative) burden of Cr^{6+} must *have to have been reached* before any tumors were initiated; this Reviewer does not accept that paradigm. Therefore, in the absence of any other major issues dealing with exposure-cancer endpoints *within* a given species (rat or mouse), **the NTP study design has been deemed to be scientifically sound**.

Given that it has been concluded that for carcinogenic endpoints: in the absence of sound human data, it is appropriate that animal study data instead be utilized; the NTP data set is the only scientifically-sound animal-model-driven data set available; and, the NTP study design is sound, **the determination has been made that this point-of-science was based on sound scientific knowledge, methods, and practices.**

3. Appropriateness of the risk assessment methodology used for extrapolation to human exposures to Cr^{6+} in drinking water.

A cancer potency estimate of 0.6 (mg/mg-day)$^{-1}$ derived following standard guidance from the U.S. EPA and OEHHA resulted in an extrapolated one in one million lifetime cancer risk level for Cr^{6+} in tap water of 0.06 ppb.

Determinations as to the accuracy or the information presented on metabolism, toxicity, MOA, and exposures presented in the Draft document, as well as the soundness of selection of the NTP data set for use in generating PHG values for cancer and non-cancer endpoints have been

rendered. A determination can now be made as to the appropriateness of the risk assessment (RA) methodologies employed by OEHHA for extrapolation to human exposures to Cr^{6+} in drinking water.

This Reviewer is mindful of all of the comments on this matter from both the 2008 Reviewers and the Public sector. It seems that the major scientific issues about methodology used to generate the critical values come down to three points: (1) was it proper to utilize an LED_{10} rather than an ED_{10} value for determining the slope factor to be used in establishing the PHG value?; (2) was it acceptable to use linear analyses (rather than non-linear ones) when analyzing/extrapolating values from the NTP data sets to be used in these subsequent calculations?; and (3) was it correct to utilize data from the male mice alone rather than taking into account that of the female mice as well as that of the male and female rats?

In many of the responses to the 2008 Reviewers, the OEHHA makes clear that the US EPA 2005 *Guidelines for Carcinogen Risk Assessment* is the basis from which all determinations and calculations provided in the Draft were made. Because the OEHHA is one of five agencies under the umbrella of the California Environmental Protection Agency (Cal/EPA), this is appropriate. Thus, the answers to these three questions and ultimately the determination as to the appropriateness of the RA methodologies used for extrapolation to human exposures to Cr^{6+} in drinking water must be based on the US EPA Guideline.

Section 3.2.4 (Page 3-17) of the Guideline states that "Conventional cancer bioassays, with≈ 50 animals per group, generally can support modeling down to an increased incidence of 1-10%; epidemiologic studies, with larger sample sizes, < 1%. Various models commonly used for carcinogens yield similar estimates of the POD at response levels as low as 1%. Consequently, response levels at or below 10% can often be used as the POD. As a modeling convention, the lower bound on the doses associated with standard response levels of 1, 5, and 10% can be analyzed, presented, and considered." While this affirms the appropriateness of using either an LED_{10} or ED_{10} (indicating that the point of departure [POD] is the dose at which a 10% increase in tumor incidence above background is noted) for the PHG calculations, it is curious why a POD of 1% is not utilized, especially in dealing with a potential for cancer. However, this concern is mitigated by information from the 2005 Guideline (c.f. Appendix A, Page A-5) which states that "It is recognized that animal studies (and epidemiologic studies as well) have very low power to detect cancer effects. Detection of a 10% tumor incidence is generally the limit of power with standard protocols for animal studies (with the exception of rare tumors that are virtually markers for a particular agent, e.g., angiosarcoma caused by vinyl chloride). In some situations, the tested animal species may not be predictive of effects in humans; for example, arsenic shows only minimal or no effect in animals, whereas it is clearly positive (carcinogenic) in humans."

