PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

BARIUM

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Public Health Goal for
Barium
in Drinking Water

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PREFACE

Drinking Water Public Health Goals
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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), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and publish PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. 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 that can cause chronic disease shall be based upon currently available data and shall be set at levels that 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 published by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published 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 intended 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 BARIUM IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 2.0 mg/L, or 2.0 ppm, for barium in drinking water. The PHG is based on absence of cardiovascular effects (hypertension) based on observations from two studies on humans exposed to barium in drinking water. In a human epidemiological study, Brenniman and Levy (1984) compared human morbidity and mortality rates between two cities in Illinois. The city of West Dundee had a mean barium concentration in drinking water of 7.3 ppm, and the city of McHenry had a 0.1 ppm drinking water concentration. The authors found no significant differences when comparing age-specific mean systolic and diastolic blood pressures as well as prevalence rates for stroke, heart disease, and kidney disease between sample populations of the two cities. The observations provide a human NOAEL of 0.2 mg/kg-day based on the absence of cardiovascular effects. The PHG is based on the use of 70-kg bw, a water consumption of 2L/day, an uncertainty factor of 3 and a relative source contribution of 1.

In the study by Wones and colleagues (1990), the authors performed a 10-week study to determine whether drinking water at higher barium levels alters known risk factors for cardiovascular disease. Eleven male adult humans received barium via drinking water at 0 ppm (two weeks), then 5 ppm (four weeks), and finally at 10 ppm (four weeks). Blood pressures, electrocardiograms, and blood chemistries (including plasma cholesterol, lipoprotein levels, serum potassium and glucose levels), and urine catecholamines were measured; all levels remained constant throughout the study period. The observations provide a human NOAEL at the 10 ppm level, estimated to correspond to 0.21 mg/kg-day in this study, based on the absence of cardiovascular effects.

Chronic oral exposure studies in rats and mice (NTP, 1994) have not demonstrated carcinogenic effects for barium. No other adequate carcinogenicity studies exist for barium.

Currently, the U.S. EPA Maximum Contaminant Level (MCL) for barium is 2 mg/l, and the California MCL is 1 mg/L.

INTRODUCTION

Barium is an alkaline earth metal, and it exists typically as salts with several different anions. Barium salts have a wide variety of commercial applications, including use in paints, soap, paper, rubber, in various alloys, and in the manufacture of ceramics and glass. Barium sulfate, which is highly insoluble, has commonly been used as a radiopaque agent for gastrointestinal x-rays. Chronic oral studies in rats and mice sponsored by the National Toxicology Program (NTP, 1994) have not demonstrated carcinogenic effects for barium. No other adequate carcinogenicity studies exist for

barium. Non-cancer toxic effects of barium in humans are principally cardiovascular (especially increased blood pressure), gastric upset, and neurological (including stimulation at lower levels and paralysis at higher doses). Adverse effects have also been observed on kidneys in animal studies. Barium salts vary from highly soluble to highly insoluble in water. Acute and chronic toxicity by the oral route increases directly with the water solubility of the barium salt.

The purpose of this document is to develop a PHG for barium in drinking water. In this document, the available data on the toxicity of barium are evaluated, with the primary focus on the literature related to oral exposures, which may be most relevant for the establishment of a PHG for drinking water. The studies that are appropriate for identification of public health-protective levels are reviewed and summarized. The results of this evaluation are described below.

CHEMICAL PROFILE

Chemical Identity

Barium is a member of the alkaline earth metals (atomic number 56) in group II A of the periodic table. Elemental barium oxidizes readily in moist air and reacts with water. In nature, barium is found as the divalent cation in combination with other elements. The physical and chemical properties of barium and barium compounds are given below in Table 1 (ATSDR, 1992; U.S. EPA, 1998; WHO, 1990).

Physical and Chemical Properties

Barium metal is highly reactive and does not occur naturally in the metallic state (ATSDR, 1992). Barium salts vary widely in solubility. The more water-soluble salts of barium are barium acetate (588 g/L at 0^{o} C) and barium chloride (375 g/L at 20^{o} C). By contrast, barium sulfate is practically insoluble in water with a solubility of 0.00115 g/L at 0^{o} C (ATSDR, 1992), and 0.002 g/L at 18^{o} C (HSDB, 2002).

Table 1. Physical and Chemical Properties of Barium and Selected Barium Compounds

	Barium (metal)	Barium acetate	Barium carbonate	Barium chloride	Barium hydroxide	Barium oxide	Barium sulfate
CAS registry number	7440-39-3	543-80-6	513-77-9	10361-37-2	17194-00-2	1304-28-5	7727-43-7
Molecular formula	Ba	$Ba(C_2H_3O_2)_2$	$CaCO_3$	$BaCl_2$	$Ba(OH)_2$	BaO	$BaSO_4$
Physical state	Malleable metal	Crystalline	Heavy powder or crystals	Flat crystals	White powder	Powder or crystals	crystals
Molecular weight	137.3	255.45	197.37	208.27	171.38	153.36	233.4
Melting point ^oC	710	41	1,740	960	408	1,920	1,580
Boiling point ^oC	1,600	No data	Decomp at 1,300	1,560	760	2,000	1,149
Vapor pressure, mm Hg	10 at 1,049 ^oC	No data	Essentially zero	Essentially zero	No data	Essentially zero	No data
Water solubility, g/L	Decomposes	588 at 0^o C, 750 at 100 ^oC	0.02 at 20 ^oC	357 at 20 ^oC	16.7 at 0 ^oC	1,500 at 0 ^oC Soluble in water	0.002 at 18 ^oC
Organic solvent solubility, g/L	Soluble in benzene	1 g/700 mL alcohol	Insoluble in alcohol	Soluble in methanol	1.67 g/L in alcohol (0^o C)	Soluble in alcohol	Insoluble
Specific gravity	3.5 at 20 ^oC	2.02 below 24.7 ^oC	4.43	3.1	2.18 at 16 ^oC	5.72	4.58

Sources: ATSDR, 1992; U.S. EPA, 1998; HSDB, 2002.

Production and Uses

Most barium compounds are derived from barite (barium sulfate). World production of barite was estimated at 5.7 million tonnes in 1985 (WHO, 1990). Industrial barium emissions result principally from mining, refining, or processing of barium minerals and manufacture of barium products (WHO, 1990). Barium has many industrial uses, including oil drilling muds, paper manufacture, soap, rubber, linoleum, dyes, pyrotechnics, metallurgy, and ceramics manufacture. Barium compounds are often found as pigments in paints and textiles. Barium alloys are used as "getter" materials to absorb trace gasses from vacuum tubes. The highly insoluble barite is frequently used, in purified form, as a benign, radio-opaque aid to x-ray diagnosis of gastrointestinal disease in humans (Tarasenko *et al.*, 1977; ATSDR, 1992).

