Public Health Goal for Chromium In Drinking Water

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical

feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR CHROMIUM IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 2.5×10^{-3} mg/L (2.5 µg/L, 2.5 ppb) for total chromium. The California Maximum Contaminant Level (MCL) is currently 0.05 mg/L (50 ppb) for total chromium in drinking water. There are two forms of chromium, chromium VI and chromium III, that may be significant as drinking water contaminants. OEHHA believes that the health protective goals of the California Safe Drinking Water Act of 1996 are best served by assuming that chromium VI is carcinogenic when ingested. Based on this assumption, a health protective level of 0.2 µg/L, or 0.2 ppb is calculated for chromium VI, based on tumor development in female mice (Borneff et al., 1968). This study involved exposure of male and female mice to potassium chromate in drinking water at a level of 500 mg/L. The female mice exposed to potassium chromate had increased incidence of benign and malignant stomach tumors relative to controls. The cancer potency for chromium VI was calculated using ToxRisk, based on the increased incidence of these forestomach tumors in the female mice.

A non-cancer health protective level for chromium VI in drinking water of 70 ppb was determined based on a chronic drinking water study in rats (MacKenzie et al., 1958). This study showed no adverse effects at a level of 2.4 mg/kg-day. The health protective level was arrived at using an overall uncertainty factor of 500, and a relative source contribution (RSC) of 40%.

The health protective level for chromium III is 200 mg/L, or 200,000 ppb, based on a rat drinking water study (Ivankovic and Preussmann, 1975) which provided a NOAEL of 1,468 mg/kg-day, the only dose level tested in this study. This health protective level includes an uncertainty factor of 100 for extrapolation from animals to humans, and for intraspecies variability.

OEHHA estimates that total chromium would be made up of no more than 7.2% chromium VI. The PHG for total chromium was calculated from the health protective level for chromium VI (cancer endpoint) using 7.2% as the percentage of chromium VI in total chromium.

INTRODUCTION

Chromium is an industrially important metal, which has the potential to contaminate drinking water sources. Chromium VI is more water soluble, more easily enters living cells, and is much more toxic than chromium III. Chromium VI is a human carcinogen, as determined by the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (U.S. EPA), and OEHHA (NTP, 1998; IARC, 1990; U.S. EPA, 1998b; Siegel, 1990). OEHHA has made a health protective assumption that chromium VI is a potential human carcinogen by the oral

route (Siegel, 1990). Chromium III has not been shown to be carcinogenic to animals or humans by the oral route (IARC,1990; U.S. EPA, 1998a; ATSDR, 1993 and 1998).

The health protective level for chromium VI is based on carcinogenicity in a mouse drinking water study (Borneff et al., 1968). The health protective level for chromium III is based on a NOAEL derived from a rat drinking water study (Ivankovic and Preussmann, 1975). The values for the two chemical forms differ greatly, and they are based on different health effects. The PHG for total chromium is based on the health protective level for chromium VI, assuming that total chromium is made up of no more than 7.1% chromium VI.

CHEMICAL PROFILE

Chemical Identity

Chromium is a metallic element with an atomic number of 24. It is a member of group VIB on the periodic table, along with molybdenum and tungsten. Chromium possesses one electron in its outer electron shell. There are four naturally occurring isotopes of chromium. The most common ones are ^{52}Cr (83%) and ^{53}Cr (9.5%). None of the natural isotopes is radioactive (Weast et al., 1988).

Physical and Chemical Properties

Chromium generally occurs in small quantities associated with other metals, particularly iron. The atomic weight of chromium is 51.996. Chromium melts at 1,875° C, and boils at 2,680° C. The specific gravity of chromium is 7.19. The most common valences are +3 and +6. Chromium forms a number of salts, which are characterized by a variety of colors, solubilities and other properties. The name “chromium” is from the Greek word for color. The most important chromium salts are sodium and potassium chromates and dichromates, and the potassium and ammonium chrome alums (Hodgman, et al., 1961).

Production and Uses

The metal is usually produced by reducing the chromite ($FeCr_2O_4$) ore with aluminum (Weast et al, 1988). The combined production of chromium metal and chromium ferroalloys in the United States in 1988 was 120,000 metric tons (ATSDR, 1993). Most of this metal is used in the manufacture of automobiles, appliances and other consumer products.

Chromium is used to harden steel, in the manufacture of stainless steel, and in the production of a number of industrially important alloys (Weast et al., 1988). Chromium is used in making of pigments, in leather tanning and for welding. Chromium plating produces a hard mirror-like surface on metal parts that resists corrosion and enhances appearance.