This information, while helping to validate the use of the 10% POD, does not resolve whether LED_{10} rather than ED_{10} was proper for determining the slope factor (cancer potency) value. The 2005 Guideline (Section 3.2.4, Page 3-17) indicates that "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"; moreover, "it may be appropriate to emphasize lower statistical bounds in screening analyses and in activities designed to develop an appropriate human exposure value, since such activities require accounting for various types of uncertainties and a lower bound on the central estimate is a scientifically-based approach accounting for the uncertainty in the true value of the ED_{10} [or central estimate]." However, the consensus of the SAB in 1997 was that "both point estimates and statistical bounds can be useful in different circumstances", and it recommended that the Agency "routinely calculate and present the point estimate of the ED_{10} and the corresponding upper and lower 95% statistical bounds". The SAB further noted that "risk assessors should calculate, to the extent practicable,

and present the central estimate and corresponding upper and lower statistical bounds (such as confidence limits) to inform decision makers". Optimally, the OEHHA should have presented calculated PHG values based upon both the ED_{10} and the LED_{10} (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 LED_{10} was appropriate for generating the PHG for human exposures to Cr^{6+} in drinking water.**

The 2005 Guideline - oddly enough, in conjunction with an issue raised in some of the Public sector comments - provides the needed context for making a determination as to acceptability of the OEHHA using linear analyses (rather than non-linear ones) when analyzing/extrapolating values from the NTP data sets. In Section 3.3 (Page 3-20), it is noted that "When a dose-response model is not developed for lower doses, another form of low-dose extrapolation is a safety assessment that characterizes the safety of one lower dose, with no explicit characterization of risks above or below that dose…. At this time, safety assessment is the default approach for tumors that arise through a non-linear mode of action; however, EPA continues to explore methods for quantifying dose-response relationships over a range of environmental exposure levels for tumors that arise through a non-linear mode of action". 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 Cr^{6+} level in drinking water is not linear. In Section 3.3.1 (Choosing an Extrapolation Approach [Pages 3-21 to 3-22]), it is stated that "when the weight-of-evidence evaluation of all available data are insufficient to establish the MOA for a tumor site and when scientifically plausible based on the available data, linear extrapolation <u>is used as a default approach</u>….. Non-linear approaches generally <u>should not be used in cases where the MOA has not been ascertained</u>" and "a *non-linear approach* should be selected when there are sufficient data to ascertain the MOA and conclude that it is not linear at low doses …". Because the OEHHA is following the guidelines established by the US EPA, and as noted in several Public sector comments "there is/are still no defined MOA for how Cr^{6+} might cause cancer in the stomach/GI", **the determination has been made that it was acceptable to use linear analyses (rather than non-linear ones) for the PHG calculations when analyzing/extrapolating values from the NTP data sets that were used**.

A determination also has to be made as to whether it was acceptable for the OEHHA to utilize data from the male mice alone rather than taking into account those from the female mice (as well as that of the male and female rats). In one of the responses to a 2008 Reviewer, the OEHHA indicated that "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". In this case, the response indicated that these choices were mandated by recommendation and statute (i.e., the *California Guideline for Chemical Carcinogen Risk Assessments and Their Scientific Rationale* [California Department of Health Services, 1985] and the *California Code of Regulations* [Title 27, Chapter 3, Safe Drinking Water and Toxic Enforcement Act of 1986 [Article 7 (Significant Risk Levels), §25703, (Quantitative Risk Assessment)]). Thus, as clearly presented in the Draft (Pages 76-77), the data from the male mice regarding development of small intestine (as opposed to oral) tumors during the course of a 2-year exposure to Cr^{6+} in their drinking water represents the data from the more sensitive species (mouse vs. rat) and from the more 'consistent' (i.e., no need for exclusion of a dose-group) sex in the test species. Based on this, **the determination has been made that it was**

acceptable to use data from the male mice alone without inclusion of those from the female mice (or from the male/female rats) in the PHG calculations. (Reviewer comment: The information provided in the OEHHA response to the Reviewer noted here 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 matters).

Having determined that the approaches used with respect to this point-of-science were based on sound scientific knowledge, methods, and practices, there are three issues that remain to be addressed about the PHG value, i.e., *a cancer potency estimate of 0.6 (mg/kg-day)$^{-1}$….. that resulted in an extrapolated one in one million lifetime cancer risk level for Cr^{6+} in tap water of 0.06 ppb*.

