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Ser N40JRR.cs/0024
October 30, 2009

Mr. Michael Baes
Pesticide and Environmental Toxicology Branch, Office of Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street, 16th Floor
Oakland CA 94612

Subject: PROPOSED PUBLIC HEALTH GOAL (PHG) FOR HEXAVALENT CHROMIUM (Cr6+)

Dear Mr. Baes,

I am writing as the Deputy Department of Defense (DoD) Regional Environmental Coordinator (REC) for Federal Region 9 on behalf of the military services in California in regard to the public health goal project. We appreciate the opportunity to comment on California's draft Public Health Goal (PHG) for hexavalent chromium (Cr6+) and share the desire to protect human health and the environment. As you may be aware, the Department of Defense showed federal leadership by issuing a proactive policy in April 2009 that will significantly minimize the use of Cr6+ throughout DoD and require the use of safer substitutes that meet performance requirements.

We note that the proposed PHG is unique in two regards. It is based on a cancer endpoint and it is valence-specific. Current state and federal maximum contaminant levels (MCLs) for drinking water are established for total chromium and are based on a non-cancer endpoint. 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. 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 incidence predicted by the risk assessment on which the draft PHG is based. This will provide needed perspective on the proposed PHG for the public.

Our scientists have reviewed the derivation of the draft PHG and their comments are attached in enclosure (1). If you need any additional information concerning this issue, please contact Mr. Baha Zarah at (415)977-8843 or Michael Huber at (619)532-2303.

Sincerely,

C. L. Stathos
By Direction

Enclosure: (1) Department of Defense Comments on CA OEHHA "Draft Technical Support Document on Proposed Public Health Goal for Hexavalent Chromium in Drinking Water"

Enclosure 1

DEPARTMENT OF DEFENSE COMMENTS ON CA OEHHA "DRAFT TECHNICAL SUPPORT DOCUMENT ON PROPOSED PUBLIC HEALTH GOAL FOR HEXAVALENT CHROMIUM IN DRINKING WATER"[Dated 08/20/09]

General Comments:

(1) The Department of Defense appreciates the opportunity to provide comments to the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (CA EPA) for their consideration in response to their invitation for public comment on their *Draft Public Health Goal for Hexavalent Chromium in Drinking Water* document dated August 2009.

(2) The data presented in the draft PHG document indicate that Cr+6 behaves differently than Cr+3, both at the site of contact and systemically. 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:

a. Cr+6 is highly reactive and is therefore likely to produce its greatest damage at a point of contact.
b. The cancer sites in rodents differ by route of administration, i.e., lungs for inhalation and GI tract for ingestion.
c. No statistically significant *systemic* tumors were observed in the rodent study that initiated concerns about oral exposure to Cr+6 (NTP, 2007).
d. In the epidemiological/occupational studies presented:
   - The limited finding of GI tract tumors from inhalation exposure could be caused by ingestion as the airborne particles were cleared from the lungs; and
   - The potential non-site-of-contact tumors observed in the human studies were not consistently found in most of the epidemiological studies.

(3) While chromium has been extensively studied, toxicity data specifically associated with particular valence states are limited. Thus, the data presented may not be sufficient to support a mode of action for carcinogenesis analysis for Cr+6. 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. Although this is a California analysis, the alternative presented in the previous sentence is recommended by EPA's 2005 cancer guidelines.

(4) In particular, if the observations below are substantiated and part of a mode of action analysis, they are likely to result in a mode of action that (again, according to EPA's cancer guidelines) would use a nonlinear extrapolation from the point of

departure (in this case the LED10). A nonlinear extrapolation would substantially alter the estimated risk. The following observations suggest either use of a non-standard, dose-response analysis and/or a nonlinear mode of action will be warranted when more data are available.

a. Chromium is an essential element. In other cases where more data are available, it has been found that, if the standard, default approach is used for essential elements, the "acceptable" level of exposure is often below the recommended daily allowance (RDA), which is an estimate of the minimum necessary for good health. Note, however, that for oral exposure for chromium, e.g., assumed for an RDA, the conventional assumption has been that essentially most of the Cr+6 (>90%) would be converted to Cr+3 in the stomach (as stated in the draft PHG document).
b. 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 two lower doses. These would support a nonlinear extrapolation from the point of departure.
c. 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.

(5) It is worth noting that the draft PHG document discusses the potential for Cr+6 to be a systemic mutagen. Even if supported by additional data, a finding of systemic mutagenicity – absent a finding of systemic carcinogenicity – would not necessarily be indicative of a mutagenic mode of action for the tumors observed in rodents. The high reactivity of Cr+6 indicates that it might interact directly with DNA, proteins, etc., at the site of carcinogenicity, but also that it could cause other effects such as cytotoxicity. 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.

