FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25707(b). SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK HEXAVALENT CHROMIUM

This is the Final Statement of Reasons for a proposed regulatory amendment that would remove the reference to "chromium (hexavalent compounds)" as a chemical that presents no significant risk of cancer by ingestion for purposes of Proposition 65[1] in Title 27, California Code of Regulations, section 25707(b)(4).[2]

On September 16, 2011, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to remove the reference to "chromium (hexavalent compounds)" in Section 25707(b)(4). The Initial Statement of Reasons set forth the grounds for the proposed amendment. It is based on currently available scientific information that shows oral exposures to hexavalent chromium can pose a significant cancer risk.

A 45-day public comment on the proposed amendment was initiated on September 16, 2011 and extended until November 30, 2011, based on a request from the American Chemistry Council and the California Manufacturers and Technology Association. OEHHA received six sets of written public comments from:

1) American Chemistry Council (ACC)
2) Plumbing Manufacturers International (PMI)
3) Environmental Working Group (EWG)
4) A group made up of: Center for Public Environmental Oversight, Clean Water Action, Environmental Working Group, Erin Brokovich, Inc., Integrated Resource Management, Inc., and Natural Resources Defense Council
5) Edward Hou
6) Robert Matias

On September 22, 2011, OEHHA provided the notice of proposed rulemaking and the initial statement of reasons for the proposed regulation to the members of the Proposition 65 Carcinogen Identification Committee for their review and comment as required by Health

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986; Health and Safety Code, section 25249.5 et seq.
[2] All further section references are to Title 27 of the California Code of Regulations, unless otherwise noted.

and Safety Code section 57004. No comments were received from any committee members.

SUMMARY AND RESPONSES TO COMMENTS RECEIVED

OEHHA relied upon scientific information presented in OEHHA's 2011 Public Health Goal (PHG) [3] risk assessment for hexavalent chromium and the conclusions in the PHG document regarding the carcinogenicity of hexavalent chromium by the oral route as the basis for the proposed regulatory action. Most of the comments on the content of the PHG document are not directly related to the proposed regulatory amendment to section 25705(b). Many of these comments pertain to the cancer dose response analysis and method of calculation of the PHG, neither of which are relevant to the proposed change to the regulation. The proposed change does not adopt a specific No Significant Risk Level for hexavalent chromium and does not involve calculating dose response relationships. Instead, it repeals the existing provision that determined, based on the scientific data available at that time, that there was no significant risk at any exposure level for hexavalent chromium via ingestion. The earlier determination is inconsistent with current scientific knowledge. This knowledge is summarized in the PHG document.

OEHHA is not required by the Administrative Procedure Act[4] to respond to comments that are not related to the proposed action or the procedures used to adopt the regulation. However, OEHHA has summarized and responded to some comments that are not directly related to the proposed action in order to provide context for its decision to proceed with the proposed change to the regulation. The absence of a response in this final statement of reasons to irrelevant comments should not be construed to mean that OEHHA agrees with them. Detailed responses to all the major comments received on the PHG document, including many identical comments submitted on this proposed regulatory action, were summarized and responded to in the PHG response document[5] that is included with this Final Statement of Reasons as an attachment to provide context.

[3] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.
[4] Specifically, Government Code section 11346.9(a)(3)
[5] OEHHA (2011) Responses to Major Comments on Technical Support Document. Public Health Goal for Hexavalent Chromium (Cr VI) in Drinking Water. July 2011. Available on the OEHHA web site at url: http://www.oehha.ca.gov/water/phg/pdf/Cr6PHGresp072911.pdf

Comments from the American Chemistry Council (ACC)

The comments submitted by ACC are comprised of ACC's comment letter signed by Ann Mason dated November 30, 2011, with two attachments (Attachment A is a consultant's report authored by Ted Simon, Ph.D., DABT, of Ted Simon LLC; Attachment B is an annotated timeline of the development of the PHG for hexavalent chromium) and a December 6, 2011 letter from Ann Mason correcting a typographical error in Attachment A. Ms. Mason's letter made no reference to Attachment B, which is not relevant to this regulatory action and therefore is not responded to in this Final Statement of Reasons.

Comment ACC-1: "OEHHA's sole basis for this proposed rule change is the Public Health Goal (PHG), which was released on July 27, 2011. The PHG is significantly flawed and cannot be used to support a departure from the existing 'no significant risk of cancer' exemption." [ACC comment letter, p. 1]

"Based on the foregoing, the PHG is not an adequate basis for the proposed amendment to remove hexavalent chromium [Cr(VI)] from the list of five chemicals that present no significant risk of cancer by the route of ingestion. The best available science continues to support OEHHA's 1990 determination that Cr(VI) presents no significant risk of cancer by the route of ingestion." [ACC comment letter, p. 5]

> Response ACC-1. As stated in the Initial Statement of Reasons, the proposed amendment is based on the currently available scientific information that shows oral exposures to hexavalent chromium can pose a cancer risk. The National Toxicology Program (NTP, 2008) tested hexavalent chromium by the oral route in two-year studies in male and female rats and mice, finding clear evidence of carcinogenicity in each of the four experiments. These data are reviewed in the PHG document[6], as are data from studies in humans demonstrating absorption of hexavalent chromium following exposure by the oral route. The PHG document for hexavalent chromium underwent two rounds of external scientific peer review by the University of California before it was made final. The scientific basis for the proposed action is sound.
>
> No changes to the regulation were made in response to this comment.

[6] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

Comment ACC-2: "The attached technical comments (Attachment A) show that OEHHA's assumption in the final PHG of a mutagenic mode of action (MOA) and use of linear extrapolation from the risk at high doses to one-in-one million risk level at a dose close to zero is not supported by the best available science." [ACC comment letter, p. 1]

Response ACC-2. This comment is not relevant to the proposed action. While the PHG document did establish a numerical public health goal for hexavalent chromium in drinking water, the current action does not propose any numerical level for this chemical. Thus, the arguments presented in the comments concerning calculation of the PHG are not relevant to the proposed action deleting hexavalent chromium from Section 25705(b).