Sources

The principal ore of chromium is chromite ($FeCr_2O_4$), found in Zimbabwe, Russia, Transvaal, Turkey, Iran, and other countries (Weast et al., 1988). The ore has not been mined in the United States since 1961 (ATSDR, 1993). Ore is imported into the U.S. from the above mentioned countries, and refined in the U.S. into chromium metal and alloys. In California there are over a hundred industrial facilities that process imported chromium (ATSDR, 1993).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Chromium is present in the atmosphere in particulate form, usually as very small particles (approximately 1 μm in diameter). Chromium can enter the ambient air from anthropogenic point sources such as smelters, or from windblown soil, road dust or seawater. Cigarette smoke contributes chromium to indoor air. Chromium levels in the air in the U.S. are typically <0.01 $\mu g/m^3$ in rural areas, and in the range of 0.01 to 0.03 $\mu g/m^3$ in urban areas (ATSDR, 1993).

Soil

Chromium occurs naturally in crustal rocks, but the main source of chromium in soil is probably disposal of commercial products. Chromium is present in soil primarily in the form of the insoluble oxide, Cr_2O_3. Chromium is generally not mobile in soil (ATSDR, 1993).

Water

Chromium enters environmental waters from anthropogenic sources such as electroplating factories, leather tanneries and textile manufacturing facilities. Chromium also enters groundwater by leaching from soil. Chromium can exist in water as either Cr III or Cr VI. Cr VI in water will eventually be reduced to Cr III by organic matter. The rate at which this occurs depends on the amount of organic matter present in the water, and on the pH and redox potential of the water (Clifford and Man Chau, 1988). Rivers in the U.S. have been found to have from <1 to 30 μg/L of chromium. U.S. lakes usually have < 5 μg/L of chromium. When high levels are present, they can usually be related to sources of pollution. A survey of drinking water sources in the U.S. conducted for 1974 to 1975 found chromium levels ranging from 0.4 to 8.0 μg/L, with a mean of 1.8 μg/L (ATSDR, 1993).

California water monitoring data from 1984 to 1996 (California Department of Health Services, 1997) show that chromium (as total chromium) was detected in 822 of 9,604 drinking water sources, or approximately 9% of the sources surveyed. The practical detection limit was 10 μg/L. The range of total chromium levels in the samples where chromium was detected was from 10 μg/L up to a maximum of 1,100 μg/L, with a mean of

23 μg/L and a median of 17 μg/L. The chromium was not speciated, so we do not know how many of these sources would have had detectable amounts of chromium VI.

There are very few data available on which to base an estimate of the chromium VI fraction of total chromium in potential drinking water sources. Only one study was located in the literature which deals with speciation of chromium in potential drinking water supplies (Kacynski and Kieber, 1993). In order to determine the relative amounts of the two species, the investigators sampled a number of surface water sources, including both salt and fresh water sources. They analyzed the samples using iron hydroxide coprecipitation of chromium followed by graphite furnace atomic absorption spectroscopy. This method enables Cr III and Cr VI to be determined from the same samples, with a low detection limit (0.02 nM Cr III and total chromium). Two lakes in North Carolina were chosen for study because they were relatively free of tidal action and currents which would complicate the sampling. Samples were taken at different times of day and during different seasons. The research paper does not explain the sampling design in terms of the locations within the lakes where the samples were taken. The following table gives the mean chromium levels for these two lakes.

	Cr III (nM) nM=nanomolar	Cr VI (nM)	Total Cr (nM)	Percentage of Total Cr as Cr VI
Singletary Lake	0.168	0.003	0.171	1.8%
Greenfield Lake	0.032	0.013	0.045	29%
Geometric Mean				7.2%

These are very limited data from two potential drinking water sources in another state, but there were no data available on speciation of chromium in California drinking water sources.

Food

Virtually all foods contain some chromium, ranging from 20 to 590 μg/kg (U.S. EPA, 1985). The foods with the highest levels of chromium are meats, mollusks, crustaceans, vegetables, and unrefined sugar (U.S. EPA, 1985).

Chromium is only slightly bioconcentrated in fish. Trout exhibit a bioconcentration factor (BCF) for chromium of 1. Mollusks bioconcentrate chromium to a much greater extent, with BCFs ranging from 86 to 192 (ATSDR, 1993).

Dietary intake of chromium by humans has been estimated to range from 5 to 500 μg/day, with a typical value of approximately 100 μg/day (U.S. EPA, 1985).

Other Sources of exposure

Workers in chromium production, stainless steel production and welding, chromium plating, ferrochrome and chromium pigment industries may have occupational exposures to chromium III and chromium VI (ATSDR, 1993). Occupational exposure is mainly by inhalation. Ingestion exposures could occur in industry if industrial hygiene rules are not followed. See ATSDR (1993) for a complete list of industries that may contribute to sources of chromium exposure.

METABOLISM AND PHARMACOKINETICS

Absorption

Approximately 0.5% to 2% of chromium III is absorbed in the gastrointestinal tract of humans (ATSDR, 1993). Chromium VI appears to be better absorbed, however, chromium VI is readily converted to chromium III in the gastric environment (Kerger et al., 1997). The amount of chromium absorbed depends on the amount in the diet. More chromium (approximately 2%) is absorbed when dietary levels are low (approximately 10 µg per day). When dietary levels are higher (40 µg per day or higher) the degree of absorption declines to approximately 0.5% (Anderson, 1986).