Natural Sources

In nature, barium occurs in a combined, mineral state, principally barite (barium sulfate) and witherite (barium carbonate). Small quantities of barium are found in igneous rocks and fossil fuels, and are also present in air, water, and soil (WHO, 1990). Barium can also be taken up by plants and may occur in foods, as discussed below.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Barium is emitted to the atmosphere principally via industrial processes that use barium salts or refine barium ores. Combustion of coal and oil also emit barium to the atmosphere (U.S. EPA, 2001). Airborne releases of barium are either as particulate emissions from drying and calcining or as fugitive dust during the processing of barite ore (ATSDR, 1992). In 1987, 0.6 million pounds of barium were released to the atmosphere, nationwide, as barium and its compounds as a result of industrial activity (ATSDR, 1992). The average concentration in urban air was reported to be 0.005 $\mu g/m^3$ (range 0 to 1.5) in 18 U.S. cities (Friberg *et al.*, 1986). The human intake of barium via inhalation has been estimated to vary from 0.03 to 22 μg/day, based upon National Air Surveillance Network data showing air concentrations ranging from 0.0015 to 0.05 $\mu g/m^3$ (U.S. EPA, 1990).

Soil

In 1987, approximately 15 million pounds of barium and barium-containing compounds were released to soils from industrial processes using barium compounds and ores. A major portion of this was petroleum and natural gas exploration, which generates barium-containing waste muds that are land-farmed. Land-farmed barium may be either taken up by vegetation or transported though soils (ATSDR, 1992). Barium is not very mobile in most soil systems (U.S. EPA, 2001). Barium mobility in soils is reduced by the precipitation of barium carbonate and barium sulfate.

Water

Barium occurs naturally in most surface and groundwaters, with groundwaters generally higher in concentration due to leaching and eroding of sedimentary rocks (ATSDR, 1992). Average surface water concentrations were reported as 43 ppb (U.S. EPA, 2001). Drinking water concentrations are usually below 200 ppb, although many communities in Illinois, Kentucky, Pennsylvania, and New Mexico are supplied with drinking water at much higher concentrations, as much as ten times higher than the MCL of 2000 ppb (U.S. EPA, 2001). However, the average concentration of barium in U.S. drinking water was estimated at 28.6 ppb in 1977 sampling. In water, the more soluble (and hence more toxic) barium salts generally precipitate out as the less soluble sulfates and carbonates (U.S. EPA, 2001). As reported by the California Department of Health Services (2002), out of 11,729 water samples taken within the state over a period from 1984-2001, 3,270 samples contained detectable barium; the detection limit for the purposes of reporting is 0.1 mg/L.

Food

Dietary barium intake has been estimated as an average of about 0.67 mg/day (ATSDR, 1992), and as up to 1.3 mg/day (Friberg *et al.*, 1986). The intake from food is probably less variable among the population than intake from drinking water, because barium is a trace component of most foods (thus averaging over many sources), whereas drinking water tends to be from a more limited number of sources for each individual. Certain foods, such as Brazil nuts, contain relatively high levels of barium that range between 3,000 and 4,000 ppm (ATSDR, 1992). However, these are not substantial components of the U.S. diet.

METABOLISM AND PHARMACOKINETICS

Absorption

Barium is absorbed via the gastrointestinal tract, the lungs, and the nasal mucosal membranes. The degree of absorption of barium from the lungs and gastrointestinal tract varies widely, depending upon species, contents of the gastrointestinal tract, and age (U.S. EPA, 1990; WHO, 1990). Morrow *et al.* (1964) evaluated clearances of barite from the lower respiratory tract in the dog. The authors observed that the persistence in lungs was extremely brief for an "insoluble" substance with a biological half-time of only 8 days. Phagocytosis was mentioned as one of the possible mechanisms of the second clearance phase of insoluble barium sulfate dust from the lower respiratory tract.

Taylor *et al.* (1962) studied the absorption of barium from the gastrointestinal tract of the rat. Female brown-hooded August rats, aged between 14 days and 70 weeks, were intubated with $^{140}BaCl_2$ and terminated 7 hours later. Absorption was calculated as the sum of the labeled barium in the carcass after seven hours plus that in the urine minus that in the gastrointestinal tract. At 14-18 days of age, about 50 percent of the barium was absorbed. For animals six to eight weeks of age, barium absorption decreased to seven percent. Deprivation of food before administration markedly increased the absorption of barium (Taylor *et al.*, 1962).

Differences in rates of absorption of barium compounds with different anions were investigated by McCauley and Washington (1983). Male Sprague-Dawley rats were orally administered 10 mg/kg-day ^{131}Ba/liter as sulfate (SO_4), chloride (Cl_2) or carbonate (CO_3) salts at pH 7.0. Animals were terminated at 2, 5, 10, 20, 30, 60, and 120 minutes and 24 hours after intubation. $Ba(SO_4)$ was administered as a suspension. For the chloride salt, blood barium rose linearly for ten minutes then less rapidly until 60 minutes. At 24 hours, ^{131}Ba was still at peak levels. For the SO_4 and CO_3 anions, ^{131}Ba in blood was respectively 85 percent and 45 percent of the levels achieved with the Cl_2 anion (McCauley and Washington, 1983).

Gastrointestinal absorption of barium in humans has not been definitively investigated. Tipton *et al.* (1969) determined the long-term balance of dietary barium (among other elements) in two humans. The authors determined the barium amounts for intake and excreta for two men for 50 weeks. Five percent of the total ingested barium was absorbed.

Lisk *et al.* (1988) examined barium absorption and excretion in humans. One human male consumed 179.2 mg barium in 92 grams of Brazil nuts. The authors calculated that at least 92 percent of the dose was absorbed.

At low environmental levels, the absorption of barium sulfate from drinking water would likely be the same as that of barium chloride because the salts are fully dissociated in solution and the hydrochloric acid environment of the stomach would tend to maintain the solubilization of the barium in (U.S. EPA, 1998). A default value of 20 percent gastrointestinal absorption of dissolved barium in drinking water was assumed by the Safe Drinking Water Committee of the National Research Council, National Academy of Sciences (NRC, 1982; Wones *et al.*, 1990).