OEHHA previously responded to public comments submitted on the PHG[7] that are similar to this comment (See for example page 116 of OEHHA's Response to Cr VI PHG Comments document[8]).

No changes to the regulation were made in response to this comment.

Comment ACC-3: "Importantly, new research sponsored by ACC supports a non-mutagenic MOA and indicates a threshold for effects." [ACC comment letter, p. 1]

"Additionally, in developing the PHG, OEHHA did not consider newly developed data presented to them directly by researchers that indicate that Cr(VI) does not act by a mutagenic MOA and shows a threshold for toxic effects in mice, which are precursor or sentinel effects for cancer as defined by USEPA. The new research indicates that Cr(VI) carcinogenesis in mouse small intestine occurs by a non-mutagenic MOA that involves oxidative stress, tissue damage and compensatory growth." [ACC comment letter, p. 3]

"No references to either Thompson *et al.* (2011a) or Thompson *et al.* (2011b) can be found in either the draft or final PHG, indicating that the ACC-sponsored MOA research program was not considered." [See Attachment A to ACC comment letter, page 14]

[7] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

[8] OEHHA (2011) Responses to Major Comments on Technical Support Document. Public Health Goal for Hexavalent Chromium (Cr VI) in Drinking Water. July 2011. Available on the OEHHA web site at URL: http://www.oehha.ca.gov/water/phg/pdf/Cr6PHGresp072911.pdf.

"Thompson *et al*. (2011a) hypothesize that diffuse epithelial hyperplasia represents regenerative proliferation in response to Cr(VI)-induced tissue injury." [See Attachment A to ACC comment letter, page 26]

Response ACC-3. The current action does not depend on whether or not hexavalent chromium has a non-mutagenic mode of action (such as proliferation induced by tissue injury), but rather whether exposures to hexavalent chromium by the route of ingestion present no significant risk of cancer.

The concept of a "threshold for effects" raised in the comment pertains to the cancer dose response relationship. It refers to the situation where above the threshold dose cancer can occur, below the threshold it cannot. The shape of the dose-response curve only becomes important when calculating a specific "No Significant Risk Level" (NSRL) under Section 25701. OEHHA is not proposing such a level in this regulatory action.

OEHHA considered the ACC-sponsored research referred to in the comments as Thompson *et al*. (2011a)[9] and Thompson *et al*. (2011b)[10] in the preparation of the PHG document. Thompson *et al.* (2011a)[11] did not contain original data, only analyses of previously published papers containing original data. OEHHA chose to present the original data from the original papers in the PHG document[12]. Thompson *et al.* (2011b)[13] dealt with toxicological endpoints other than cancer (*e.g*., cell death, hyperplasia, ratio of reduced to oxidized glutathione) and did not demonstrate that these endpoints are related to tumor formation. Neither these papers, nor a more recent publication by these researchers[14], provide a basis for

[9] Thompson, C.M., Haws, L.C., Harris, M.A., Gatto, N.M. and Proctor, D.M. (2011). Application of the U.S. EPA mode of action framework for purposes of guiding future research: a case study involving the oral carcinogenicity of hexavalent chromium. Toxicol Sci 119, 20-40.

[10] Thompson, C.M., Proctor, D.M., Haws, L.C., Hebert, C.D., Grimes, S.D., Shertzer, H.G., Kopec, A.K., Hixon, J.G., Zacharewski, T.R. and Harris, M.A. (2011). Investigation of the mode of action underlying the tumorigenic response induced in B6C3F1 mice exposed orally to hexavalent chromium. Toxicol Sci 123, 58-70.

[11] Thompson, C.M., Haws, L.C., Harris, M.A., Gatto, N.M. and Proctor, D.M. (2011). Application of the U.S. EPA mode of action framework for purposes of guiding future research: a case study involving the oral carcinogenicity of hexavalent chromium. Toxicol Sci 119, 20-40.

[12] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

[13] Thompson, C.M., Proctor, D.M., Haws, L.C., Hebert, C.D., Grimes, S.D., Shertzer, H.G., Kopec, A.K., Hixon, J.G., Zacharewski, T.R. and Harris, M.A. (2011). Investigation of the mode of action underlying the tumorigenic response induced in B6C3F1 mice exposed orally to hexavalent chromium. Toxicol Sci 123, 58-70.

[14] Thompson CM, Proctor DM, Suh M, Haws LC, Hebert CD, Mann JF, Shertzer HG, Hixon JG and Harris MA (2012). Comparison of the effects of hexavalent chromium in the alimentary canal of F344 rats and

concluding that hexavalent chromium presents no significant risk of cancer by the route of ingestion.

No changes to the regulation were made in response to this comment.

Comment ACC-4: "Because the MOA and pharmacokinetics (PK) data *[resulting from new research sponsored by ACC]* are likely to change the PHG, the PHG is not definitive support for removing Cr(VI) from the Section 25707(b) list." [ACC comment letter, p. 2]

Response ACC-4. OEHHA disagrees. The PHG document[15] comprehensively reviews the current scientific evidence on the carcinogenicity of hexavalent chromium by the ingestion route. The scientific information in the PHG document provides the basis for removing "chromium (hexavalent compounds)" from Section 25707(b) as presenting no significant risk of cancer by the route of ingestion. Evidence reviewed in the PHG document supporting this action includes the clear evidence of carcinogenicity in male rats, female rats, male mice, and female mice exposed to hexavalent chromium by the oral route in studies conducted by the National Toxicology Program (NTP, 2008) and evidence from several studies in humans of absorption of hexavalent chromium in the gastrointestinal tract.

The ACC sponsored research on hexavalent chromium pharmacokinetics (*i.e*., absorption, distribution, metabolism, and elimination) and MOA published to date in the scientific literature does not demonstrate that hexavalent chromium poses no significant risk of cancer by ingestion.