Distribution

Studies of the distribution of chromium in human tissues indicate that chromium accumulates mainly in the liver and kidneys after acute exposure (in a 14-year-old boy who ingested 7.5 mg chromium VI/kg body weight) (Kaufman et al., 1970) or chronic exposure, as indicated by autopsy studies performed in the United States on individuals of various ages (Schroeder et al., 1962). The autopsy studies indicate that the levels in the liver and spleen increase up to approximately age 20 years, and decline thereafter. Recent studies in human volunteers (Kerger et al., 1997) show that when chromium VI is administered in drinking water, chromium is taken up and distributed to all parts of the body, and excreted. It cannot be determined from these experiments whether the chromium remains in the hexavalent state or is converted to chromium III.

Studies of mice exposed to chromium in drinking water indicate that whereas chromium III goes primarily to the liver, chromium VI is distributed to all organs, particularly the kidneys and spleen. Accumulation of chromium in the liver was 40 to 90 times higher in the chromium VI treated group, as compared to the chromium III treated group (Maruyama, 1982). After exposure to chromium III, chromium was found in liver, kidney, spleen, hair, heart and red blood cells in rats (Aguilar et al., 1997).

Metabolism

Chromium VI is unstable in the body and is reduced to chromium V, chromium IV, and ultimately to chromium III by many substances including ascorbate and glutathione. Chromium VI readily enters mammalian cells, where it becomes reduced to chromium III by NADPH (Petrilli et al., 1986). It is believed that the toxicity of chromium within the cell results from damage to cellular components during this process through generation of free radicals (ATSDR, 1998). Chromium III forms complexes with a variety of nucleic acids and proteins (ATSDR, 1998). Chromium III is eliminated from the body as a chromium III-glutathione complex (ATSDR, 1998).

A physiologically based model of chromium kinetics in the rat has been developed recently (O'Flaherty, 1996). The model involves parallel absorption and disposition schemes for chromium VI and chromium III, linked by reduction processes occurring throughout the body.

Excretion

Unabsorbed chromium (III and VI) is eliminated in the feces. Chromium VI that is absorbed into the circulation is reduced to chromium III, mainly in the liver. Chromium III forms a complex with glutathione and is then excreted in the urine (ATSDR, 1998).

Physiological/Nutritional Role

Chromium III is an essential nutrient. Chromium III complexes with other components (not completely characterized) to form glucose tolerance factor (GTF). GTF facilitates the binding of insulin to its cell membrane receptor, thereby playing a role in metabolism of glucose, proteins and lipids (ATSDR, 1993). Chromium deficiency can result in high blood glucose levels.

The Committee on Dietary Allowances, Food and Nutrition Board of the National Research Council has recommended a daily intake of 50 to 200 µg/day for adults based on the absence of chromium deficiency signs in the major part of the U.S. population consuming an average of 50 µg chromium/day (NRC, 1989).

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

Oral LD_{50}s (median lethal doses) have been determined for chromium III compounds in rats. Chromium acetate was reported to have an LD_{50} in rats of 2,365 mg Cr/kg (Smyth et al., 1969). Chromium nitrate had much lower LD_{50}s than chromium acetate, probably because

of greater water solubility. The LD_{50}s for chromium nitrate were 183 mg Cr/kg in female rats, and 200 mg Cr/kg in male rats (Vernot et al., 1977). The signs of toxicity in the animals included hypoactivity, lacrimation, and diarrhea (Vernot et al., 1977).

Oral LD_{50}s for chromium VI compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) ranged from 13 to 19 mg Cr/kg in female rats, and 21 to 28 mg Cr/kg in male rats (Gad et al., 1986).

In general chromium VI salts had greater acute toxicity than Cr III salts, and female rats were slightly more sensitive to both chromium III and chromium VI salts (ATSDR, 1998).

Subchronic Toxicity

Ivankovic and Preussmann (1975) reported a 90-day feeding study in which chromium oxide green (Cr_2O_3) was administered to BD rats in their feed at doses of 2% and 5%. This experiment revealed no toxic effects of the chromium III by the oral route. The experiment was followed by a 2-year feeding study reported in the same paper and discussed below.

Genetic Toxicity

Genotoxicity studies of chromium compounds have been reviewed by Cohen et al. (1993). Chromium VI compounds were found to be mutagenic in both bacterial and mammalian cell assays. In E. coli, base substitution mutations were detected following treatment with potassium chromate, but only at near cytotoxic levels (Cohen et al., 1993). Chromium VI compounds were found to be mutagenic in several *Salmonella typhimurium* strains in the Ames test (Cohen et al., 1993). Chromate primarily caused base substitution mutations in this assay.

