Corrected portions of draft PHG document for hexavalent chromium, from pages originally numbered 1, 91-96, 106 and 115. Deleted text has been removed, inserted text is italicized in red.
PUBLIC HEALTH GOAL FOR HEXA VALENT CHROMIUM IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) is proposing a Public Health Goal (PHG) for hexavalent chromium of 0.02 parts per billion (ppb) or micrograms per liter (µg/L) in drinking water. OEHHA has reviewed the available data on the toxicity of hexavalent chromium and has identified the proposed PHG level as protective against all identified toxic effects from both oral and inhalation exposure to hexavalent chromium that may be present in drinking water.

While hexavalent chromium has long been recognized as a potent carcinogen via inhalation, there is now 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). To calculate the proposed PHG, OEHHA utilized an oral cancer slope factor of 0.5 (mg/kg-day)-1, based on a dose-related increase of tumors of the small intestine in male mice (NTP, 2008). OEHHA also used an inhalation cancer slope factor of 510 (mg/kg-day)-1, based on occupational studies, with an exposure assessment (Keating and McKone, 1993) to estimate inhalation of waterborne hexavalent chromium during showering, for estimating inhalation risk. The combined-route cancer risk is dominated by the oral exposure despite the much higher inhalation potency, because the inhalation of water droplets during showering is very small. The PHG was adjusted to account for increased sensitivity associated with early-in-life exposures.

A health-protective level of 0.3 ppb for non-carcinogenic effects is also proposed based on liver toxicity (mild chronic inflammation, fatty changes) in female rats in the NTP study (2008). Other studies have indicated adverse effects in the liver and blood forming tissues.

Chromium is a heavy metal that occurs throughout the environment. The soluble hexavalent form is relatively toxic, while the less-soluble trivalent form has very low toxicity and is a required nutrient. The two forms are inter-convertible in the environment.

Available studies characterized the carcinogenic and non-carcinogenic activity of hexavalent chromium resulting from inhalation or oral exposure in both experimental animals and humans. Most of the toxicity studies investigated carcinogenic activity, because hexavalent chromium has been identified as a carcinogen. Other studies focused on the pharmacokinetics of hexavalent and trivalent chromium. The findings of these studies are very important in understanding the toxic actions of this metal.

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. Increases in blood/plasma chromium levels following oral hexavalent chromium administration.
NTP, 2007 - Doses of 1.6 to 21.4 mg/kg-day of Cr VI were administered to male rats for thirteen weeks in this study. A LOAEL of 1.6 mg/kg-day was identified based on effects on blood forming tissues (decreased erythrocyte levels, mean cell volume, mean cell hemoglobin (total and concentration) and platelet concentrations). The uncertainty factors appropriate to provide an adequate margin of safety for human exposure to Cr VI in drinking water include 10 for extrapolating from a subchronic study, 10 to extrapolate between species, and 10 to protect potentially sensitive human subpopulations (including antacid users). An additional factor of 3 or 10 could be considered for limited data (small number of animals/group, short study, only a few tissues examined). The aggregate factor is limited to 3,000.

\[
\text{HPD} = \frac{1.6 \text{ mg/kg-day}}{3,000} = 0.00053 \text{ mg/kg-day}
\]

NTP, 2008 - Female rats received 0.2, 0.9, 2.6 or 7.0 mg/kg-day of Cr VI administered in drinking water. A LOAEL of 0.2 mg/kg-day was identified based on effects in the female rat liver (mild chronic inflammation, fatty changes). The uncertainty factors appropriate to provide an adequate margin of safety for human exposure to Cr VI in drinking water include 10 for using a LOAEL, 10 to extrapolate between species, and 10 to protect potentially sensitive human subpopulations (including antacid users). The aggregate uncertainty factor is 1000.

\[
\text{HPD} = \frac{0.2 \text{ mg/kg-day}}{1,000} = 0.00002 \text{ mg/kg-day}
\]

A public health-protective concentration (C, in mg/L) for Cr VI in drinking water for noncarcinogenic endpoints is calculated from the HPD as follows:

\[
C = \frac{\text{HPD (mg/kg-day)} \times \text{RSC}}{\text{water intake (L/kg-day)}}
\]

where,

- RSC = relative source contribution (usually in the range of 20 to 80 percent);
- Water intake = values for drinking water intake, calculated on a body weight basis, are derived from values in U.S. EPA (2008).

The maximum default relative source contribution of 0.8 is used in this case, based upon the assumption that the major source of Cr VI is likely to be from drinking water. Little or no Cr VI exposure is expected from air, food, and incidental inhalation, dermal and oral exposure to soil and dust. For drinking water intake, either 90 or 95 percentile water consumption values may be considered to be health-protective.