No changes to the regulation were made in response to this comment.

Comment ACC-5: "OEHHA included Cr(VI) on the list of chemicals that 'present no significant risk of cancer by the route of ingestion' in Section 25707(b) in 1990 after it determined that 'the available data suggest that the cancer risk from ingestion of these listed substances is minimal, principally due to the poor absorption of these substances across the intestinal mucosa and in the blood stream of those who may ingest them.'" [ACC comment letter, p. 2]

B6C3F1 mice following exposure in drinking water: implications for carcinogenic modes of action. *Toxicol Sci* 125(1), 79-90.

[15] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

"The PHG does not present any scientific evidence that Cr(VI) is better absorbed across the intestinal mucosa and into the blood stream than OEHHA determined in 1990." [ACC comment letter, p. 4]

> Response ACC-5. Since 1990, significant new scientific information has become available demonstrating the carcinogenicity of hexavalent chromium by the oral route (*i.e*., there was clear evidence of hexavalent chromium- induced cancer in four two-year cancer bioassays conducted in rats and mice of both sexes (NTP, 2008)). In addition, significant new data have become available since 1990 documenting the absorption of hexavalent chromium by the oral route in humans. The PHG document discusses a number of studies published since 1990 which demonstrate the absorption of hexavalent chromium following oral ingestion (see Metabolism and Pharmacokinetics section of the PHG document). In particular, see pp. 10-12 of the PHG document for examples of human studies demonstrating absorption of hexavalent chromium by the oral route at environmentally relevant concentrations (see e.g., Finley *et al.* (1996)).
>
> No changes to the regulation were made in response to this comment.

Comment ACC-6: "OEHHA's use of the linear low-dose extrapolation (no-threshold) method is based on a finding that Cr(VI) causes cancer in mice that a single review article speculated was due to a mutagenic mode of action (MOA). Other review papers, also available to OEHHA that offered alternative MOA action were not considered." [ACC comment letter, p. 3]

"In the final PHG, OEHHA makes a determination that Cr(VI) acts via a mutagenic MOA; however, no weight of evidence approach was conducted and only a single literature review/interpretation paper (McCarroll *et al.*, 2010) was used to support OEHHA's decision." [See Attachment A to ACC comments, page 14]

"In mice, no increase in oxidative DNA damage measured by 8-hydroxydeoxyguanine (8-OHdG) was observed at any dose. This finding is consistent with that of De Flora *et al.* (2008)…In rats, no dose-related changes in 8-OHdG were observed." [See Attachment A to ACC comments, page 21]

"There are data that strongly suggest that Cr(VI) does not act by a mutagenic MOA.…Cr(VI) itself does not react directly with DNA; it is the short-lived intermediate valence species, Cr(V) and Cr(IV) that bind to DNA (Chiu *et al.*, 2010).…Oxidative DNA damage was not increased in any treatment group (Thompson *et al.*, 2011b).…Cancer did not occur in small intestines of mice until 450 days or later (NTP, 2008). If mutation

was an early event in the carcinogenic process, the tumors would have occurred earlier." [Attachment A to ACC comments, page 21]

"U.S. EPA's *Framework for Determining a Mutagenic Mode of Action for Carcinogenicity [External Peer Review Draft]* discusses the use of toxicogenomics for determination of a mutagenic MOA (U.S. EPA, 2007). Briefly, toxicogenomics explores changes in the patterns of gene expression as a result of a dose of a toxic agent. These patterns of expression are good indicators of an animal's early response to chemical insults…Without consideration of which genes were differentially expressed, Figure 8 above shows that changes in gene expression in the mouse small intestine do not occur above [*sic*] 10 mg [SDD]/L, 100 times higher than the current federal MCL…In mice exposed to Cr(VI) as part of the ACC study, the gene expression profile did not match that of known genotoxic carcinogens (Thompson et al., 2011c). " [Attachment A to the ACC comment letter, pages 23-24]

Attachment A to ACC comments takes issue with the Cr VI PHG document's citation of a publication by US EPA staff (McCarroll et al., 2010) as supporting OEHHA's findings and conclusions [*regarding MOA and calculation of the numerical PHG for Cr VI*]. "An objective approach would have used the weight of the evidence, where negative results are considered along with positive results. Use of the weight of evidence approach is consistent with the U.S. EPA Cancer Risk Guidelines and the U.S. EPA Framework for Determining a Mutagenic Mode of Action [*External Peer Review Draft*]." [See Attachment A to ACC comments, pages 28 - 29]

> Response ACC-6. Comments concerning the mode of action of hexavalent chromium and the calculation of the numerical public health goal are not relevant to the proposed action. The comment that changes in gene expression did not occur [below] a particular dose of SDD (sodium dichromate dehydrate) is not relevant to the current regulatory action, since the shape of the dose-response curve would be taken into account in the calculation of an NSRL, and the current action does not establish an NSRL.
>
> OEHHA previously responded to similar public comments on hexavalent chromium's mode of action submitted on the PHG[16] document. For example, see page 25 of the Response to PHG Comments document[17] .

[16] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

[17] OEHHA (2011) Responses to Major Comments on Technical Support Document. Public Health Goal for Hexavalent Chromium (Cr VI) in Drinking Water. July 2011. Available on the OEHHA web site at URL: http://www.oehha.ca.gov/water/phg/pdf/Cr6PHGresp072911.pdf.

No changes to the regulation were made in response to this comment.

Comment ACC-7: "The MOA research studies demonstrate a threshold in mice between 100 ppb and 1000 ppb." [ACC comment letter, p. 3]

"As discussed in Section 5 of Attachment A, the ACC-sponsored study indicates a threshold for effects in mice somewhere between 100 ppb and 1000 ppb. No effects were observed at the current Federal MCL of 100 ppb." [ACC comment letter, p. 5]

Response ACC-7. These comments are not relevant to the proposed action. As noted above in Response ACC-3, the shape of the dose-response curve is taken into account when calculating an NSRL. The current action does not establish an NSRL.