Chromium III compounds are not as active as chromium VI compounds in cellular genotoxicity assays because of their poor uptake (Cohen et al., 1993). However, trivalent chromium has been shown to interact with isolated nuclei, chromosomes or nucleic acid in vitro. Under these conditions, chromium III was shown to produce DNA-protein crosslinks, and to modify the fidelity and kinetics of DNA replication. In summary, both chromium VI and chromium III have genotoxic activity, but chromium VI is a more potent genotoxin in whole cells because of its greater ability to enter the cell (Cohen et al, 1993).

Developmental and Reproductive Toxicity

Chromium III was not reported to be fetotoxic or teratogenic in rats. Male and female rats fed 1,806 mg chromium III per kg of body weight for 60 days prior to mating and throughout the gestation period (for females) produced normal healthy offspring (Ivankovic and Preussman, 1975). Chromium III was also found not to cause reproductive effects in rats. Male and female rats fed chromium III as described above had normal fertility, gestational duration and litter size (Ivankovic and Preussmann, 1975).

Mice exposed for seven weeks to 9.1 mg chromium III/kg-day as chromium sulfate in the diet had reduced sperm count and degeneration of the outer cellular layer of the seminiferous tubules. Morphologically altered sperm were observed in mice given diets with 28 mg chromium III/kg-day as chromium sulfate (Zahid et al., 1990; ATSDR, 1998).

Chromium VI however caused severe developmental effects when tested in mice. Pregnant mice were exposed daily to 46 mg chromium VI per kg body weight in drinking water throughout gestation, resulting in increased fetal resorptions and post-implantation loss of fetuses as well as gross abnormalities such as subdermal hemorrhage, decreased cranial ossification and tail deformation. Crown to rump length and fetal weight were also significantly decreased. The incidence and severity of these abnormalities were increased at higher doses. Maternal toxicity, as evidenced by decreased body weight gain, was observed in animals exposed to 98 mg chromium VI per kg body weight or more (Trivedi et al., 1989; ATSDR, 1998). Under the same experimental conditions, chromium VI also caused severe reproductive effects in mice. Pregnant mice exposed as above showed increases in pre- and post-implantation fetal loss, and decreased litter size (Trivedi et al., 1989).

Zahid et al (1990) examined the effects of chromium VI and chromium III in the diet on mouse testes and spermatogenesis. Mice were fed 100, 200 or 400 ppm Cr VI or Cr III in the diet. Degenerated tubules were found at all three dosage levels for both forms of chromium, but not in the controls. Sperm counts were likewise depressed at all three dosage levels for both kinds of chromium, but the effect was greater for Cr VI.

Ingestion in drinking water of trivalent and hexavalent chromium compounds by adult male and female mice caused adverse effects on fertility and reproduction in experiments reported by Elbetieha and Al-Hamood (1996), however these experiments involved very high doses, 2000 to 5000 mg/L, so their relevance to human exposures is limited.

Kanojia et al (1996) found that pregestational exposure of female rats to chromium VI at doses of 250, 500 and 750 ppm as potassium dichromate via drinking water led to embryo- and fetotoxic effects in the form of a significant reduction in the number of implantations and fetuses. There was dose-dependent reduction in fertility in all three dosage groups relative to untreated controls. Skeletal abnormalities (reduced ossification) were also found in the fetuses of chromium VI treated mothers. Reduced parietal and inter-parietal ossification was observed only in the highest dosage group, whereas reduced caudal ossification was observed in all dosage groups.

Immunotoxicity

Daily exposure of rats to 16 mg chromium VI per kg body weight for three weeks led to sensitization of the animals as evidenced by increased proliferation of T and B lymphocytes in response to the mitogens concanavalin A and liposaccharide (Snyder and Valle, 1991; ATSDR, 1998).

Johansson et al. (1987) studied the effect of inhalation by rabbits of trivalent chromium ($Cr(NO_3)_3$) at a concentration in air of 0.6 or 2.3 mg/m^3. They found nodular intra-alveolar accumulation of enlarged macrophages with granular, eosinophilic cytoplasm in the lungs of rabbits exposed to both dosage levels. This study shows that administration to rabbits of trivalent chromium at levels close to the NIOSH occupational threshold limit value results in structural abnormalities in alveolar macrophages. No studies were located on the immunotoxic effects (if any) of orally administered trivalent chromium.

Neurotoxicity

No abnormalities of the brain or nervous system was found during histological examination of rats fed 2,040 mg chromium III/kg/day in the diet for two years (Ivankovic and Preussmann, 1975). Wistar albino rats exposed to 98 mg chromium VI/kg/day in drinking water for 28 days exhibited decreased motor activity and disturbed balance (Diaz-Mayans et al., 1986).