Distribution

WHO (1990) states that the average 70-kg human body contains about 22 mg of barium, 91 percent of which is localized in bones. Trace quantities are found in the eye, aorta, heart, kidney, spleen, pancreas and lung. Barium has been found in samples from stillborn babies, suggesting that it crosses the blood/placental barrier.

U.S. EPA (1990) reports that retention of barium following exposure is principally due to skeletal deposition that occurs preferentially on bone surfaces and in areas of active bone growth. The skeletal accretion rate for barium is approximately twice that for calcium. Accretion is the formation of bone salts, and is generally regarded as irreversible (Bauer *et al.*, 1956).

In an inhalation study, Cuddihy *et al.* (1974) observed that the uptake of barium from aerosols of barium chloride in Beagle dogs appeared to be rapid. One day following inhalation exposure to barium chloride aerosols, 78 percent of the total body burden of $^{131}BaCl_2$ was found in the skeleton.

Metabolism

Barium is not metabolized in the body, but it may be metabolically transported or incorporated into other tissues (ATSDR, 1992). The mechanisms by which barium is deposited in the body tissues are not well characterized, although general patterns of uptake show similarities to calcium and strontium (WHO, 1990). Transportation and incorporation of barium closely

parallels that of calcium (U.S. EPA, 1990). Barium, possibly by reacting with PO_4^{-3} ions, is deposited in bone, partly by ionic exchange with calcium at the actively calcifying surface and partly by surface adsorption (Bauer *et al.*, 1956, 1957; Bligh and Taylor, 1963; Ellsasser *et al.*, 1969).

Excretion

According to WHO (1990) barium is eliminated in the urine and feces, with the elimination rate varying with the route of administration. At a human intake level of 1.33 mg/day (1.24, 0.086, and 0.001 mg/day respectively, from food, water, and air), approximately 90 percent of the barium is excreted in the feces and about 2 percent in the urine (Schroeder *et al.*, 1972). In a rat study, a small amount of barium was found to be excreted into the bile after parenteral administration of $^{133}BaCl_2$ (Edel *et al.*, 1991).

In 1966, an Atomic Energy Commission study examined the uptake and retention of orally administered radium and barium. Eight dogs were dosed with tracer doses of uranium and barium via the dietary route, then maintained in metabolism cages for 30 days. The authors reported that more than 85 percent of the dose was excreted via the feces during the first 48 hours after feeding (Della Rossa *et al.*, 1967).

Richmond *et al.* (1960) studied interspecies differences in excretion of ^{131}Ba administered by various routes to mice, rats, and dogs. The rodents received intravenous doses of $BaCl_2$ and the dogs were dosed orally. For each species, initial elimination half-times were about 12 hours (Richmond *et al.*, 1960).

Tipton *et al.* (1969) analyzed the diets and urinary and fecal excretion from two men for a period of 50 weeks. The authors reported that two to five percent of the dietary barium was excreted via the urinary pathway and 95 to 98 percent was excreted via the fecal pathway.

Rundo (1967) examined retention times of ^{131}Ba from a previous retention study of a single intravenous dose of ^{131}Ba in a healthy male human. The author concluded that the biological half-life of barium followed three distinct components: 1) 21.9 percent of injected dose eliminated by 3.6 days, 2) an additional 4.1 percent of dose by 34.2 days, and 3) an additional 5.6 percent of barium eliminated by 1033 days. A later study in six human males on the metabolism and long-term retention of injected ^{133}Ba showed a mean whole-body retention of 8 percent after 50 days (range 4.5 to 12 percent) (Newton *et al.*, 1991). The retained component of barium, deposited in bone, had a half-life of 10.74 years.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Barium stimulates muscle tissue. The mechanism most probably occurs in the blocking of calcium-activated potassium channels that control cellular potassium efflux. Thus, barium

intoxication results in a rise of intracellular potassium and a corresponding drop of extracellular potassium, leading to hypokalemia (Goyer and Clarkson, 2001).

The acute oral toxicity of barium salts depends upon their solubility in water (Goyer and Clarkson, 2001). The relative acute toxicity decreases in the following order of barium anions: carbonate, chloride, sulfide, and sulfate, correlated with their decreasing water solubility (Tardiff *et al.*, 1980).

Roza and Berman (1971) studied the pathophysiology of $BaCl_2$ given intravenously to mongrel dogs. Thirteen canine subjects were used in the study. The total intravenous dosages of barium ranged from 22 to 154 μg/kg over periods of 20 to 100 minutes. The authors observed, in rough chronological order, arterial hypertension and within five minutes, premature supraventricular and ventricular contractions. Spontaneous skeletal muscle contraction and salivation and then watery diarrhea followed these symptoms. Generalized muscle twitching, increased respiratory rate, and decreased respiratory depth were then observed. More severe premature ventricular contractions then appeared. These symptoms led to paralysis of skeletal and respiratory muscles followed by ventricular tachycardia, fibrillation and death. The authors concluded that $BaCl_2$ infusion produced a decrease in plasma potassium concentration accompanied by a rise in red blood cell potassium concentration, the hypokalemia being due to a shift of potassium from extracellular to intracellular water. Arterial hypertension was then observed (Roza and Berman, 1971).

Tardiff *et al.* (1980) conducted acute oral toxicity studies of barium, as $BaCl_2$, in weanling and adult male and female rats. For the study, $BaCl_2$ was dissolved in distilled water and given as a single oral gavage. Each LD_{50} determination used eight dose levels with 10 rodents per level. Animals were observed for two weeks following dosing. The acute oral LD_{50} for weanling rats was about 220 mg/kg and the acute oral LD_{50} for adult rats was approximately 132 mg/kg. The LD_{50} values were reported as "approximate" with no mention as to differences in response between males and females (Tardiff *et al.,* 1980).

Hicks *et al.* (1986) examined the cardiotoxic and bronchoconstrictor effects of barium via inhalation by guinea pigs of barium-containing fumes. Dunkin-Hartley guinea pigs (cannulated for mechanical ventilation) were administered barium aerosols via the trachea and the resulting effects were compared with those obtained from intravenous injection of $BaCl_2$. The authors observed dose related pressor effects and bronchoconstrictor effects due to exposure via both pulmonary and i.v. routes.