No changes to the regulation were made in response to this comment.

Comment ACC-8: "In the PHG, OEHHA dismissed the experimental evidence for rapid reduction of Cr(VI) to [Cr(III)]. Moreover, OEHHA did not consider the results of the ACC-sponsored research studies." [ACC comment letter, p. 4]

Response ACC-8. This statement is not correct. The Metabolism and Pharmacokinetics section of the PHG document[18] contains extensive discussion of the reduction of hexavalent chromium to Cr III (trivalent chromium) in the gastrointestinal tract. In particular, see the section entitled "Pharmacokinetics of Trivalent versus Hexavalent Chromium."

Human absorption studies (Kerger *et al*., 1996a, Finley *et al*., 1996b; Finley *et al*., 1997; Donaldson and Barreras, 1966) reviewed in the PHG document provide no support for the hypothesis that the oral absorption of hexavalent chromium only begins to occur when the reducing capacity of the stomach is exhausted. With regard to consideration of the results of ACC-sponsored research studies, OEHHA is not aware of any published data from these studies which demonstrate that hexavalent chromium is completely reduced to trivalent chromium in the human gastrointestinal tract, or otherwise call into question the findings of gastrointestinal tract absorption of hexavalent chromium in humans from the studies noted above.

[18] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

No changes to the regulation were made in response to this comment.

Comment ACC-9: "Preliminary data from this study indicate that human stomach fluid reduces Cr(VI) at a much higher rate than does rodent stomach fluid. These data will be used to develop a physiologically-based pharmacokinetic (PBPK) model for Cr(VI) in both rodents and humans." [ACC comment letter, p. 4]

"The percentage of Cr(VI) reduced in the stomach is a function of the amount of Cr(VI) ingested. Less and less Cr(VI) is reduced as the amount ingested increases, primarily because the amount of reductants in the stomach becomes depleted. Thus the dose of Cr(VI) available for transport into a cell is not a constant percentage of the ingested dose. This fact alone causes a Cr(VI) dose-response curve for cancer to be nonlinear over a large range of doses. (Proctor *et al*. in press)." [See Attachment A to ACC comments, page 24]

"Because humans have much more stomach acid than rodents, most, if not all, of ingested Cr(VI) will be reduced to Cr(III) in the gastrointestinal tract (Donaldson and Barreras, 1966; De Flora, 2000; Proctor *et al*., 2002)." [See Attachment A to ACC comments, page 25]

Response ACC-9. Absorption of hexavalent chromium in the gastrointestinal tract of humans has already been demonstrated in a series of studies (e.g., Kerger *et al*., 1996a, Finley *et al*., 1996b; Finley *et al*., 1997), as noted above in Response ACC-5 and Response ACC-8. Moreover, these human studies provide no support for the hypothesis that the oral absorption of hexavalent chromium only begins to occur when the reducing capacity of the stomach is exhausted. Since release of the PHG document[19], Zhitkovich (2011)[20] analyzed data on gastric reduction of hexavalent chromium from human, animal, and *in vitro* studies, and reached a similar conclusion, based on analyses demonstrating that the rate of hexavalent chromium reduction in the stomach following ingestion in water is independent of the concentration of Cr VI ingested. The *in vivo* findings in humans are not negated by the *in vitro* stomach fluid studies

[19] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.
[20] Zhitkovich, A (2011). Chromium in drinking water: sources, metabolism, and cancer risks. Chem Res Toxicol 24(10), 1617-1629.

conducted in animals (Proctor *et al*., 2012[21]), or the *in vitro* stomach fluid studies being conducted in humans.

No changes to the regulation were made in response to this comment.

Comment ACC-10: "Low levels of Cr(VI) exist naturally in groundwater…The presence of naturally occurring levels of Cr(VI) in California groundwater will result in significant and costly modifications by water purveyors to treat natural source waters used for drinking water." [ACC comment letter, p. 4]

Response ACC-10. This comment is not relevant to the proposed regulatory action.

OEHHA notes that public water purveyors are not subject to Proposition 65 requirements.[22]

No changes to the regulation were made in response to this comment.

Comment ACC-11: Section 2 of Attachment A to ACC comments, entitled "The Role of Thresholds in Risk Assessments" sets out the commenter's critical view of the use of linear low-dose extrapolation in carcinogen risk assessment. These comments are accompanied by a series of three figures (labeled Figures 1, 2 and 3 on pages 4 and 5 of Attachment A) showing "idealized" dose-response data. In discussing Figure 2, the claim is made that linear low-dose extrapolation ignores the likelihood of a threshold and overestimates the slope of the dose-response curve.

Response ACC-11: These comments are not directly relevant to the proposed action. As noted above in Response ACC-3, the shape of the dose-response curve is taken into account in the calculation of an NSRL. The current action does not establish an NSRL for hexavalent chromium.

The comments, while not directly relevant to the proposed action, exhibit a number of errors and misconceptions about low-dose linear extrapolation.