Chronic Toxicity

U.S. EPA based a reference dose (RfD) for chromium VI on a rat drinking water study with a duration of one year (MacKenzie et al., 1958). In this study, groups of eight female Sprague-Dawley rats were given drinking water containing 0-11 mg/L hexavalent chromium as K_2CrO_4 for one year. The control group (ten males and ten females) received distilled water. A second experiment involved three groups of twelve male and three female rats in each group. The first group was given 25 mg/L chromium VI as K_2CrO_4. The second group received 25 mg/L chromium III as chromic chloride. The controls received distilled water. No significant adverse effects were observed in appearance, weight gain, or food consumption. There were no pathologic changes in the blood or other tissues in any treatment group. The rats receiving 25 mg/L chromium VI as K_2CrO_4 exhibited a reduction in drinking water consumption of approximately 20%. This exposure level corresponds to a dose of 2.4 mg/kg-day based on actual body weight and water consumption data from the experiment. This study identified a NOAEL of 2.4 mg/kg-day for chromium VI in rats by ingestion. Overall, there was no effect reported at all dose levels, the highest being 25 mg/L, corresponding to 2.4 mg/kg-day.

Mortality was not increased in rats fed 1,468 mg Cr III/kg per day as chromium oxide in the diet (5% of diet by weight) for 600 days (Ivankovic and Preussmann, 1975; U.S. EPA, 1998). Thus the NOAEL for noncarcinogenic effects of chromium III in rats is 1,468 mg/kg/day determined in this study using a single treatment level.

Carcinogenicity

Chromium VI has been shown to be carcinogenic in animals by inhalation (Cohen et al., 1993; IARC, 1990; U.S. EPA, 1998b). Mice chronically exposed to chromium VI as $CaCrO_4$ dusts or chromic acid mists developed lung adenomas and carcinomas, although the incidences were not statistically significant (Cohen et al., 1993). Weekly intratracheal instillations of Cr VI compounds, in both mice and rats, produced numerous lung tumors (Cohen et al., 1993). In summarizing the available data from all the animal studies performed, the IARC Working Group on the Evaluation of Carcinogenic Risk of Chemicals to Humans concluded that there was sufficient evidence for the carcinogenicity of soluble calcium chromate and several relatively insoluble hexavalent chromium compounds in laboratory rodents (IARC, 1990).

The "preponderance of data" indicates that chromium III does not give rise to tumors by inhalation (Cohen, et al., 1993). With the exception of the Borneff study (discussed below) the animal bioassays for the carcinogenicity of chromium VI and chromium III by the oral route have yielded negative results (Cohen, 1993).

The potential of chromium VI to be carcinogenic by the oral route was studied in mice (Borneff et al, 1968). In this experiment, 2 of 66 female mice exposed to drinking water with 500 mg of potassium chromate (K_2CrO_4) per liter of drinking water were found to have malignant tumors of the forestomach, compared with none in the control mice. This was not a statistically significant result. Although it is not possible to determine from the report whether the two carcinoma-bearing mice also had papillomas, the assumption that they did not would give an incidence of papilloma or carcinoma of 11/66 treated female mice and 2/79 control female mice, which would give statistical significance of p=0.003 by the Fisher exact test.

Chromium VI has caused contact site tumors in laboratory animals (Hueper, 1955; Maltoni 1976).

No evidence of carcinogenicity was found in male or female rats fed diets containing chromium III at 1,468 mg/kg/day for 600 days, nor in the offspring of these rats (Ivankovic and Preussmann, 1975).

Toxicological Effects in Humans

Acute Toxicity

All reports of humans acutely poisoned by chromium compounds have involved compounds of chromium VI (ATSDR, 1993). A 14-year old boy died in the hospital eight days after ingesting 7.5 mg CrVI/kg as potassium dichromate. Death resulted from gastrointestinal ulceration and severe damage to the liver and kidneys (Kaufman et al., 1970). Other reports of humans dying from ingestion of chromium VI involved large amounts of the chemical (ATSDR, 1993 and 1998).

Effects on the cardiovascular, respiratory, gastrointestinal, hematological, hepatic and renal systems are observed in humans who die after ingestion of large amounts of chromium VI (ATSDR, 1998). A 22-month-old boy died of cardiopulmonary arrest after ingesting an unknown amount of sodium dichromate (Ellis et al., 1982). In another case report, a 17-year-old male died of cardiac arrest after ingesting potassium dichromate at 29 mg chromium VI/kg (Clochesy, 1984).

Chronic Toxicity

Ingestion by humans of chromium VI in drinking water or diet has been shown to have chronic effects as described below.

Hematological Effects

A village in the People's Republic of China had a drinking water well contaminated from a nearby alloy plant with 20 mg CrVI/L. A cross sectional study of people living in this village revealed that they suffered from leukocytosis and immature neutrophils (Zhang and Li, 1987). The alloy plant began operation in 1961, and the study was conducted in 1965. It was not clear whether the drinking water was free of chromium contamination before the plant began to operate. Similar results were reported by Zhang and Li (1987) from other villages in China.

