EXHIBIT A

(to the comment letter)

From: Harold Singer [mailto:HSinger@waterboards.ca.gov]
Sent: Thursday, May 26, 2011 11:48 AM
To: Lauri Kemper
Cc: drew@jdp-law.com; DAG6@pge.com; MCKd@pge.com; Kim Niemeyer; Reed Sato
Subject: Whole-house Replacement Water

Ms. Kemper

Based on recent statements at Water Board meetings and documents in the Water Board files, I understand that the Water Board Prosecution Team is developing an order to address a directive from the Water Board to evaluate the need for whole-house replacement water for Hinkley residents affected by the historic chromium discharge from the PG&E Compressor Station. Given that the groundwater in this area is well below the current MCL for total chromium and that a public health goal is still in draft form, any order would likely have significant technical, legal and policy considerations. Because of this, it is important to provide affected and interested public and PG&E an opportunity to respond to the factual, legal and technical assertions in the order and to develop a record to support any Water Board action relative to this issue. Therefore, I am requesting that if the Prosecution Team proposes an order for whole-house replacement water that this order be transmitted to me in draft form along with a mailing list of potentially affected and interested persons. The transmittal should also include any evidence that the Prosecution Team is relying on to support the draft order. I will transmit the proposed draft order and supporting information to potentially affected and interested persons, along with instructions for providing comments.

thank you
harold singer

7/11/2011

EXHIBIT B

(to the comment letter)

November 2, 2009

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

Re: Public Health Goal for Hexavalent Chromium in Drinking Water

Dear Dr. Baes:

I am writing to you on behalf of the Hexavalent Chromium Panel (Panel) of the American Chemistry Council regarding the draft Public Health Goal (draft PHG) for Hexavalent Chromium (Cr (VI)) issued on August 20, 2009, by the Office of Environmental Health Hazard Assessment (OEHHA). The Panel consists of members who have an interest in the production or use of hexavalent chromium in North America. After reviewing available toxicity data, OEHHA published the draft PHG of 0.06 parts per billion as being "protective against all identified toxic effects from both oral and inhalation exposure to hexavalent chromium that may be present in drinking water."[1] As discussed below, the Panel urges OEHHA to await additional research findings anticipated in 2010 before finalizing the draft PHG.

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

[1] The draft PHG is available online: http://www.oehha.ca.gov/water/phg/pdf/Cr6PHGdraft082009.pdf

a 90-day drinking water study; 2) genomic studies on tissues from the 90-day study; 3) pharmacokinetic modeling; 4) in *vivo* mutation analysis and 5) high data content *in vitro* studies. [2] This research is expected to be completed in 2010.

In a memo dated October 23, 2008, from Dr. David Berry, Senior Toxicologist with the Human and Ecological Risk Division of the Department of Toxic Substances Control, to Dr. Jeff Wong, Chief Scientist of the Department of Toxic Substances Control, the Hamner research program was recognized as critical in addressing the mode of action of chromium and the studies should be "prerequisites to any revisions to the OEHHA public health goal for Cr^{+6}." In issuing the draft PHG prematurely, however, OEHHA has failed to consider the anticipated mode of action research. (*See* Appendix A) We agree with DTSC comments regarding how important it is to use current scientific principles and recent advances such as incorporating mode of action are preferable to using outdated default assumptions. We urge OEHHA to await additional research findings anticipated in 2010 before finalizing the draft PHG.

The Panel appreciates your consideration of these comments. If you have questions, or would like to discuss the studies sponsored by the Panel, please contact me at (703) 741-5614 or kristy_morrison@americanchemistry.com.

Sincerely yours,

Kristy L. Morrison

Kristy L. Morrison
Manager, Hexavalent Chromium Panel
Chemical Products & Technology Division
American Chemistry Council

[2] More information on the SAB can be found online here: http://www.tera.org/Peer/Chromium/Chromium.htm

APPENDIX A

Linda S. Adams
Secretary for
Environmental Protection

Department of Toxic Substances Control

Maureen F. Gorsen, Director
8800 Cal Center Drive
Sacramento, California 95826-3200

Arnold Schwarzenegger
Governor

MEMORANDUM

TO: Jeff Wong, Ph.D.
Chief Scientist
Department of Toxic Substances Control
1101 I Street, 25th Floor
Cal/EPA
Sacramento, CA 95814

FROM: David L. Berry, Ph.D. David L. Berry
Senior Toxicologist
Human and Ecological Risk Division
8810 Cal Center Drive
Sacramento, CA 95836-3200

DATE: October 23, 2008

SUBJECT: Hexavalent Chromium Public Health Goal

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

General Comments

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

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

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

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

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

Specific Comments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Recommendations

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

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

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

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

Relative Source Contribution and Bioavailability

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

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

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

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

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

References

Baetjer, A.M. 1950. Pulmonary carcinoma in chromate workers. II. Incidence on the basis of hospital records. Arch. Ind. Hyg. Occup. Med. 2: 505-516.

Bloomfield, J.J. and Blum, W. 1928. Health hazards in chromium plating. Pub.Health Repts. 43: 2330-2347.