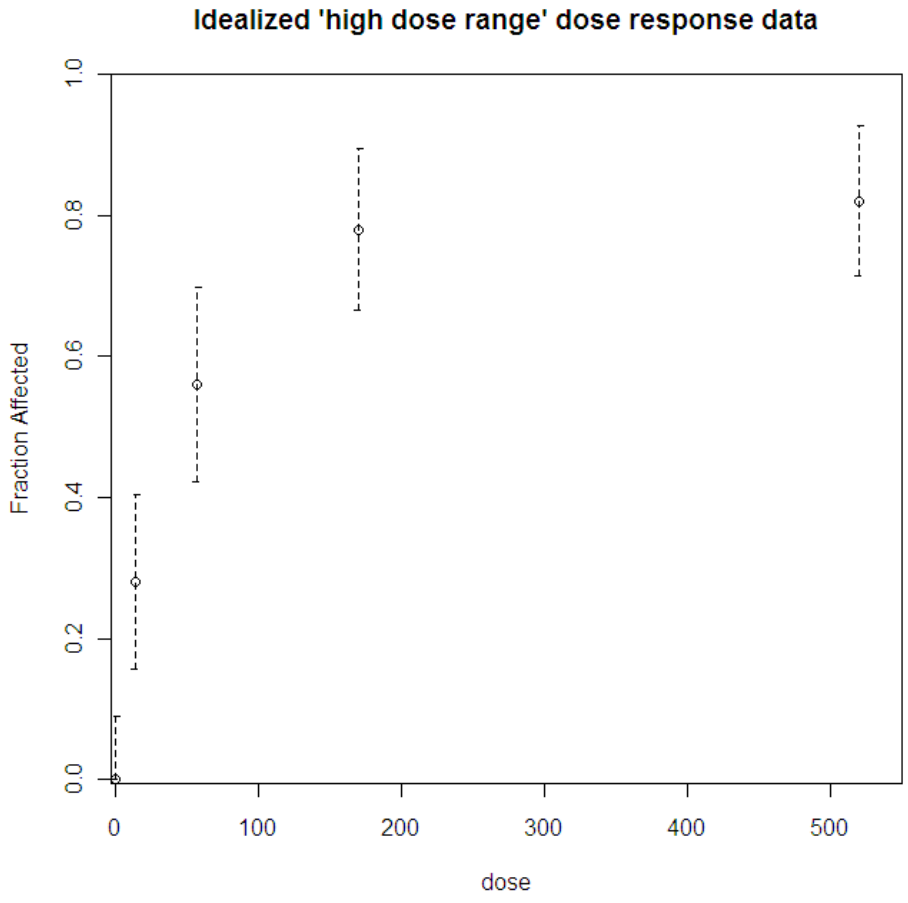
Figures 1, 2 and 3 do not graphically show the idealized dose-response curves used in linear low-dose extrapolation because in reality, the extrapolation

[21] Proctor DM, Suh M, Aylward LL, Kirman CR, Harris MA, Thompson CM, Gurleyuk H, Gerads R, Haws LC, and Hays SM (2012). Hexavalent chromium reduction kinetics in rodent stomach contents. Chemosphere 89(5):487-93.

[22] Health and Safety Code section 25249.11(b); Title 27, Cal. Code of Regulations, sections 25401 and 25502.

procedure is done using a linear scale for dose, not the log scale used in each of the commenters' figures. Plot A below shows dose plotted against tumor incidence for the exact same hypothetical "high dose" data as that shown in Figure 2 in the comments. The relationship between dose and incidence shown in Plot A below is the same as that in Figure 2, but the graph looks different because a scale linear in dose is used. The circles represent the data points shown in Figure 2 and the vertical bars are 95% confidence bounds for cancer incidence (fraction affected) assuming each dose group contained 50 animals as was implied in the comments.

When viewing the hypothetical data with the appropriate scale for dose, it is clear that a threshold is not indicated for the "idealized" data set presented in Figure 2 of the comments.



Plot A

No changes to the regulation were made in response to this comment.

Comment ACC-12: The figure on page 12 of Attachment A to ACC comments, entitled "Figure 4, Understanding how linear low dose extrapolation works," plots cancer incidence versus dose. It intends to show how the LED_{10} *[lower 95% confidence limit on the effective dose producing a 10% response]* and ED_{10} *[effective dose producing a 10% response]* are derived.

"From this graph, it is clear that linear extrapolation from a chosen point of departure to zero dose (green line) overestimates the slope and thus the risk in the low dose region."

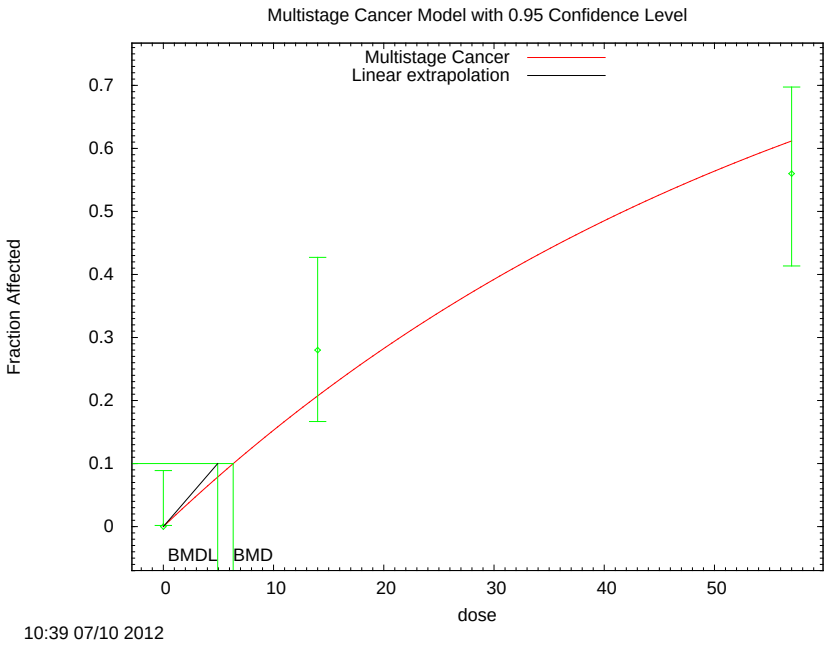
"Using the 95% lower confidence level on the ED_{10} as the POD for linear extrapolation (red line) overestimates the risk to an even greater extent. Dr. Michael Kelner in his peer review comments on the 2009 draft PHG points out how the selection of the LED_{10} could overestimate risk (Kelner, 2009)."

"Based on the foregoing *[comparing Figure 2 and Figure 3 on page 4 of Attachment A]*, it is clear that both the biology of a carcinogenic chemical and the design of the experiment or bioassay used to assess its carcinogenicity can alter the understanding of the MOA and the choice of whether to use linear low-dose extrapolation." [See Attachment A to ACC comments, pg. 5.]