Subchronic Toxicity

Tardiff *et al.* (1980) exposed rats of both sexes to 0, 10, 50, or 250 ppm of barium as $BaCl_2$ in drinking water for 4, 8, or 13 weeks. The barium doses were approximately 0, 2.75, 13.7, and 66.25 mg/kg-day at the beginning of the study and 0, 1.7, 6.6, and 31.5 mg/kg-day at the end of the study. The shift in doses occurred from a combination of animal growth and decrease in water uptake (high dose level). No adverse effects were observed on food consumption, clinical signs, body weight, hematologic parameters (such as hemoglobin, hematocrit, red cell count, leukocyte count, prothrombin time and fibrinogen), serum enzyme activities (such as SGOT, SGPT, and BUN) and serum sodium, potassium and calcium. Other than a slight decrease in the

relative weight of adrenal glands of treated versus controls, no conclusive signs of barium toxicity were observed. Unfortunately, blood pressure was not measured in the test rodents.

NTP (1994) studied groups of ten male and ten female B6C3F_1 mice receiving barium chloride dihydrate in drinking water at concentrations of 0, 125, 500, 1,000, 2,000, or 4,000 ppm for 13 weeks. The concentrations corresponded to average daily doses of 15, 55, 100, 205, or 405 mg/kg-day of barium for males and 15, 60, 100, 200, or 495 mg/kg-day barium for females. Final mean body weights of males and females in the high dose groups were significantly lower (>30 percent). The authors observed treatment-related nephropathy in 10 male and nine female rodents of the high dose group, including mild to moderate tubule dilation, regeneration, and atrophy. Atrophy of the thymus and spleen was observed in the majority of the early dead animals treated at the highest level. At this level, 6/10 male and 7/10 female mice died, with most deaths occurring on or after week five. No animals died at other dosage levels.

NTP (1994) conducted an identical study in F334 rats with the same concentrations of barium chloride in drinking water, corresponding to average daily doses of 10, 30, 65, 110, or 200 mg/kg-day in males and 10, 35, 65, 115, or 180 mg/kg-day in females. As with mice, the final mean body weights were significantly lower in rats treated at the highest dose than those of control animals (males decreased by 13 percent and females by eight percent). Treatment-related kidney lesions occurred in 3/10 female rats at 4,000 ppm, and included minimal to mild dilation of the proximal tubules. The absolute and relative kidney weights for females in the 2,000 and 4,000 ppm groups and also the relative kidney weights of the males in the 2,000 ppm group were significantly greater than the controls, and were associated with the above-described kidney lesions. The LOAELs were therefore 110 mg/kg-day in males and 115 mg/kg-day in females, with an estimated NOAEL of 65 mg/kg-day in both sexes.

Genetic Toxicity

Sirover and Loeb (1976) tested barium (among other metal salts) for its ability to affect the accuracy of DNA synthesis *in vitro*. Barium chloride (2, 6, and 10 mM) and barium acetate (10 mM) were tested in a system containing synthetic polynucleotide templates and purified avian viral polymerases. The barium salts did not affect DNA replication and the authors categorized them as negative in the "carcinogenic or mutagenic" data column of their results table.

Nishioka (1975) performed a "rec" assay, which utilizes wild and recombination-deficient strains of *Bacillus subtilis* along with 3 strains of *E. coli* to screen for mutagenic activity in the assay. The author screened several metal compounds including $BaCl_2$. Barium chloride tested negative for mutagenic activity in all strains (Nishioka, 1975).

Barium chloride and nitrate were found to be negative with and without metabolic activation in Ames tests using *Salmonella* strains TA 1535, 1537, 1538, 97a, 98, and 100 (Monaco *et al.*, 1990, 1991). Barium was also found not mutagenic in *S. typhimurium* mutagenicity tests reported by Zeiger *et al.* (1992) and Rossman *et al.* (1991).

Developmental and Reproductive Toxicity

Dietz *et al.* (1992) administered barium dichloride dihydrate via drinking water to $B6C3F_1$ mice and Fischer 344/N rats. Four dose levels were used; 0, 500, 1,000, and 2,000 ppm in mice and 0, 1,000, 2,000, and 4,000 in rats, each group containing 20 rodents of each sex. Dose levels were estimated at 55, 100, and 205 mg/kg-day for treated male mice and 60, 110, and 200 mg/kg-day for treated female mice. Levels for treated rats were estimated at 65, 110, and 200 mg/kg-day for males and 65, 115, and 180 for females (U.S. EPA, 1998). Males were exposed for 60 days and females for 30 days prior to mating. Live offspring were evaluated on their birth day and 5 days following parturition. Dams were terminated on days 96 and 97; the vagina, cervix, oviducts and ovaries were examined, and implantation sites on uteri were counted. Evaluations were performed on sperm morphology and motility, male reproductive organ weights, and vaginal cytology between treated and control groups. Pregnancy rates were below generally accepted norms for both control and treated groups in both mice and rats, with no explanation found in the text. Rats treated at the highest dose level yielded offspring with marginally smaller birth weights, compared with control pups. Otherwise, notwithstanding below-normal pregnancy rates observed in all groups, drinking water exposure to barium chloride in rats and mice dosed at the above levels did not result in observed reproductive toxicity (Dietz *et al.*, 1992).

Immunotoxicity

Animal data regarding immunological effects due to barium exposure are quite limited. Borzelleca *et al.* (1988) reported that exposure of rats to doses of barium chloride at doses ranging from 10-300 mg/kg-day (for either one or 10 days) was not associated with changes in thymus weight. In the NTP (1994) subchronic study, lymphoid depletions in the spleen and thymus were observed in high-dose rats (200 mg/kg-day in males and 180 mg/kg-day in females) that died during the study. A depression in absolute thymus weights was also observed in the high-dose female group; this was attributed by the authors to a decrease in body weight in these animals.

Neurotoxicity

Animal data regarding neurological effects of barium are limited to a few reports. Borzelleca *et al.* (1988) reported that no brain weight changes or brain lesions were associated with acute gavage exposure of rats to doses at and below 198 mg/kg.

Tardiff *et al.* (1980) exposed young adult rats of both sexes to 0, 10, 50, or 250 ppm of $BaCl_2$ in drinking water for 4, 8, or 13 weeks. No gross or microscopic abnormalities were observed in the brain. Additionally, relative and absolute brain weights were not statistically different from controls.

In the subchronic portion of the NTP (1994) study, statistically significant decreases in motor activity were observed near the end of the study (at 90 days) in the high-dose rats of both sexes (180-200 mg/kg-day) (Dietz *et al.*, 1992). This was attributed to the generally poor condition of the animals at this dose. Three out of 10 males and 1/10 females died during this last week of the study. No other statistically significant changes were observed on the other behavioral tests

(tail-flick thermal sensitivity, startle response, forelimb or hindlimb grip strength, and hindlimb foot splay).