The results of six studies were evaluated for derivation of a health protective concentration for Cr VI based on non-cancer toxic endpoints (Table 16). In five of the studies, toxic effects were detected (NTP 1997a; Chopra et al., 1966; Acharya et al., 2001; NTP, 2007, 2008) although a NOAEL was not identified in four of these studies.
(Chopra et al., 1966; Acharya et al., 2001; NTP, 2007, 2008). The MacKenzie et al. (1958) study did not identify toxic effects, but this was not its purpose.

When several toxicity studies are available, it is advisable to employ studies that are clearly superior to identify sensitive toxicological endpoint(s). The most sensitive endpoint is then identified and employed to derive a health-protective concentration. The 2008 NTP study is clearly the best of the available studies for deriving a health-protective concentration. Therefore it is proposed that the health-protective level for non-carcinogenic effects be based on the LOAEL from this study.

Table 16. Health Protective Concentrations for Hexavalent Chromium based on Non-cancer Endpoints

<table>
<thead>
<tr>
<th>Study</th>
<th>HPD (mg/kg-day)</th>
<th>Health Protective Concentration (mg/L)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Child</td>
</tr>
<tr>
<td>NTP, 2007</td>
<td>0.00053</td>
<td>0.0068</td>
</tr>
<tr>
<td>NTP, 2008</td>
<td>0.0002</td>
<td>0.0026</td>
</tr>
<tr>
<td>NTP, 1997a</td>
<td>0.00033</td>
<td>0.0043</td>
</tr>
<tr>
<td>MacKenzie et al., 1958</td>
<td>0.0025</td>
<td>0.032</td>
</tr>
<tr>
<td>Chopra et al., 1966</td>
<td>0.0005</td>
<td>0.0065</td>
</tr>
<tr>
<td>Acharya et al., 2001</td>
<td>0.00033</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

<sup>a</sup>Upper 95 percentile water intakes for a child (0 to <11 years) and adults (16 to 70 years) are 0.062 and 0.038 L/kg-day, respectively (U.S. EPA, 2008; Kahn and Stralka, 2009).

Alternatively, a composite value (usually a median or mean value) of the various health protective concentrations can be employed to derive the health-protective concentration, when the studies are of a similar quality. The matrix of potential health protective concentrations based exclusively on non-cancer effects in the six studies described above, as shown in Table 16, presents health protective concentrations for children and adults based on their body weight and their water consumption rates. Five of the studies yielded similar health protective concentrations for children (the most sensitive receptor) that ranged from 0.003 to 0.007 mg/L with a median value of 0.005 mg/L (NTP, 1997a; NTP, 2007; Chopra et al., 1966; Acharya et al., 2001). The health protective concentration of 0.003 mg/L based on the 2008 NTP study is similar to the values derived from the other studies.

**Carcinogenic Effects**

Calculation of a health-protective concentration to protect against carcinogenic effects of Cr VI considered three routes of exposure: water ingestion, inhalation of water droplets generated during showering, and dermal exposure during showering. All three of these routes could be relevant because of the concern that Cr VI may be carcinogenic by each of these exposure routes. However, as explained earlier in this document, the dermal contribution to exposure is very small, and is expected to add little compared to the risk posed by other exposure routes. A health-protective concentration (C) that addresses the inhalation and oral routes of exposure for carcinogenic effects is derived using the
following general equation, which collapses the separate calculations for each exposure period (shown above in the Dose Response section) into a single bracket for convenience of expression:

\[
C = \frac{R}{P_o \times (\sum_j [ASF_j \times d_j \times conso_j]) + P_i \times (\sum_j [ASF_j \times d_j \times consi_j])}
\]

where:

- \( R \) = a default risk level of one in one million, or \( 10^{-6} \);
- \( P_o \) = oral cancer potency, in mg/kg-day;
- \( P_i \) = inhalation cancer potency, in mg/kg-day;
- \( \sum_j \) = sum of contributions at each age range;
- \( ASF_j \) = age sensitivity factors for the 3rd trimester + infants, children and adults;
- \( d_j \) = duration of exposure factors for the 3rd trimester + infants, children and adult life stages;
- \( consi_j \) = equivalent water exposure values for each age range.

Estimates of the oral potency of Cr VI were obtained from the results of an animal study (NTP, 2008) because epidemiology studies of human exposure to Cr VI were judged to be unsuitable for deriving a dose-response relationship for Cr VI. Cancer potency values could not be reliably calculated for the stomach tumor data reported by Zhang and Li (1987) because of inadequate exposure information. Similarly, estimates of the amount of Cr VI that was inhaled and then swallowed in occupational studies are highly uncertain.