Hepatic Effects

No reports were found of humans suffering hepatic effects as a result of chronic ingestion of chromium VI or chromium III.

Renal Effects

No reports were found of humans suffering renal effects as a result of chronic ingestion of chromium VI or chromium III.

Gastrointestinal Toxicity

Cross sectional epidemiological studies have been conducted on villagers in China who consumed water from wells contaminated with chromium VI (Zhang and Li, 1987). Drinking water from one of these wells contained 20 mg chromium VI/L. The villagers who drank this water experienced oral ulcer, diarrhea, abdominal pain, indigestion and vomiting. The dose was estimated to be 0.57 mg chromium VI/kg/day (Zhang and Li, 1987).

Developmental and Reproductive Toxicity

No studies in humans of developmental or reproductive effects caused by ingested chromium were found in reviews of past literature (ATSDR, 1993 and 1998) or in a computer search of current literature. Chromium is not listed under Proposition 65 (The California Safe Drinking Water and Toxic Enforcement Act of 1986) as a chemical known to the State to cause reproductive or developmental harm.

Immunotoxicity

Chronic dermal exposure to chromium VI in workers has led to contact dermatitis (ATSDR, 1998). This dermatitis is exacerbated by oral administration of 0.04 mg chromium VI/kg as potassium dichromate (Goitre et al., 1982).

Neurotoxicity

Autopsy of a 14-year old boy who had ingested 7.5 mg CrVI/kg revealed enlarged brain and cerebral edema. However, this effect may be secondary to kidney failure rather than a direct effect on the nervous system (Kaufman et al., 1970). No other reports of the effects of chromium on the nervous system in humans were located.

Carcinogenicity

Occupational exposures to chromium VI in the dichromate production industry over a period from the 1930s to the 1980s has been shown in numerous epidemiological studies to be correlated with increased risk of respiratory cancers (cancers of the lungs and respiratory tract)(ATSDR, 1998). Because of this positive evidence in humans, it has been concluded that chromium VI is a known human carcinogen by the inhalation route (IARC, 1990; ATSDR, 1998; U.S. EPA, 1998; NTP, 1998).

Although chromium VI is carcinogenic to humans by inhalation, some reviewers have concluded that it is unlikely to be carcinogenic to humans by the oral route (Cohen, 1993). A study of chrome workers, exposed to chromium VI by inhalation, found an elevated mortality due to stomach cancers and liver cancers, but no relationship was found between duration of employment in this industry and risk of death from these two cancers. There have been a number of other studies of gastrointestinal tumors in chrome industry workers. These have been reviewed by Cohen et al. (1993).

Zhang and Li (1997) reported a study of approximately 10,000 villagers exposed to drinking water with chromium VI levels as high as 20 mg/L. Cancer death rates for these villagers who lived along a chromium-contaminated river, were compared with villagers from two other provinces that had no detectable chromium VI in their drinking water. The authors did not report on exposures to other potential carcinogens in either the “exposed” or “control” areas. The period between the beginning of the exposures (1965) and the end of the period when cancer mortalities were studied (1970 to 1978) was only 13 years. This may not be long enough for cancers to develop. There was no statistical increase in cancer mortality in the three most-exposed villages, as compared to the control provinces (Zhang and Li, 1997).

Because of this epidemiological evidence, and because chromium VI is converted to chromium III in the gastric environment, some reviewers doubt that chromium VI would be carcinogenic by the oral route (Cohen et al., 1993). The reduction of chromium VI to chromium III in the gastric environment would not preclude the possibility that chromium VI could produce tumors in the stomach.

Others have argued strongly that chromium VI should be regarded as carcinogenic by the oral route. Costa (1997) reviewed evidence that supports the conclusion that hexavalent chromium is taken up by the GI tract and transported to all tissues of the body. He also reviewed epidemiological evidence that exposure to hexavalent chromium causes increased risk of cancer in bone, prostate, stomach and other organs.

OEHHA reviewed the evidence, and decided that chromium VI should be assumed to be carcinogenic by the oral route (OEHHA, 1991; Siegel, 1990; Siegel, 1991). The arguments supporting this position are as follows.

- Chromium is a known human carcinogen by the inhalation route.
- Non-respiratory cancers have been found in workers exposed to chromium VI by inhalation.
- Inhaled chromium VI causes respiratory tumors in rats.
- Chromium VI causes contact site tumors in laboratory animals.
- Ingested chromium VI has been associated with stomach tumors in mice.
- Chromium VI has been positive in a number of assays for genotoxicity.

For the protection of public health, it is safer to assume that a substance which is carcinogenic by one route may also be carcinogenic by other routes. This is the assumption OEHHA will make in evaluating chromium VI for a PHG determination.