> Response ACC-12: These comments are not directly relevant to the proposed action. The shape of the dose-response curve is taken into account in the calculating an NSRL. The current action does not establish an NSRL for hexavalent chromium.
>
> The comments exhibit a number of errors and misconceptions about low-dose linear extrapolation.
>
> The numbers displayed in Figure 4 of Attachment A do not reflect the tumor incidence data from any of the animal carcinogenesis experiments conducted with hexavalent chromium. For this reason the generalizations made about this Figure do not apply to the hexavalent chromium data.
>
> The U.S. EPA's Benchmark Dose Software (BMDS) can be used to fit the multistage cancer model to cancer dose-response data. This is a standard approach used for linear extrapolation in which the dose associated with the benchmark response (BMR) is calculated as well as a lower 95% confidence bound on that dose (BMDL). The intersection of the BMR and the BMDL is called the 'point of departure' (POD) and the linear approximation for the low-

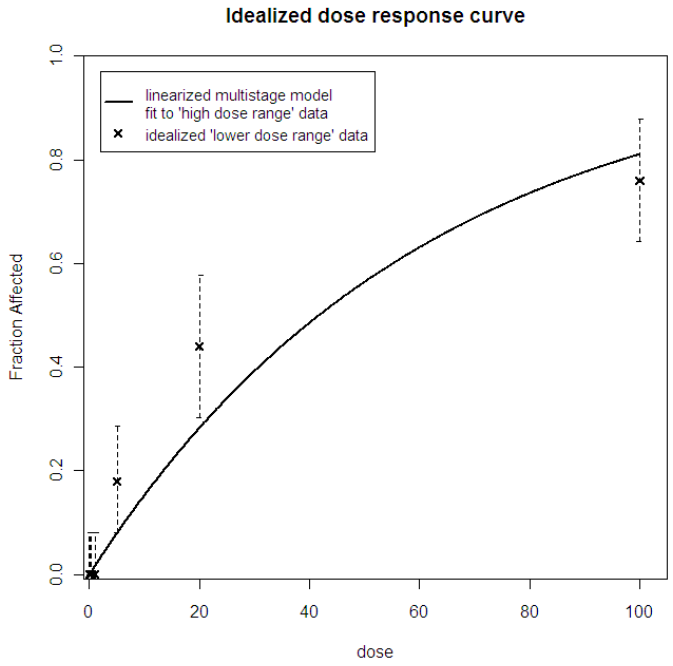
dose region of the dose-response curve is created by drawing a line between the (x,y)-coordinate associated with the control group to the POD.

Plot B below shows the output generated by BMDS using standard methods with the hypothetical “high dose” data from Figure 2 of Attachment A. This hypothetical data was also the basis for the attempted linear extrapolation given in Figure 4 of Attachment A. The control group and the first two dose groups are shown in Plot B; the top two dose groups of the hypothetical data set were removed in order to achieve sufficient goodness of fit for the model, according to the standard practice. Plot B illustrates that when data are presented in the standard manner using a scale linear in dose, the data and the linear extrapolation look quite different than that shown in Figure 4 of the comments.



Plot B

Plot C below shows the hypothetical “lower dose range” data originally presented in Figure 3 of Attachment A. These data values are plotted using a linear scale in dose along with the linearized multistage model fit to the hypothetical “high dose range” data. The plot does not demonstrate a threshold and does not demonstrate that incidence in the low dose range is under predicted when extrapolating from high doses.



Plot C

No changes to the regulation were made in response to this comment.

Comment ACC-13: "The lowest concentration that was used in the NTP study was 14 mg/L, almost 300 times greater than the California MCL (Johnson, 2002)." [See Attachment A to ACC comments, page 13]

Response ACC-13. This comment is not relevant to the proposed action since it addresses the numerical value established in the PHG document.

No changes to the regulation were made in response to this comment.

Comment ACC-14: "In addition, OEHHA did not consider the work of Nickens *et al.* who state: "*The transcriptional regulation of survival genes and the signaling pathways they control have proven to be critical in the survival of Cr(VI)-exposed cells. Taken together, survivors of Cr(VI) exposure harboring altered repair and survival signaling mechanisms may form the basis for the development of a population of neoplastic precursor cells, which may lead to tumor cell formation*. *(Nickens et al., 2010)"* [See Attachment A to ACC comments, page 14]

Response ACC-14. This comment regarding possible mechanisms of tumor formation by hexavalent chromium is not relevant to the proposed regulatory

action. In addition, this statement is not correct. The work of Nickens *et al.* (2010) was considered and is cited in two places in the final PHG document[23].

No changes to the regulation were made in response to this comment.

Comment ACC-15: "Dr. Anatoly Zhitkovich is a full professor in the Department of Molecular Pharmacology, Physiology and Biotechnology at the Brown University Medical School. He also was chair of the external peer review committee for U.S. EPA's Toxicological Review of Hexavalent Chromium in support of the IRIS risk assessment. Zhitkovich *et al.* (2005) state that 'the spectrum of mutations observed in chromium-induced human lung tumors is more consistent with the mutator phenotype of cancer cells rather than reflecting the direct mutagenic activity of Cr(VI).'" [See Attachment A to ACC comments, page 15]

Response ACC-15. This comment regarding a possible MOA of hexavalent chromium is not relevant to the proposed regulatory action.

In addition, OEHHA is aware of Dr. Zhitkovich's extensive research into the toxicology of hexavalent chromium, and his conclusion regarding the carcinogenicity of hexavalent chromium via ingestion in his most recent paper (Zhitkovich, 2011)[24] on this topic: "Multispecies and multisite carcinogenicity of Cr(VI) along with its broad genotoxicity provide a strong basis for a classification of Cr(VI) exposures through drinking water as likely to be carcinogenic in humans." The paper goes on to state: "Diverse lines of evidence demonstrate the importance of a DNA-reactive mutagenic mechanism in Cr(VI) carcinogenicity, lending mechanistic support for a linear low-dose extrapolation of cancer risks in humans."