(6) A little more information and a few calculations might bring a useful perspective to the proposed PHG. At the top of page 6, the draft PHG document states that the oral exposure to chromium from food ranges from 5 to 500 ug/per day with "a typical value of approximately 100 ug/day ..." The proposed PGH for Cr+6 is 0.06 ug/L or, assuming 2L of water per day, 0.12 ug/day. 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.

(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.

(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.

(9) The data from human exposure to Cr+6 is highly variable and only involved a few people. Moreover, as the document states, "Within the same individual, chromium levels sometimes markedly increased at one dose, but *no response was observed at a higher dose* (Finley *et al.*, 1997). [italics added]" Thus, data from this study is at best suggestive of the findings.

(10) Relevance to humans exposed to orders of magnitude lower concentrations of Cr+6 in drinking water of the NTP 2007 male mice small intestine tumor data has been the subject of much scientific debate. 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 guideline.

Specific Comments:

(1) Page 2, *"Summary"*
Pages 41-42, *"Mechanism of Genotoxicity and Carcinogenicity"*

Page 2 states that *"Studies of the mechanism of action of hexavalent chromium suggest a carcinogenic response if hexavalent chromium enters cells, regardless of the route of exposure. Orally administered hexavalent chromium results in genotoxicity at sites distal to the site of entry, the gut, which indicates that chromium reaches those sites in the hexavalent form."* Contrary to this statement, as the draft document states on page 41, it is not clear which species of Cr (Cr+3, Cr+4, or Cr+5) is the "active" form. Furthermore, the ability of chromium to have effects distal to the site of entry does not suggest carcinogenicity at those sites. Many chemicals have non-cancer, toxic effects at sites other than those at which they produce cancer. Organ-specific toxicity (or lack thereof) for a chemical is the norm.

Page 42 of the Draft states *"Hexavalent chromium carcinogenesis is thought to be mediated through this DNA damage."* However, as an NTP 2007 reviewer noted *"Histiocytic infiltration was observed in the liver, in the intestine, and in pancreatic and mesenteric lymph nodes, suggesting chronic irritation of the intestinal epithelium. Based on these findings, NTP concluded that the intestinal*

epithelial hyperplasia is a pre-neoplastic lesion related to the intestinal tumors" (Comments Regarding NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate for May 16-17, 2007 Peer Review.") 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" (Cotran et al. 1994, Quah et al. 2005, Wilkinson and Killeen 1996). The NTP conclusion is also supported by the mode of action (MOA) for lung tumor formation from occupational inhalation of much higher concentrations of Cr+6 in air, which is believed to be initiated via a "point-of-contact" MOA. As noted in the 2008 ATSDR *Draft Toxicological Review of Chromium "No studies were located regarding genotoxic effects in humans after oral exposure to chromium or its compounds."* Thus, it appears uncertain whether the MOA for hexavalent chromium carcinogenesis is a mutagenic MOA and this statement should be clarified. The finding of mutagenicity and carcinogenicity is necessary but not sufficient for a finding of a mutagenic mode of action for carcinogenicity, at least as defined by EPA's cancer guidelines and supplemental guidance.

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.

(2) Page 2, *"Summary"*
Page 121-126, Appendix B, *"Mouse Cancer Study of Borneff et al. (1968")*

Page 2 states *"Administration via drinking water of hexavalent chromium to mice (Borneff et al., 1968) resulted in a statistically significant increase in stomach tumors compared to controls (OEHHA analysis)."* 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. Although, in response to a University peer reviewer's concerns with the Borneff et al. 1968 study, CA EPA stated *"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."* We believe that a disproportionate amount of space still has been allocated to an in-depth discussion of this study in Appendix B. This does not appear to be justified based on the studies' weaknesses and in comparison to the much more limited discussions of other important topics, such as studies with negative results for

carcinogenicity related to ingestion of drinking water. (http://www.oehha.ca.gov/water/phg/pdf/CrResponse090909.pdf).

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.

(3) Pages 9-22, "*Metabolism and Pharmacokinetics*"

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 then that for mice (NTP 2007).

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 reviewer's 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.

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.

(4) Page 50, Figure 12. *Body weights of female mice compared to control*

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.

(5) Pages 58-72, "*Toxicological Effects in Humans: Carcinogenicity*"
Pages 60-67, "*Cancers of ingestion- and digestion-related organs reported in occupational studies*"

Although numerous studies with statistically significant human epidemiological evidence are presented that demonstrate that Cr+6 is a potential human carcinogen via the inhalation route of exposure, very few human studies of ingestion of Cr+6 are currently available that provide statistically significant data suitable for use in a human health risk estimation.