Borneff, J., Engelhardt, K., Greim, W., Kunte, H., Reichert, J. 1968. Carcinogens in water and soil. XXII. Mouse drinking water experiments with 3,4-benzopyrene and potassium chromate. Arch. Hyg. Bakteriol. 152(1):45-53.

Clewell, H.J., Andersen, M. E. and Barton H.A. 2002. A consistent approach for the application of pharmacokinetic modeling in cancer and noncancer risk assessment. Environ. Hlth. Perspect. 110(1):85-93.

Cole, P. and Rodu, B. 2005. Epidemiologic studies of chrome and cancer mortality: A series of meta-analyses. Regul. Toxicol. Pharmacol. 43:225-231.

Crump, C., Crump, K., Hack, E., Luippold, R., Mundt, K, Liebig, E., et al., 2003. Dose-reponse and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Anal. 23(6):1147-1163.

Fisher, J.W. 2000. Physiologically Based Pharmacokinetic Models for Trichloroethylene and Its Oxidative Metabolites. Environ. Hlth. Perspt. 108(S2): 265-273.

Gibb, H.J., Lees, P.S., Pinsky, P.F. and Rooney, B.C. 2000. Lung cancer among workers in chromium chemical production. Am J. Ind. Med 38(2):115-126.

Gross, E. and Kosch, F. 1943. Lung cancer in the chromate dye industry. Arch. Gewerbepath. Gewerbehyg. 12: 164-170.

Manciso, R.F. and Hueper, W.C. 1951. Occupational cancer and other health hazards in a chromate plant: A medical appraisal. I. Lung cancers in chromate workers. Ind. Med. Surg. 20: 358-363.

McKone, T.E. 1987. Human exposure to volatile organic compounds in household tap water: The indoor inhalation pathway. Environ. Sci. Technol. 21: 1194-1201.

McKone, T.E. and Knezovich, J.P. 1991. The transfer of trichloroethylene (TCE) from a shower to indoor air: Experimental measurements and their implications. J. Air Waste Mgmt. 41(6): 832-837.

National Academy of Sciences. 2006. Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues. The National Academies Report in Brief, Washington, D.C.

National Toxicology Program, 2007a. NTP Technical Report on the Toxicity Study of Sodium Dichromate Dihydrate Administered in Drinking Water to Male and Female F344/N Rats and B6C3F1 Mice and Male BALB/c and an3-C57B/6 Mice, toxicity Report Series, Number 72, January 2007.

National Toxicology Program, 2008. NTP Technical Report on the Toxicology and Carcinogensis Studies of Sodium Dichromate Dihydrate in F344/N Rats and B6C3F1 Mice (Drinking Water Studies), NTP TR546, NIH Publication No. 08-5887.

O'Flaherty, E.J. 1966. A physiologically based model of chromium kinetics in the rat. Toxicol. Appl. Pharmacol.138: 54-64.

O'Flaherty, E.J., Kerger, B. D., Hays, S.M., and Paustenbach, D.J. 2001. A physiologically based model for the ingestion of chromium (III) and chromium (VI) by humans. Toxicol. Sci. 68:196-213.

Othmer, K. 2001. Chromium and Chromium Alloys, In: Encyclopedia of Chemical Technology 3rd Edition, Vol. 6 pp. 54-60. John Wiley & Son, Inc., New York

Park, R.M., Bena, J.F., Stayner, L.T., Smith, R.J., Gibb, H.J. & Lee, S.J. 2004. Hexavalent Chromium and Lung Cancer in the Chromate Industry: A Quantitative risk Assessment. Risk Anal. 24(5):1099-1108.

Park, R. M. & Stayner, L.T., 2006. A Search for Thresholds and other Nonlinearities in the Relationship between Hexavalent Chromium and Lung Cancer. Risk Anal. 26(1): 79-88.

Paustenback, D.J., Finley, B.L., Mowat, F.S. and Kerger, B.D. 2003. Human health risk and exposure assessment of chromium (VI) in tap water. J. Toxicol. Environ. Health, Part A. 66:1295-1339.

Proctor, D.M., Otani, J.M., Finley, B.L., Paustenbach, D.J., Bland, J.A., Speizer, N., and Sargent, E.V. 2002. Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. J. Toxicol. Environ. Hlth. Part A 65:701-746.

Proctor, D.M., Panko, J., Liebing, E., Paustenbach, D.J. 2004. Estimating historical occupational exposure to airborne hexavalent chromium in a chromate production plant: 1940 – 1972. J. Occup. Environ. Hyg. 1:752-767.

U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. EPA/630/P03/001B.

World Health Organization. 2005. Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use in Dose/Concentration-Response Assessment. World Heath Organization, Geneva.

World Health Organization. 2008. Principles of Characterizing and Applying Physiologically-based Pharmacokinetic and Toxicokinetic Models in Risk Assessment. Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals. World Health Organization, Geneva.

Zhang, J. and Li, S. 1987. Cancer mortality in a Chinese population exposed to hexavalent chromium in water. J. Occup. Environ. Med. 39:315-319.

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