No changes to the regulation were made in response to this comment.

Comment ACC-16: In discussing whether hexavalent chromium acts by a mutagenic MOA, and whether the target cell/tissue is exposed to the ultimate DNA-reactive chemical *[e.g.,, Cr VI, or a lower valence state or chemical intermediate formed during the reduction of Cr VI to Cr III]*, the commenter asserts "At high doses, chromium accumulates in mouse small intestine in a dose-dependent fashion (Thompson *et al.*,

[23] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.
[24] Zhitkovich, A (2011). Chromium in drinking water: sources, metabolism, and cancer risks. Chem Res Toxicol 24(10), 1617-1629.

2011b). However, no chromium accumulation was observed at the Federal MCL of 100 ppb." [See Attachment A to the ACC comment letter, page 22]

Response ACC-16. The MOA of hexavalent chromium is not relevant to the proposed regulatory action. In addition, chemical accumulation is not the same thing as chemical exposure, nor is it required for exposure to occur. Furthermore, the methodology used in Thompson *et al.* (2011b)[25] was not sensitive enough to measure chromium accumulation at the low dose levels tested, or in the controls (*i.e*., below the detection/reporting limits of the assay as discussed in the legend to Figure 4 in the publication). Therefore, it is not possible to conclude anything about chromium accumulation in animals receiving water containing 100 ppb compared to tap water controls (*i.e.* animals receiving water containing 100 ppt Cr VI) based on that study.

No changes to the regulation were made in response to this comment.

Comment ACC-17: "OEHHA cites a very recent ecologic epidemiology study from Greece, Linos *et al*. (2011).…[The authors] did not account for confounders such as alcoholism and viral hepatitis, both of which are associated with primary liver cancer, or with smoking that is known to be associated with lung cancer. Stomach cancer in Linos et al. (2010) was not elevated, in contrast to Zhang and Li (1987)." The use of this study to support the human relevance of the mouse data is incorrect and inappropriate. [See Attachment A to ACC comment letter, page 29]

Response ACC-17. OEHHA disagrees with the characterization of the Linos *et al*. (2011) study as an ecologic epidemiology study, and with the claim that this study was used to support the human relevance of the mouse data. The PHG document[26] reviewed this study, which is a historical cohort study, as part of the human evidence relating to the carcinogenicity of hexavalent chromium when ingested, not as a validation of the positive findings observed in animals (NTP, 2008). While evidence of carcinogenicity from cancer epidemiology studies conducted in humans was considered, it was not the primary basis for concluding that oral exposures to hexavalent chromium can pose a cancer risk. The PHG document concluded there is "sufficient evidence that hexavalent chromium is also carcinogenic by the oral route of exposure, based on studies in rats and

[25] Thompson, C.M., Proctor, D.M., Haws, L.C., Hebert, C.D., Grimes, S.D., Shertzer, H.G., Kopec, A.K., Hixon, J.G., Zacharewski, T.R. and Harris, M.A. (2011). Investigation of the mode of action underlying the tumorigenic response induced in B6C3F1 mice exposed orally to hexavalent chromium. Toxicol Sci 123, 58-70.

[26] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

mice conducted by the National Toxicology Program (NTP, 2008)." In reviewing the epidemiology evidence, the PHG document concluded "this evidence provides further support to consider hexavalent chromium to be carcinogenic by the oral exposure route."

OEHHA agrees that Linos *et al.* (2011) did not account for alcohol consumption, viral hepatitis, or smoking, and that lack of data on these factors is a limitation of the study. Linos *et al.* noted their lack of smoking data, but they did not mention their lack of data on alcohol consumption or viral hepatitis. To be confounding, these characteristics would have to be different between the hexavalent chromium-exposed cohort (Oinofita residents) and the comparison population (the entire prefecture), and OEHHA is not aware of evidence of such differences.

No changes to the regulation were made in response to this comment.

Comment ACC-18: "Finally, the final PHG dismisses epidemiological studies that do not show a relation between Cr(VI) exposure and health effects." [See Attachment A to the ACC comment letter, page 30]

Response ACC-18. In general, well conducted epidemiological studies that provide evidence of an association between a chemical exposure and a cancer outcome in humans are regarded as more important than epidemiological studies that do not find evidence of such an association. There are many reasons why an epidemiological study (*i.e*., a study of the distribution and patterns of health-related conditions, including diseases, and their causes, within a population). can fail to find an association, even when one exists. For this reason OEHHA does not necessarily give equal weight to "positive" and "negative" studies.

The PHG document[27] examined the epidemiology evidence, noted limitations of individual studies, and concluded "this evidence provides further support to consider hexavalent chromium to be carcinogenic by the oral exposure route."

No changes to the regulation were made in response to this comment.

Comment ACC-19: "6.1.2 OEHHA Ignored Studies of Residents Living Near Cchromate Plants in Mexico. …Armienta-Hernandez and Rodriguez-Castillo (1995) provide results to suggest that Cr(VI) does not pose a risk to human health at current

[27]OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

regulatory levels…More importantly, the authors were unable to find any health effects in any of the exposed populations. This resident population studied was albeit quite small; however, the lack of health effects at 0.5 mg/L suggests this level as a no-effect concentration or NOEC. Application of the default uncertainty or safety factor of 10 for human variability would result in a value of 0.05 mg/L, the same as the current California MCL of 50 parts per billion." [See Attachment A to ACC comments, page 30-31]

Response ACC-19. These comments are not relevant to the proposed action. The shape of the dose-response curve is taken into account in calculating an NSRL. The current action does not establish an NSRL. In addition, the study of Armienta-Hernandez and Rodriguez-Castillo (1995) is not an epidemiologic study of cancer. The only reference to cancer in the publication is the sentence, "In the same period no cases of lung cancer have been detected." No other cancer data were presented.

No changes to the regulation were made in response to this comment.