The 2009 PHG Draft document reported an "association" between human ingestion of Cr+6 in drinking water and stomach/intestinal cancer. However, we believe that these data are merely "suggestive" and are not suitable for use in the derivation of an oral cancer slope factor for Cr+6. CA OEHHA also does not appear to place much weight on these human data due to the great amount of uncertainty associated with them. 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.

(6) Pages 60-67, "*Cancers of ingestion- and digestion-related organs reported in occupational studies*"
Pages 62-67, Table 7, "*Summary of Results for Selected Cancers and Nonmalignant Respiratory Diseases Reported in Studies of Occupational Populations Potentially Exposed To Hexavalent Chromium*"
Page 68, Table 8, "*Occupational Studies That Reported Results for Stomach Cancer, Sorted by Rate Ratio, in Descending Order*"

The last paragraph of page 61 states, "*For stomach cancer, 18 of 25 (72 percent) estimated a rate ratio above 1, while in 7 out of 25 studies, the rate ratio was below 1 (suggesting a reduction in stomach cancer) (Table 7 and 8). The rate ratios were above 1 in 18 of 26 studies for cancer in all digestive organs, 8 out of 11 studies for cancer of the esophagus and 12 out of 16 studies for cancer of the*

rectum. Interestingly, for stomach cancer, only 3 out of 25 studies did the lower confidence interval of the rate ratio exceed 1 (Table 7)." It appears that CA OEHHA simply counted the number 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 (http://www.oehha.ca.gov/water/phg/pdf/Cr_Gwiazda090909.pdf). We also believe that additional discussion of cancers of the rectum, etc., are needed for clarification, especially as only cancers of the stomach seem to be discussed in more depth.

(7) Pages 69-71, *"Ingestion studies"*
Pages 72-73, *"Sensitive Subpopulations"*
Pages 126-137, Appendix B, *"The Helicobacter Hypothesis,"*
"Potential Influence of Helicobacter Infections on Stomach Tumors"

The draft PHG document devotes a large section of Appendix B to a discussion of the potential influence of *Helicobacter Infections* on stomach tumors. It discusses the fact that the single reported study of a population in a China rural village with a high concentration of Cr+6 in well water, that identified a statistically significant stomach cancer risk from drinking well water (Zang and Li1987), had severe limitations.

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. . Stomach cancer mortality in the regions with contaminated water was more substantially elevated in comparison with the regions without contaminated water (1.82; 1.11-2.91) and the whole province (1.69; 1.12-2.44). While these data are limited, they are consistent with increased stomach cancer risk in a population exposed" to Cr+6 in drinking 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). This should be clarified in the text. In addition, epidemiological evidence on the direct relationship between stomach cancer and nutrition has been well documented and shows a distinct international difference as compared to the U.S. (see Comment #8). This evidence adds to the uncertainty of these studies, with unclear village exposure analysis, water palatability concerns, noted presence of *H. pylori* bacteria, etc. which makes it difficult to demonstrate a cause and effect relationship.

The high rate of infection with the *Helicobacter pylori* bacteria in the stomachs in Chinese populations was also reported to increase susceptibility to stomach cancer from ingestion of high concentrations of Cr+6 in well water, implying potential synergistic effects. Thus the draft PHG document identified individuals infected by *H. pylori* as "sensitive subpopulation." (CA OEHHA's Responses to Major Comments on Technical Support Document, September 2009). 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. Thus, since the data from the China population was presented as supporting information for Cr+6-induced stomach cancer we believe that this topic requires further clarification. It would be beneficial to provide additional pertinent information concerning the prevalence of gastrointestinal cancer in developing countries versus the U.S. The draft PHG document included a number of additional "Sensitive Subpopulations" studies in the Draft, in the "References Section" that also mentioned infection with the *H. pylori* bacteria and gastric illnesses/cancers and medications that can result in increased stomach pH, implying decreased amount of Cr+6 reduction to Cr+3 in the stomach.

For example, Asaka et al. (1998) reported that the probability of developing stomach cancer is much higher in the populations of developing countries, due to various environmental factors, such as diet, age when infected with the *H. pylori* bacteria, how long the infection lasted, how infectious the *H. pylori* strain is, and a number of other factors, including inherited factors making individuals more susceptible to gastric cancer, etc. (Asaka M.et al. Long-term Helicobacter pylori infection--from gastritis to gastric cancer. Aliment Pharmacol Ther. 1998, Feb; 12 Suppl 1:9-15).

Lambert R et al. (2007) also discusses the particularly high incidence of stomach cancer and other gastric illnesses in the Asian populations due to causal factors such as *H. pylori* bacterial infections, diets poor in fruits and vegetables, as well as having other pre-cancerous conditions, such as that found in alcoholics that may increase one's susceptibility to stomach cancer (Lambert R et al., "The Multidisciplinary Management Of Gastrointestinal Cancer. Epidemiology of Oesophagogastric Cancer." Best Pract Res Clin Gastroenterol. 2007; 21(6):921-45).