There is no evidence that chromium III is a human carcinogen by the oral route (Cohen et al., 1993; ATSDR, 1998; IARC, 1998; U.S. EPA, 1998).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The only study on which an assessment of the noncarcinogenic toxicity of chromium VI in drinking water may be based is the chronic drinking water study in rats reported by MacKenzie et al. (1958). This study was used by the U.S. EPA in calculating the RfD for chromium VI (U.S. EPA, 1996). It is the only chronic oral study in animals that was located. No other study was located in a computer search of the recent literature. This study yielded a NOAEL for chromium VI of 2.4 mg/kg-day.

For chromium III the best study is that of Ivankovic and Preussmann (1975). This is a two-year rat feeding study that yields a NOAEL of 1,468 mg/kg-day. No better study was located in a computer search of the literature.

Carcinogenic Effects

The cancer potency value for chromium VI by ingestion in humans will be calculated from the mouse drinking water study by Borneff et al. (1968). In this study there was only one exposure level, which was 500 mg potassium chromate/L. Stomach tumors were observed in both control and treated mice, but the frequency was increased in the female mice treated with potassium chromate. The tumor frequency increased from 2/79 in the female control group, to 11/66 in the female treated group. Of the 11 tumors in the female treated group, two were malignant carcinomas, and the remainder were benign papillomas with hyperkeratosis. All of the tumors in the control group were benign. These data from the

female mice were used to calculate a cancer potency for chromium VI using ToxRisk. The q_1* calculated in this way was 0.21 $(mg/kg\text{-}day)^{-1}$. The cancer slope factor (based on the LED_{10}) calculated from the same data was 0.19 $(mg/kg\text{-}day)^{-1}$, almost the same. The cancer slope factor will be used to calculate a PHG for chromium VI in drinking water.

Chromium III has not been shown to be a carcinogen by the oral route (ATSDR, 1998).

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, for preparing foods and beverages. It is also used and for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for ***chromium VI*** in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL	=	No-observed-adverse-effect-level
BW	=	Adult body weight (a default of 70 kg for male or 60 kg for female)
RSC	=	Relative source contribution (a default of 20% to 80%)
UF	=	Uncertainty factors (typical defaults of a 10 to account for inter-species extrapolation, a 10 for uncertainty from the subchronic nature of the principal study and a 10 for potentially sensitive human subpopulations)
L/day	=	Adult daily water consumption rate (a default of 2 L/day)

The NOAEL for chromium VI is 2.4 mg/kg/day from the MacKenzie et al. study (1958) discussed above. This was a chronic drinking water study in rats. No significant adverse effects were observed at all dosage levels up to 2.4 mg/kg-day, so a NOAEL but no LOAEL was derived from this study. The total uncertainty factors will be 500, based on a factor of 10 for extrapolating between species, and 10 to protect potentially sensitive human subpopulations, and 5 to compensate for the fact that the duration of the study was less than a full lifetime (one year rather than two years). An uncertainty factor of 10 is sometimes

used to correct for the use of a short-term study. In this case the study lasted for half a lifetime, so a smaller factor of 5 was employed. U.S. EPA also used a factor of 5 for this purpose in calculating a RfD of for chromium VI (U.S. EPA, 1998).

Food is a significant source of human exposure to chromium (see above under "Environmental Occurrence and Human Exposure"). According to U.S. EPA (1985), a typical value for chromium exposure from food is approximately 100 µg/day. The mean and median levels of chromium in California drinking water sources are about 20 µg/L of total chromium (Storm, 1994). Neither source of chromium has been analyzed for hexavalent chromium, so we assume that the ratio of chromium VI to total chromium is the same in both sources. This would suggest a relative source contribution of 40%, based on two liters per day water consumption. OEHHA will use a relative source contribution of 40% based on the above considerations.

The calculation for chromium VI is as shown below:

$$C = \frac{2.4\ \text{mg/kg/day} \times 70\ \text{kg} \times 0.4}{500 \times 2\ \text{L/day}} = 0.067\ \text{mg/L}$$

The value of 0.067 mg/L is rounded off to 0.07 mg/L, or 70 ppb.

In the case of ***chromium III***, the NOAEL is 1,468 mg/kg-day, based on a rat chronic, two-year feeding study (Ivankovic and Preussmann, 1975) where no effect was observed following treatment at a single dose level. An uncertainty factor of 100 will be used for extrapolating from animals to humans, and the account for variability in sensitivity within the human species.

The calculation for chromium III is as follows:

$$C = \frac{1{,}468\ \text{mg/kg/day} \times 70\ \text{kg} \times 0.4}{100 \times 2\ \text{L/day}} = 205\ \text{mg/L}$$

The value of 205 mg/L is rounded off to 200 mg/L, or 200,000 ppb.