Statistically significant increases in tumors (adenoma or carcinoma) were observed in the oral cavity of male and female F344 rats and the small intestine of male and female B6C3F1 mice following Cr VI administration in drinking water (NTP, 2008). The findings in male mice were judged to yield the best dose-response relationship for oral exposure to Cr VI and therefore are the basis of the oral slope factor of 0.5 (mg/kg-day)\(^{-1}\). For the inhalation route, the human cancer potency value of 510 (mg/kg-day)\(^{-1}\) as derived above in the dose response assessment section was used.

Drinking water exposure is estimated for this calculation for the age ranges used above in the Dose Response section. The drinking water consumption values utilized are upper 95\(^{th}\) percentile values estimated by OEHHA of 0.114, 0.041, and 0.038 L/kg-day for infancy, childhood, and adult life stages (U.S. EPA, 2008; Kahn and Stralka, 2009). The value for exposure to water droplets in showering is 3.86x10\(^{-7}\) L/kg-day (Keating and McKone, 1993), which is applied to children and adults only, since infants are presumed not to take showers.

Estimation of the drinking water exposures x age sensitivity factors and duration adjustments in the equation above for each life stage (\( ASF_j \times d_j \times consi_j \)) provides values in the units of equivalent L\(_{ingest}/kg\)-day as in the standard risk calculation (\( C = R / (potency \times dose) \)), as shown in Table 17.
Table 17. Calculation of Adjusted Exposures by Life-stage (ASF \textsubscript{j} x d\textsubscript{j} x cons\textsubscript{j}) for Hexavalent Chromium

<table>
<thead>
<tr>
<th>Life Stages</th>
<th>ASF\textsubscript{j} x d\textsubscript{j} x cons\textsubscript{j}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>3\textsuperscript{rd} Trimester</td>
<td>0.0014</td>
</tr>
<tr>
<td>Infant (0-2)</td>
<td>0.0326</td>
</tr>
<tr>
<td>Child (2-16)</td>
<td>0.0246</td>
</tr>
<tr>
<td>Adult (16-70)</td>
<td>0.0293</td>
</tr>
<tr>
<td>Exposure Totals (L/kg-day)</td>
<td>0.0878</td>
</tr>
</tbody>
</table>

Inserting the exposure values in the equation above,

\[
C = \frac{R}{0.5 \text{ (mg/kg-day)}^{-1} \times (0.0878) + 510 \text{ (mg/kg-day)}^{-1} \times (5.432 \times 10^{-7})}
\]

\[
C = \frac{10^{-6}}{0.0439 + 0.00028} = 2.26 \times 10^{-5} \text{ mg/L} = 0.02 \text{ µg/L or ppb (rounded)}
\]

As shown above, the proportion of the total cancer risk contributed by inhalation is very small (~0.6%), despite the high cancer potency by the inhalation route. The proposed PHG for Cr VI is therefore set at 2 µg/L or 0.02 ppb, representing a lifetime cancer risk of 1 in 1 million. Other toxic effects associated with Cr VI were observed at higher exposure levels. The PHG for carcinogenic effects is protective against these other toxic effects.

**RISK CHARACTERIZATION**

The proposed PHG for Cr VI of 0.02 µg/L is based on risk associated with the ingestion of drinking water, with a very small contribution from the inhalation of aerosol droplets generated during showering. Various sources of uncertainty regarding the development of health-protective criteria for the oral and inhalation route are discussed.

**Hazard Identification** - While there is considerable evidence that occupational inhalation exposures of humans to Cr VI have resulted in increased incidences of lung cancer, studies in humans characterizing the carcinogenicity of oral exposures to Cr VI are more limited. Only one epidemiological study was identified that specifically addressed human exposure to Cr VI in drinking water (Zhang and Li, 1987). Five long-term cancer bioassays, three in mice and two in rats, have been conducted in which Cr VI was administered in the drinking water (Borneff et al., 1968; NTP, 2008). OEHHA’s analysis of findings of Borneff and coworkers found a statistically significant increase in tumors of the forestomach in the female mouse. There is uncertainty associated with this finding because of a viral infection that caused substantial intercurrent mortality, a single dose level, differences in the length of survival in different generations, and other factors. Although there is no evidence that the increase in tumors was due to the viral infection,
or that other factors limiting this study would have led to these findings, the results have been judged inappropriate for quantitative risk assessment.

The recent NTP cancer bioassays in rats and mice of both sexes (NTP, 2008) revealed statistically significant dose related increases in tumors in the oral cavity in male and female rats and tumors of the small intestine in male and female mice. The data in mice were judged to be suitable for quantitative risk assessment.