The first issue is that as noted on Page 90 of the document, "three routes of exposure, ingestion, inhalation and dermal contact with domestic water are addressed in developing the PHG". However, on Page 95, while the OEHHA states "All three of these routes could be relevant because of concern that Cr^{6+} may be carcinogenic by each of these exposure routes" it also concludes that "the dermal contribution to exposure is very little compared to the risk posed by other exposure routes" and so its use in the HPD and PHG calculations was dropped. It would have been preferable for the OEHHA to have included the dermal contribution in the PHG equation denominator; however, it is clear that the estimated < 0.2 ng Cr^{6+}/day that could be absorbed via skin exposure (in a system with 10 µg Cr^{6+}/L in the water; Pages 8-9) would have had little impact (in comparison with the much greater other two denominator values) in the equation. Therefore, **the determination has been made that the dropping of the dermal contribution from the PHG estimate is a reasonable step by the OEHHA.**

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). If there is consistency between the two estimates, then use of the 3.7 L/day value will give rise to a PHG of ≈ 0.031 ppb; conversely, if the value of 2 L/day is employed, then the adult male HPC is now 0.0056 mg/L. Therefore, **the determination has been made that a <u>single standard value</u> for daily water consumption should be employed in both the HPC and PHG estimates to make the corresponding final values accept-able and sound.**

The third and final issue is that if the OEHHA converts (for use in PHG estimate) the crude model potency estimate (for after inhalation exposure; Table 18, Page 88) of 0.15 (µg/m^3)$^{-1}$ to 510 (mg/kg-day)$^{-1}$ by using the equation "potency (mg/kg-day)$^{-1}$ = (unit risk [(µg/m^3)$^{-1}$] * (70 kg /20 m^3) * 1000 (µg/mg)", this presumes a 13.9 LPM minute volume; this is a level reasonable for a person doing work/exercising but well above an average resting rate (i.e., 5-8 LPM). As the inhalation potency portion of the denominator in the PHG estimate only slightly modifies the impact of the oral ingestion contribution (using the current 13.9 LPM variable, values of 0.0138 vs. 1.20, respectively), any re-calculation based on resting rates (using an 8 LPM results in a similarly small value [i.e.,≈ 0.0246]) would not significantly alter the outcome of the final estimate. While it was appropriate for the OEHHA to perform RA calculations based on analyses of 'most-susceptible' populations (i.e., here, individuals exposed to Cr^{6+} in their work environment), a clearer explanation justifying the 20 m^3 value in the calculation(s) would have substantively strengthened the overall accuracy and completeness of this Draft. In spite of this, **the determination has been made that no modification of the inhalation potency portion of the final estimate is required.**

Based on all of these findings, it is the determination of this Reviewer that the calculation used to prepare the final PHG estimate is sound and, further, that the 0.06 ppb value

should be accepted as one based upon sound scientific knowledge, methods, and practices.

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

Considering all the uncertainties, OEHHA believes the incorporation of health protective assumptions provides an acceptable level for public health protection.

In each HPD and ultimately, the PHG, the Draft document indicates that several types of uncertainties were considered and built into the calculations. Uncertainty factors (UF) were incorporated into the calculations to account for: "use of the NOAEL from an animal study; use of a less-than-lifetime study to establish a NOAEL for chronic exposure; extrapolating a NOAEL from a LOAEL; and, with human variability". As correctly noted on Page 91, "there is concern that certain human populations (such as infants) may have extra sensitivity not encompassed by the default factor of 10. In the case of hexavalent chromium, there is also a question as to whether antacid consumption or GI disease may result in marked increases in the absorption of hexavalent chromium from drinking water. Also, individuals with liver disease may be particularly sensitive to the hepatotoxic effects of hexavalent chromium, given that their livers are already compromised".

In the majority of the HPD calculations performed (Pages 90-93), UF values for the categories were set at 10; at those times where a different value (i.e., a UF of 3) was utilized, sound justification was provided. In general, use of an UF of 10 is merited; here, as in reviews of other toxic agents, the use of a full UF of 10 was deemed to be prudent in order to "provide an adequate margin of safety for human exposure to hexavalent chromium in drinking water" on the basis of the results of a given animal study. An aggregate uncertainty factor (maximum limit) of 3,000 was accepted by the OEHHA and used when appropriate. This maximum is based on the established recommendations of California's Risk Assessment Advisory Committee (1996) and the U.S. EPA (2002b). The wisdom of setting any such "cap" is questioned, especially when it pertains to critical health outcomes (including cancer); nevertheless, in the absence of any additional guidance on this matter, the 3000 aggregate UF must be accepted as appropriate.

In light of the above comments, **this particular point-of-science is deemed as one based on sound scientific knowledge, methods, and practices.**