Neither study mentioned ingestion of drinking water with Cr+6 as a potential causative factor. Both studies noted an inflammatory response in the stomach in regard to being infected with this strain of bacteria. Thus, we believe that it would increase the reader's understanding if the Draft stated that although the association of Cr+6 in drinking water and a particular populations' increased incidence of stomach cancer may be noted, it may not be the direct cause of the stomach cancer. 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 protocol designs and study evaluations. (http://www.asbestos.com/cancer/gastrointestinal.php).

(8) Pages 58-72, "*Toxicological Effects in Humans: Carcinogenicity*"
Pages 69-71, "*Ingestion studies*"
Pages 72-73, "*Sensitive Subpopulations*"
Pages 126-137, Appendix B, "*The Helicobacter Hypothesis,*"
"*Potential Influence of Helicobacter Infections on Stomach Tumors*"

Page 129 states "*In 2000, cancer of the stomach resulted in the third (females) or second (males) highest rates of mortality of all tumor sites worldwide (IARC, 2000). Mortality from stomach cancer is highest in developing countries (e.g., China) (Centers for Disease Control, 2002). The high incidence of stomach cancer in developing countries has been attributed to dietary factors, nutritional status, and the lack of refrigeration. These countries are also characterized by a widespread occurrence of H. pylori in the population (Lynch, 2002). Greater than 80 percent of the population in China is believed to be infected with H. pylori. Individuals infected with H. pylori have a 2- to 6-fold increased risk of developing gastric cancer and mucosal-associated, lymphoid-type lymphoma compared to uninfected individuals (Centers for Disease Control, 2002).*"

We believe that this information is important and should be placed in the body of the main document so that it is readily available to the general reader – perhaps under human population ingestion studies and the potential influence of helicobacter infections on stomach tumors. Page 137, "Future Studies," states that stomach cancer is one of the most common sites of neoplasms in humans. Although this may be true internationally, the stomach cancer figures may be much lower for the U.S. population. Thus, we thought it would be helpful to review the 2009 U.S. Surveillance Epidemiology and End Results (SEER) stomach and small intestine cancer statistical data currently available to see what the latest statistical data showed for cancers of the stomach and small intestine in the U.S. population (http://seer.cancer.gov/statistics/).

The 2009 SEER statistics were based on cases diagnosed/physician deaths reported in 2002-2006 from 17 SEER geographic areas for both stomach and small intestine cancer **from all causes** [added emphasis] for the U.S. population, with data also available by age, sex, and race. The age-adjusted death rate for cancer of the small intestine was 0.4 per 100,000, where the median age of death was 71 years of age. Based on rates from 2004-2006, 0.21% of men and women born today will be diagnosed with cancer of the small intestine during their lifetime. For stomach cancer, the incidence rates are 11.0 per 100,000 for all races. Asian/Pacific Islander males had the highest incidence rates by race and sex (16.8 per 100,000 men, with American Indian/Alaska Native males and then Hispanic males having the next highest incidences, which lends additional support to other studies showing that certain ethnic populations are at greater risk for developing stomach cancers, believed to be mainly due to dietary deficiencies, prevalence of

inflammation resulting from H. *pylori* bacterial infections in their stomachs. (See comment #7).

Based on rates from 2004-2006, 0.89% of men and women born today will be diagnosed with cancer of the stomach at some time during their lifetime from all known causes. Thus, compared to the lifetime risk of cancers of the lung, breast, etc., U.S. populations have a much lower lifetime risk of developing cancers of the small intestine and stomach. Thus, it appears that humans may be much less susceptible than other animals to Cr+6-induced gastrointestinal (GI) tract cancers from ingesting low levels of Cr+6 in drinking water than the adenomas or carcinomas of the duodenum, jejunum, or ileum reported in mice exposed to about 6 orders of magnitude higher active concentrations of Cr+6 (NTP 2007).

Editorial Comments

(1) Page 1, "Summary"

The last paragraph of page 1 states, *"Following oral administration of hexavalent chromium to humans and experimental animals, increased* ***levels of chromium*** *in whole blood and plasma were observed, while little change was observed following trivalent chromium administration."* 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.

(2) Page 69, *Ingestion Studies*

The reference JHAS (1979) is mentioned as one of the papers with findings as the basis 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.

(3) Page 53, Figure 13 *Dose-response for combined intestinal tumors in male and female mice*

Figure 13 has no units on the x-axis. Also, the title "combined tumors" is unclear. It cannot be the sum of the tumors, because the total number of tumors in the tables exceeds the number of animals on test. Thus, it must be something like "tumor-bearing animals" but the actual title and how the data were calculated should be transparent.