Taglialatela and colleagues (1989) demonstrated that high (10-20 mM) extracellular concentrations of Ba2+ ions stimulated superperfused tuberoinfundibular neurons to release the neurotransmitter dopamine in a dose-dependant manner. Further, equimolar concentrations of Ca2+ ions did not modify the dopamine release, thus demonstrating an independence from calcium for this apparent neurological effect.

Chronic Toxicity

Perry *et al.* (1983) exposed female Long-Evans rats to 0, 1, 10, or 100 ppm barium as $BaCl_2$ in drinking water for up to 16 months. The estimated barium intake due to drinking water plus diet was 0.098, 0.17, 0.82, and 7.4 mg/kg-day (U.S. EPA, 1998). Systolic blood pressures were recorded at 1, 2, 4, 8, 12, and 16 months exposure duration. At the 10 ppm level, systolic pressures increased over the control average from the eighth month through the end of the study. A potential confounder in this study is that the laboratory chow was deficient in calcium and below recommended levels of potassium. These low metal concentrations may have artifactually predisposed the rodents to the hypertensive effects of barium (Perry *et al.*, 1983; U.S. EPA, 1998). Effects of barium on the cardiovascular system are affected by calcium and potassium levels (U.S. EPA, 1998). The study LOAEL was equivalent to 0.82 mg/kg-day, and the NOAEL to 0.17 mg/kg-day of total barium (water plus diet). However, U.S. EPA (1998) has considered this study inappropriate for determination of an RfD. OEHHA concurs.

McCauley *et al.* (1985) performed histological, electron microscopic, electrocardiographic, and blood pressure studies in rats given barium. The authors studied three exposure regimens for the histology portion: (1) groups of 12 male Sprague-Dawley rats were exposed to 0, 1, 10, 100, or 250 ppm barium as $BaCl_2$ in drinking water for 36 weeks; (2) groups of 12 female Sprague-Dawley rats were exposed to 0 or 250 ppm barium in drinking water for 46 weeks; and (3) groups of 10 male Sprague-Dawley rats were exposed to 0, 1, 10, or 100 ppm barium in drinking water for 68 weeks. The estimated total barium intakes were 1, 1.15, 2.5, 16, and 38.5 mg/kg-day for the 0, 1, 10, 100, and 250 ppm drinking water levels, which includes barium intake from lab chow. No barium-related lesions were observed in the histological studies, including evaluations of gastrointestinal tract, kidneys, liver, heart, respiratory tract, spleen, thymus, ovaries, and testes (McCauley *et al.*, 1985; U.S. EPA, 1998).

For the electrocardiographic portion of this study, McCauley *et al.* (1985) treated Sprague-Dawley rats, at 10 or 11 per group, with 0 or 250 ppm barium in drinking water for five months. Electrocardiographic evaluations were performed at 0, 4, and 60 minutes following an intravenous injection of norepinephrine (0.5 µg/kg). Barium induced a significant enhancement of bradycardia compared with controls at four minutes following norepinephrine administration; however, by 60 minutes the heart rates of the barium-exposed rodents were approaching the normal value, while rates of control animals were still depressed. No EKG abnormalities were observed. The effect on responses to epinephrine challenge represent a LOAEL of about 38 mg/kg-day, although the toxicological significance of this alteration is not clear.

McCauley *et al.* (1985) also conducted a blood pressure study with six Sprague-Dawley rats per group, sex not specified. For a period of 16 weeks, normotensive rats received 0, 3, 10, 30, or

100 ppm barium in regular drinking water or in drinking water containing 0.9 percent sodium chloride. Additionally, Dahl salt-sensitive rats were exposed to 1, 10, 100, or 1000 ppm barium in drinking water for 16 weeks. The concentrations of 0, 1, 3, 10, 30, 100, and 1,000 ppm correspond to doses of 0, 0.15, 0.45, 1.5, 4.5, 15, and 150 mg/kg-day, respectively. The authors observed no adverse blood pressure effects due to barium in the drinking water at exposure levels up to 1,000 ppm (McCauley *et al.*, 1985; U.S. EPA, 1998), for a NOAEL of 150 mg/kg-day.

NTP (1994) studied chronic toxicity of barium in B6C3F_1 mice. The authors dosed groups of 60 male and 60 female mice with barium chloride dihydrate in drinking water at concentrations of 0, 500, 1,250, or 2,500 ppm for 103 weeks (males) and 104 weeks (females). The corresponding average daily doses were 30, 75, and 160 mg/kg-day (males) and 40, 90, and 200 mg/kg-day for females. Survival rates at the highest dose levels at the end of the study (65 percent for males and 26 percent for females) were significantly lower than the rates for controls (89 percent for males and 76 percent for females). The authors also observed significant increases of nephropathic lesions at the 2,500 ppm dose level. The nephropathy was characterized by extensive regeneration of the cortical and medullary renal tubule epithelium, tubule dilation, and hyaline case formation. The lesions were accompanied by irregularly shaped brown crystals aggregated within renal tubule lumens and the interstitium. These kidney lesions were suspected to cause the sickness or death of most rodents which did not survive to the end of the study (NTP, 1994). Based upon kidney lesions and decreased survival rates at the 2,500 ppm exposure level, 1,250 ppm (corresponding to 75 mg/kg-day in males and 90 mg/kg-day in females) is the NOAEL for this chronic mouse study (U.S. EPA, 1998).

NTP (1994) performed a similar study on F334/N rats. Dose groups of 60 male and 60 female rats received barium chloride dihydrate in drinking water at concentrations of 0, 500, 1,250, and 2,500 ppm for 104 weeks (males) and 105 weeks (females). The corresponding average daily doses were 15, 30, and 60 mg/kg-day for males and 15, 45, and 75 mg/kg-day for females. At 15 months, interim evaluations were performed on 10 rodents per dose group (NTP, 1994). Statistically significant increases in relative kidney weight were observed in female rats at the 2,500 ppm dose level. This observation, along with the kidney weight increases in female rats observed at the 2,000 ppm level for the 13-week study (described earlier) are highly suggestive of potential renal effects (U.S. EPA, 1998). Thus, 1,250 ppm (45 mg barium/kg-day) is the chronic NOAEL for female rats for renal effects in this NTP study.