Comment ACC-20: "In Lecheria, a town in southern Mexico, 3,000 residents were exposed to Cr (VI) in drinking water from wells at an average concentration of 0.9 mg/L due to a nearby chromate production plant…Chromium concentrations in both the hair and urine of residents were elevated in comparison to a control population. However, there was no increase in the death rate from all cancers measured over a period of 24 years when compared to the control population (Neri *et al*., 1980, 1982)." [See Attachment A to ACC comments, page 31]

Response ACC-20. As noted above in Response ACC-17, the PHG document[28] concluded there is "sufficient evidence that hexavalent chromium is also carcinogenic by the oral route of exposure, based on studies in rats and mice conducted by the National Toxicology Program (NTP, 2008)." In reviewing the available epidemiology evidence, the PHG document[29] concluded "this evidence provides further support to consider hexavalent chromium to be carcinogenic by the oral exposure route." The Spanish language publication cited in the comments as Neri *et al*. (1980)[30] describes a planned epidemiological

[28] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.
[29] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.
[30] Neri, R., Gonzalez-Cortes, A., Gosset, G. and Quinones, A. (1980). Posibles danos a la salud de una comunidad abierta, por sales de cromo en el ambiente. I. Programa de investigacion epidemiologica

investigation in Lecheria to assess the possible chromium exposure and associated health effects. The publication cited in the comments as Neri *et al*. (1982) is in actuality Gonzales-Cortes *et al.* (1980)[31]. Gonzales-Cortes *et al*. (1980) is a review of the health effects of hexavalent chromium; it is not a report of the Lecheria study. OEHHA identified a third Spanish language publication[32] from the same group of researchers that has data for cancer in the Lecheria study population. This study was not an epidemiology study. Contrary to the commenter's assertions, this study did not calculate rates of cancer mortality for the Lecheria population or the comparison population. Also contrary to the commenter's assertions, this study reported that chromium concentrations in the hair and urine of the Lecheria study population were not different from those in the comparison population.

No changes to the regulation were made in response to this comment.

Comment ACC-21: "6.1.3 Studies of California Residents Exposed to Cr(VI) near PG&E Facilities Did Not Find Elevated Cancer." [See Attachment A to ACC comment letter, page 31]

Response ACC-21. The studies of residents living near Hinkley, California by Fryzek *et al*. (2001) and Morgan (2011) are discussed in the PHG document[33], and significant limitations in each study's design were noted.

No changes to the regulation were made in response to this comment.

Comment ACC-22: "Gatto *et al*. (2010) conducted a meta-analysis of 32 studies of workers occupationally exposed to Cr(VI)…The authors concluded that the meta-analysis did not support an association between occupational exposure to Cr(VI) and

---

comprensiva [Possible damage to the health of an open community by chromium salts in the environment. I. Program of comprehensive epidemiological research.] *Salud Publica Mex* **22**, 81-84.

[31] Gonzalez-Cortes, A., Neri, R., Quinones, A., and Mendoza, J. 1980. Posibles danos a la salud de una comunidad abierta, por sales ed chromo en el ambiente. II. Fisiologia y patologia del chromo. [Possible damage to community health by chromium salts in the environment. II Physiology and pathology of chromium.] *Sal Publica Mex* **22**, 85–90.

[32] Neri, R., Gonzalez Cortes, A., Quinones, A. (1982). Posibles danos a la salud de una comunidad abierta, por sales de cromo en el ambiente. IV. Investigacion en la poblacion de Lecheria-San Francisco Chilpan. [Possible damage to the health of an open community by chromium salts in the environment. IV. Health damages on an opened community, caused by chromium salts in the environment.] *Salud Publica Mex* **24**, 25-32.

[33] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

mortality from cancer of the gastrointestinal tract." [See Attachment A to the ACC comment letter, page 32]

Response ACC-22. The PHG document[34] noted that inclusion by Gatto *et al*. (2010) of some worker populations with little or no exposure to hexavalent chromium, as well as exclusion of some populations with significant exposure, may have affected the results.

No changes to the regulation were made in response to this comment.

Comments from PMI

Comment PMI-1: Len Swatkowski urged "all regulatory agencies including USEPA and OEHHA to rely on the best available science and to include the relevant data being developed from ToxStrategies in assessing Hexavalent Chromium."

Response PMI-1. The ToxStrategies studies referred to in this comment are the ACC-sponsored studies discussed above in the responses to ACC comments. As noted above, much of the ACC-sponsored research has already been completed. Based on the evidence reviewed in the PHG document[35], including the positive findings of carcinogenicity in male rats, female rats, male mice, and female mice exposed to hexavalent chromium by the oral route in studies conducted by the NTP, and the evidence of absorption of hexavalent chromium in the gastrointestinal tract in humans, as well as other scientific reviews published since the PHG document, the best available science supports the identification of hexavalent chromium as carcinogenic by the route of ingestion.

No changes to the regulation were made in response to this comment.

[34] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.
[35] OEHHA (2011) Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, July 27, 2011.

Comments from i) Environmental Working Group, ii) Center for Public Environmental Oversight, Clean Water Action, Environmental Working Group, Erin Brockovich, Inc., Integrated Resource Management, Inc., and Natural Resources Defense Council, iii) Ed Hou, and iv) Robert Matias

These comments supported the proposed regulatory action. No changes were made in response to these comments.

ALTERNATIVES DETERMINATION

The only alternative to this proposed amendment would be to not remove hexavalent chromium from section 25707(b)(4). Because currently available scientific information shows that oral exposures to hexavalent chromium can pose a significant cancer risk, this alternative is not scientifically justified.

Therefore, in accordance with Government Code, section 11346.9(a)(4), OEHHA has determined that no reasonable alternative considered by OEHHA or that has otherwise been identified and brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposal described in this Notice.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. It should be noted that all state and local government agencies are expressly exempt from Proposition 65. Thus, these regulatory amendments will not impose any mandate on local agencies or school districts.