Carcinogenic Effects

The human cancer slope factor derived from the Borneff et al. (1968) study can be used to calculate a potential PHG for chromium VI, based on carcinogenicity. The cancer slope factor OEHHA will use is 0.19 $(\text{mg/kg-day})^{-1}$, based on total tumors (malignant and benign) in female mice. This is the cancer slope factor we calculated using ToxRisk.

$$C = \frac{\text{b.w.} \times R}{\text{CSF} \times 2\ \text{L/day}}$$

$$C = \frac{70\ kg \times 1\times10^{-6}}{[0.19\ (mg/kg\text{-}day)^{-1}]\times 2\ L/day} = 1.8\times10^{-4}\ mg/L = 0.18\ \mu g/L \text{ or } 0.18\ ppb$$

This can be rounded off to 0.2 ppb. This is much lower than the 70 ppb calculated for chromium VI based on noncarcinogenic effects.

PHG for Total Chromium

To calculate a PHG for total chromium, we must estimate the percentage of chromium VI in total chromium. The study by Kaczynski and Kieber (1993) described above in the section on "Environmental Occurrence and Human Exposure" provides the only available data on speciation of chromium in potential drinking water sources. Using the geometric mean from these two lakes, the percentage of total chromium that is present as chromium VI is 7.2%. We can use this estimate of chromium VI in total drinking water chromium to calculate a PHG for total chromium based on the C value for chromium VI calculated above in the "Carcinogenic Effects" section.

PHG Total Chromium = (C value for Cr VI) ÷ (percentage of total Cr as Cr VI)

= 0.18 μg/L ÷ 0.072 = 2.5 μg/L or 2.5 ppb.

OEHHA therefore has developed a Public Health Goal (PHG) for total chromium of 2.5 ppb.

RISK CHARACTERIZATION

The PHG for total chromium in drinking water is based on the assumed oral carcinogenicity of chromium VI. The percentage of chromium VI in total chromium in drinking water sources was estimated based on available data from the research literature. The available data are limited to two lakes in North Carolina (Kaczynski and Kieber, 1993). This is one source of uncertainty in this PHG calculation. In the future if better data are made available, particularly for California drinking water sources, this source of uncertainty can be lessened.

There is some controversy as to whether chromium VI should be considered a carcinogen by the oral route (ATSDR, 1993). In 1990, the Standards and Criteria Work Group (SCWG) of OEHHA reviewed the evidence, and determined it would be prudent to assume that chromium VI is a carcinogen by the oral route (Siegel, 1990). This decision was made based on the fact that chromium VI is carcinogenic by inhalation, and it is prudent policy to consider a carcinogen by one route to be a carcinogen by other routes as well. It was also based on the genotoxicity of chromium VI in bacterial and mammalian cell assays. However, no positive studies have been located linking chromium in drinking water with increased incidence of cancer in human populations (Cohen et al., 1993; ATSDR, 1993). The mouse study by Borneff et al. (1968) on which this PHG is based, found no statistically

significant increase in malignant tumors in the treated mice. It was only when benign stomach tumors were included along with malignant tumors that the results became statistically significant (Borneff et al. 1968; Siegel, 1990). In developing a PHG based on carcinogenicity, OEHHA is continuing to assume that chromium VI is a carcinogen by the oral route, while acknowledging the uncertainty surrounding this issue.

The health protective level for chromium III is based on a rodent experiment, with extrapolation from animals to humans. There is always uncertainty in extrapolating from animals to humans, which is the reason for one of the uncertainty factors used in this calculation -- an uncertainty factor of 10. An additional factor of 10 (making a total UF of 100) was used to account for uncertainty about the variability in sensitivity of the human population.

Another source of uncertainty is the relative source contribution used in calculating the health protective level for chromium III. OEHHA has used a relative source contribution of 40%. OEHHA does not have exact data on which to base the relative source contribution for chromium III, so this is an estimate. In the future, if better data become available, a new relative source contribution can be calculated.

Chromium III is a nutritionally required element. The health protective level of 200 mg/L is much higher than the adult nutritional requirement of 50 to 200 µg/day (ATSDR, 1993). There is no concern that the health protective level for chromium III will interfere with the nutritional requirement. The PHG for total chromium would allow approximately 5 µg/day chromium intake. Most drinking water sources contain no detectable chromium, so nutritional requirements can be expected to be met by the food source of chromium.

OTHER REGULATORY STANDARDS

The U.S. EPA MCLG for total chromium is 0.1 mg/L. The U.S. EPA MCL is also 0.1 mg/L. There are no separate standards for chromium III and chromium VI. The U.S. EPA also has 1 day and 10 day health advisories of 1 mg/L for total chromium for children, and a "longer-term" health advisory for children of 0.2 mg/L. For adults the "longer-term" health advisory is 0.8 mg/L for total chromium. The reference dose (RfD) for adults is 0.005 mg/L (U.S. EPA, 1996).

The California MCL for total chromium is 0.05 mg/L (22 CCR, section 64431, Table 64431-A-Inorganic Chemicals).

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