Carcinogenicity

There was no evidence of carcinogenicity in both sexes of rats or mice given barium chloride dihydrate via drinking water (McCauley *et al.*, 1985; U.S. EPA, 1998). Two-year drinking water studies (described earlier) were performed on F344/N rats and B6C3F_1 mice (60 males and 60 females per group). The rodents received 0, 500, 1,250, or 2,500 ppm barium chloride dihydrate in distilled drinking water for 105 weeks (female rats), 104 weeks (male rats and female mice), and 103 weeks (male mice). For rats, the dose related barium intake was 15, 30, or 60 mg/kg-day for males and 15, 45, or 75 mg/kg-day for females. For mice, the estimated daily doses of barium were 30, 75, or 160 mg/kg-day for males and 40, 90, or 200 mg/kg-day for females. In rats, no increased incidence of neoplasia could be associated with barium chloride dihydrate administration. Interestingly, several neoplasms occurred with decreased incidence in

male rats. These included pheochromocytomas of the adrenal medulla and mononuclear cell leukemia. Similarly, in mice, no treatment-related incidents of neoplasia were observed in males or females. The incidence of hepatocellular adenoma was significantly decreased in males at the high dose level (NTP, 1994). The effective NOAELs for carcinogenic effects were the highest doses tested, 60 and 75 mg/kg-day for male and female rats, respectively, and 160 and 200 mg/kg-day for male and female mice, respectively.

Toxicological Effects in Humans

Acute Toxicity

Accidental or intentional ingestion of barium chloride and other barium salts have been described. Symptoms typically begin with rapid onset of nausea, vomiting and diarrhea following stimulation of the gastrointestinal tract. Additional symptoms include hypokalemia, cardiac arrhythmias, muscular weakness, salivation, loss of tendon reflexes, tingling in the extremities, paralysis and in the case of the severely intoxicated, death (U.S. EPA, 1990).

Agarwal *et al.* (1995) suggested that the fatal human dose of barium carbonate is about 800 mg. Potassium deficiency occurs in acute barium poisoning, possibly because barium blocks potassium channels and thereby reduces potassium efflux from the muscles. In addition, barium competitively reduces the permeability of cell membranes to potassium (Agarwal *et al.*, 1995).

Diengott *et al.* (1964) described two patients admitted to the hospital after eating sausage contaminated with barium carbonate at a party. Both patients suffered vomiting, colic, diarrhea, internal hemorrhaging, myocardial and general muscle stimulation, flaccid paralysis, and tingling in the extremities. Both patients had elevated blood pressure and cardiac arrhythmias, and both were given i.v. potassium chloride. The 62 year-old woman recovered; however, the 75 year-old male died 22 hours following admission to the hospital.

Thomas *et al.* (1998) described the attempted suicide by a 32 year-old female ceramic artist who intentionally ingested potter's glaze containing 62 percent barium sulfide. The patient (who had bipolar mood swings along with anorexia) was extremely emaciated. She suffered hypokalemia, flaccid paralysis, malignant arrhythmias, and respiratory distress; however, she ultimately recovered completely.

Subchronic Toxicity

Wones *et al.* (1990) performed a 10-week study in human volunteers to determine whether barium in drinking water at levels found in some United States communities alters known risk factors for cardiovascular disease. Eleven healthy, normotensive male humans (four black, seven white, ranging in age from 27-61 years) completed the protocol. Diet and beverages were provided (600 mg/day cholesterol, 40 percent fat, 20 percent protein, 40 percent carbohydrate; and sodium and potassium controlled at the subject's pre-protocol estimated intake), and all food was consumed in the study center. Each subject was his own control as the barium in drinking water (at 1.5 L/day) varied from 0 ppm (first two weeks), to 5 ppm (the next four weeks) and then 10 ppm (for the final four weeks). Using a 70 kg reference weight, the estimated doses were 0.11 and 0.21 mg barium/kg-day (U.S. EPA, 1998). Blood and urine samples, morning and

evening blood pressure measurements, and 48-hour electrocardiograms were taken at the beginning of the study and at the end of each study period. Systolic and diastolic pressures were unchanged throughout the study. No arrhythmias were recorded. Blood chemistries, including plasma cholesterol, lipoprotein levels, serum potassium and glucose levels, and urine catecholamines remained constant throughout. The authors noticed a trend toward increased serum calcium levels with the increased exposure to barium; however, the trend was borderline statistically significant and considered of doubtful clinical significance (Wones *et al.*, 1990). A NOAEL of 0.21 mg/kg-day for maximum exposure levels without clinical signs can be inferred from the 10 ppm exposure regime that Wones *et al.* used for the last four weeks of the study (U.S. EPA, 1998). The four weeks exposure at 10 ppm is of sufficient duration to equilibrate barium with calcium and potassium in the readily-exchangeable body pools. However, this study in eleven normotensive males cannot address whether the high barium exposure might elevate blood pressure in humans predisposed to high blood pressure or consuming diets marginally deficient in potassium.

Genetic Toxicity

No studies evaluating potential genetic toxicity of barium in humans were located in the literature.

Developmental and Reproductive Toxicity

No valid studies evaluating potential developmental or reproductive toxicity of barium in humans were located in the literature.

Immunotoxicity

No studies evaluating potential immunotoxicity of barium in humans were located in the literature.

Neurotoxicity

As mentioned previously, barium intoxication in humans is associated with neurotoxic effects resulting in symptoms such as muscular weakness, salivation, loss of tendon reflexes, tingling in the extremities, and paralysis. Many of these effects are associated with hypokalemia (Diengott *et al.*, 1964; Thomas *et al.*, 1998; U.S. EPA, 1990, 1998).

Similarly, Agarwal *et al.* (1995) reported that the most characteristic features of barium intoxication include areflexia and flaccid paralysis.

Chronic Toxicity

Pendergrass and Greening (1953) and Doig (1976) describe baritosis as a benign or non-specific form of pneumoconiosis that is caused by breathing fine particles of insoluble barium ores of barite ($BaSO_4$). In the case of baritosis, the inhaled particulate matter resides in the lungs for years without symptoms or incapacity. Lung deposits of barium, which is radio-opaque, are

fairly easily seen on chest x-rays. Several years after removal from an airborne barium particulate-laden work environment, radiological abnormalities show marked clearing (Pendergrass and Greening, 1953; Doig, 1976).