Once inside cells, Cr VI has been shown to damage DNA. The finding of genotoxicity in the liver following oral administration of Cr VI is consistent with both the toxicokinetic findings and the proposed DNA-damaging mechanism of action. Taken together, the toxicity and cancer studies in humans and animals, plus the mechanistic, toxicokinetic and genotoxicity studies, provide sufficient evidence for the carcinogenicity of Cr VI in humans.

The NTP studies in which Cr VI was administered to rodents in the feed suggest that liver and blood-forming tissues may also be affected by Cr VI (NTP, 1996, 1997a,b, 2007). Three studies in male and female rats given Cr VI orally for 22 weeks or two years suggest that the liver is a target organ (Acharya et al., 2001; Chopra et al., 1996; NTP 2008). These studies appear to indicate that Cr VI is entering liver cells, which is consistent with the findings of toxicokinetic studies in which increased chromium levels were observed in liver following oral administration of Cr VI. However, in one early study, no toxicity was reported in rats administered Cr VI for one year (MacKenzie et al., 1958).

Dose Response – cancer endpoint

Oral exposure - The available human studies provided limited information on the dose-response relationship for Cr VI by the oral route. Cancer potency values based on a dose response relationship could not be reliably calculated from the findings of Zhang and Li (1987). The Borneff et al. (1968) study in mice provided limited data regarding increases in tumors in mice and was judged unsuitable for deriving a dose-response relationship for Cr VI. The findings of the NTP (2008) studies in rats and mice of both sexes provided sufficient information for developing dose-response relationships for Cr VI. Dose-response data for tumors of the small intestine seen in male and female mice were analyzed. An acceptable fit to the multistage model in the BMDS was obtained using all dose groups in the male mouse study; for the female mouse study the high dose group was dropped. Thus the findings in male mice were judged to be the most suitable for developing a dose-response relationship for Cr VI.

Inhalation exposure - A dose-response relationship was derived from an occupational exposure to Cr VI, based on lung cancer in workers in a plant in Painesville, Ohio. A linear model was applied to correlate cumulative exposure to chromium with relative risk. Exposure estimates are relatively uncertain, but were judged adequate to develop a cancer potency factor.

Dose response – non-cancer endpoint

The recent NTP (2008) study was judged to be the best study for identifying the lowest dose associated with an adverse effect. The health-protective level for non-carcinogenic effects was developed from the LOAEL by applying appropriate uncertainty factors.
Health-protective values derived from other animal studies for the same endpoint (liver toxicity) were at similar levels (see Table 16).

**Exposure Assessment** - The proposed non-cancer health-based criterion reflects a relative source contribution of 80 percent of the total exposure coming from drinking water. While these are typical conventions employed to estimate exposure, there is uncertainty attendant with their use.

The estimate of exposure to water inhaled during showering relies on the results of a study by Keating and McKone (1993), and assumes a daily 10-minute shower. Different shower conditions including the average duration, type of showerhead, water temperature and pressure, and size and ventilation of the shower and bathroom would result in varying exposure by this route. The early-in-life exposure factor correction was not applied to infants for the inhalation route, since they generally do not take showers. We recognize that average shower duration may change markedly over the age range from two to 16, but data are not available to more precisely estimate the varying exposure. This route of exposure contributed very little to the total exposure to Cr VI in drinking water.

Cancer risk from exposure to drinking water was estimated based on the upper 95% confidence limits of exposure to tap water, by life stage, as described by *U.S. EPA (2008) and Kahn and Stralka (2009)*. The values used were derived from a study by U.S. EPA (2004) of intake measured in USDA’s 1994-1996 and 1998 continuing survey of food intakes by individuals, and represent values for tap water consumers only. These drinking water exposure values are significantly larger than the default value of 2 L/day that OEHHA has used in many previous cancer risk assessments. The use of the 95% upper confidence limit drinking water consumption value provides extra assurance that the risk to the entire population, including sensitive subpopulations, is being considered.

**Risk Characterization** – There are many sources of uncertainty in the calculation of the proposed PHG. The NTP carcinogenicity studies provide robust data for the assessment of oral cancer risk attributed to Cr IV. Protection of public health requires that health-based criteria be developed in a manner to ensure that risk is not markedly underestimated. OEHHA requests comment on the extent to which the proposed PHG level of 0.02 ppb provides adequate health protection to meet the goal of protecting California consumers of drinking water, including potential sensitive subpopulations, against the potential adverse effects of Cr VI.


Keating GA, McKone TE (1993). Measurements and evaluation of water-to-air transfer and air concentration for trichloroethylene in a shower chamber, modeling of indoor air