Brenniman and Levy (1984) performed an environmental epidemiology study to determine if human morbidity and mortality rates were significantly different between populations consuming elevated levels of barium in drinking water and populations ingesting low levels of barium in drinking water. No other chemicals in the water supplies exceeded drinking water regulatory levels. The authors studied morbidity from 1976 to 1977 in 1175 adults from West Dundee, IL (7.3 ppm mean barium concentration in drinking water) and 1203 adults from McHenry, IL (0.1 ppm mean barium concentration in drinking water). Age-specific mean systolic and diastolic blood pressure levels for adult males and females were compared between West Dundee and McHenry residents. Incidence of kidney disease in the communities was surveyed via a questionnaire. Participants included persons 18 years of age or older, in randomly selected blocks within their communities. The authors adjusted for duration of exposure, home water softeners, and blood pressure medication. No significant differences ($p<0.05$) were found between the high and low barium concentration communities. In addition to blood pressure, the authors compared prevalence rates for stroke, heart disease, and kidney disease between the two cities and found them not significantly different ($p<0.05$). Assuming 70 kg body weight and 2 L/day drinking water consumption, the mean drinking water dosage of barium in West Dundee was 0.21 mg/kg-day, whereas the mean dosage in McHenry was 0.003 mg/kg-day. Thus 0.21 mg/kg-day is a NOAEL for hypertension and also for (self-reported) kidney disease (Brenniman and Levy, 1984; U.S. EPA, 1998).

The mortality portion of the Brenniman and Levy study surveyed additional communities with a wider range of barium in their water supplies (2-10 mg/L in high-exposure versus ≤ 0.2 mg/L in low-exposure communities). This portion of the study did not control for population mobility, water softener use, medication use, smoking, diet, or exercise. Mortality rates in the elevated barium communities were higher for "all cardiovascular disease," "arteriosclerosis," and "all causes" for the years 1971-1975. However, the authors treated the outcome with "extreme caution" because of the potentially confounding variables. Thus, the study information cannot be used to assign a causal relationship between mortality and drinking water containing dissolved barium at 2-10 mg/L (0.06-0.3 mg Ba/kg-day) (Brenniman and Levy, 1984; U.S. EPA, 1998).

Carcinogenicity

No epidemiological studies associating barium exposure with carcinogenicity in humans were located in the literature.

Ayre and coworkers (1966) treated an adult female human with a single, topical application of 1.25 mM barium chloride to the squamocolumnar junctional area of the cervix, and 48 hours later, the cervix was scraped to recover squamous and endocervical cells. This procedure was repeated three times at intervals of four to six weeks. From the recovered cells, the authors observed multinucleation, nuclear enlargement, and hyperchromatism that were not present previous to treatments. The authors noted that the cells faded away via normal exfoliation between treatments.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Of the studies conducted on experimental animals, the most relevant for calculating a PHG for non-cancer effects of barium in drinking water would be that of NTP (1994). From the chronic exposure portion of this study, a NOAEL was observed in the female rat for the absence of relative kidney weight increases at the 1,250 ppm drinking water exposure level. This corresponds to about 45 mg barium/kg-day (NTP, 1994). Acute cardiovascular effects of barium associated with competition with potassium and calcium transport sites are observed at higher doses or under other conditions (WHO, 1990; Perry *et al.*, 1983; U.S. EPA 1990, 1998). The hypertensive effects of barium observed in several studies have also been hypothesized to be due to direct stimulation of arteriolar smooth muscle (Roza and Berman, 1971).

For estimation of health-protective levels, the results of two human studies are of greater significance. Wones and colleagues (1990) performed a 10-week study to determine whether drinking water at higher barium levels alters known risk factors for cardiovascular disease. Eleven male adults received barium via drinking water at 0 ppm (two weeks), then 5 ppm (four weeks), and finally at 10 ppm (four weeks). Blood pressures, electrocardiograms, and blood chemistries (including plasma cholesterol, lipoprotein levels, serum potassium, calcium, and glucose levels) and urine catecholamines were evaluated. None of the levels appeared to be affected by the treatment. The observations provide a human NOAEL of 0.21 mg/kg-day based on the absence of cardiovascular effects (Wones *et al.*, 1990).

Brenniman and Levy (1984) compared human cardiovascular parameters and morbidity rates between two cities in Illinois with different concentrations of barium in their drinking water. The city of West Dundee had a mean barium concentration in drinking water of 7.3 ppm, and the city of McHenry had a mean barium concentration of 0.1 ppm. The authors found no significant differences when comparing age-specific mean systolic and diastolic blood pressures as well as prevalence rates for stroke, heart disease and kidney disease between sample populations of the two cities (Brenniman and Levy, 1984). The observations provide a human chronic NOAEL of 0.21 mg/kg-day based on the absence of cardiovascular effects.

OEHHA selected the Brenniman and Levy (1984) NOAEL value of 0.2 mg/kg-day for chronic exposures upon which to base the PHG calculation. The Wones *et al.* (1990) short-term study NOAEL of 0.21 mg/kg-day, which is essentially the same as that Brenniman and Levy (1984), adds weight of evidence for the non-cancer NOAEL selection.

The NOAELs and LOAELs for the observed animal effects are at far higher doses than these NOAEL levels in humans, indicating that these free-standing NOAELs do not encroach on any known hazardous level or effect observed in animal toxicity evaluations.

CALCULATION OF PHG

Carcinogenic Effects

No long-term studies evaluating any potentially carcinogenic effects of barium in humans were located in the literature, and animal studies were negative. Accordingly, we did not calculate a health-protective value based on carcinogenic effects.

Noncancer Effects

Estimation of public-health protective concentrations for non-cancer endpoints require choice of a most appropriate NOAEL or LOAEL, consideration of exposure factors, and the amount of uncertainty involved in extrapolating the chosen endpoint to the entire human population. In this case the lowest applicable value for risk assessment is based on human studies, so less uncertainty is involved than in many cases. The human studies involve fairly large populations with chronic exposures, with no clear effects at barium levels in drinking water of 7.3 ppm in one community or 2-10 ppm in the multiple-community survey (Brenniman and Levy, 1984). Since these were environmental epidemiological studies, the power of the studies to detect small effects is relatively weak, but the study should have included a normal spectrum of individuals, including potential sensitive subpopulations. In the Wones *et al.* (1990) subchronic study, there were only 11 subjects, exposed to the highest barium concentration (10 ppm) for only four weeks. Therefore there is uncertainty as to the ability of this study to reveal gradual, cumulative alterations in cardiovascular parameters, as well as the normal variations among individuals or subpopulations that might be more sensitive to the effects of barium. However, since the critical dose in these two studies is a freestanding NOAEL, the endpoint incorporates some extra health protection. OEHHA has chosen to use an uncertainty factor (UF) of 3 to account for the moderate potential of unobserved human variability and sensitivity in the cited studies.

Another critical parameter is the assumption about relative exposure sources and contributions to daily intake. Dietary exposures to barium are relatively large, and comprise the majority of the normal daily exposure to barium (Friberg *et al.*, 1986; ATSDR, 1992). In the critical human studies (Brenniman and Levy, 1984), exposure to barium in food was uncontrolled, but would be expected to correspond to the normal "background" exposures of 0.67 mg/day or so. The exposures from water would therefore be more than 90 percent of the total daily dose (7.3 mg/L x 2 L/day = 14.6 mg/day) in this case, and the calculations appropriately ignore the background (food) exposures. For estimating the safety of exposures to barium in drinking water, OEHHA has decided to assume essentially all the barium would come from the water, which corresponds to the situation in these critical studies. The relative source contribution, or RSC, is therefore assumed to be 1.0 for estimation of a health-protective level of barium in water.

For the other exposure factors, default values are utilized. The calculation of the public health-protective concentration (C, in mg/L) for barium follows a general formula for noncancer endpoints:

$$C = \frac{NOAEL \times RSC \times BW}{UF \times L/day} = \text{value in mg/L}$$

where,

NOAEL = no-observed-adverse-effect-level (0.21 mg/kg-day, based upon the absence of cardiovascular effects in humans);

RSC = relative source contribution (1.0 in this case, considering that the NOAEL is based upon normal human exposures, ignoring other sources);

BW = body weight for an adult male (70 kg);

UF = uncertainty factor (default values for the use of animal studies typically might include 10 for extrapolation from a LOAEL to a NOAEL, 10 for extrapolation from another species, 10 for human variability, and/or 10 for a subchronic to chronic extrapolation, usually limited to a maximum combined factor of 3,000). For this human study, we selected a UF of 3 based on potential additional human variability;

L/day = volume of drinking water consumed by an adult (a default of 2 L/day, in this case).

Therefore,

$$C = \frac{0.20 \text{ mg/kg-d} \times 1 \times 70 \text{ kg}}{3 \times 2 \text{ L/day}} = \mathbf{2.33\ mg/L} = \mathbf{2.0\ ppm} \text{ (rounded)}$$

The PHG for barium in water is therefore set at 2.0 mg/L (2.0 ppm) based on the absence of cardiovascular effects in human studies.

RISK CHARACTERIZATION

OEHHA has developed a PHG value of 2.0 mg/L based on the human non-cancer endpoint of absence of cardiovascular effects due to barium in drinking water. For this calculation we selected a NOAEL of 0.20 mg/kg-day based on a chronic exposure study by Brenniman and Levy (1984) with support provided from a subchronic study by Wones *et al.* (1990) with a NOAEL of 0.21 mg/kg-day.

The uncertainty factor of 3 accounts for possible additional variation in human sensitivity, although little more is expected because the calculation is based on a human study in adult males, the population presumed to be most at risk from hypertensive effects of barium. Although small, the study population does include black males, who are known to have an increased risk of cardiovascular disease compared to whites in the American population. As U.S. EPA (1998) cautions, the Brenniman and Levy (1984) study may not account for all of the uncertainty regarding toxicological and toxicokinetic differences between children and adults. The chronic study by Brenniman and Levy (1984) with the same NOAEL for residents of West

Dundee, IL, is judged to provide important supporting evidence, but these results are weakened by the increased mortality rates in the companion study of other communities.

An additional area of uncertainty is the selection of human studies over the animal research. The relevant animal studies reported much higher effect levels except for the chronic rat study of Perry *et al.* (1983). In this study, the test rats were maintained on feed that was below recommended dietary guidelines in calcium and potassium, which was likely to predispose animals to the hypertensive effects of barium. The LOAEL for this study was 10 ppm of barium in water and the NOAEL was 1 ppm. The calculated daily dose of barium at the NOAEL level was 0.17 mg/kg-day, which includes the contribution of barium from food. This has been considered to represent an artifactually high toxicity (U.S. EPA, 1998). OEHHA also judges that this is an inappropriate study on which to base a health-protective level. However, it may be noted that even under these most stringent conditions, the effects were noted only on prolonged exposure to barium doses several times the health-protective level calculated above.

The animal NOAEL (45 mg/kg-day) judged to be most relevant and appropriate for toxicological comparisons (NTP, 1994) is based on decreased relative kidney weights of female rats in a chronic feeding study. A protective level based upon this value, with an uncertainty factor equal to 100 (10-fold each for interspecies and intraspecies extrapolations) and an RSC at the default of 0.2, would equal 3.2 mg/L, which is also higher and therefore less protective than the PHG value.

OEHHA concludes that the estimated health-protective concentration of 2.0 mg/L, using human data, contains less uncertainty than using the chronic animal study, and is a more appropriate and defensible calculation upon which to base the PHG. However, it must be noted that the calculations from the human studies are based upon *absence* of effects. Thus, the safe dose may be higher but is unlikely to be lower.

OEHHA concurs with U.S. EPA (1990) that 3 is the appropriate safety factor for use in calculating a public health-protective drinking water level for barium from these human studies. In its defense of a 3 vs 10 uncertainty factor, the U.S. EPA (1990) cited the following rationale:

1. The Wones *et al.* (1990) experimental study was well designed and corroborated the epidemiological evaluation of Brenniman and Levy (1984).
2. The health effect of concern, hypertension, is associated with adults and not children.
3. The Brenniman and Levy (1984) study compared blood pressure of about 2,000 adults, ranging in age from 18-75; and, in many cases the subjects were exposed for decades.
4. Because of the large size of the Brenniman and Levy (1984) study, potential sensitive sub-populations were likely represented in the study.

These judgments are restated in the current U.S. EPA Integrated Risk Information System (IRIS) file for barium (U.S. EPA, 2002; RfD last updated 1/21/1999).

OTHER REGULATORY STANDARDS

The current U.S. EPA maximum contaminant level (MCL) and MCL goal (MCLG) for barium is 2 mg/L (U.S. EPA, 2001). The U.S. EPA MCL is essentially identical to the U.S. EPA Drinking Water Equivalent Level (DWEL), which was 2.45 mg/L (rounded to 2 mg/L). Like the OEHHA value, the U.S. EPA value does not include a relative source contribution.

The following table includes selected federal regulations and guidelines for comparison to the PHG.

Table 2. Selected Guidelines and Regulations for Barium

Agency	Standard or Criterion	Level	Comment
ACGIH	TLV-TWA	0.5 mg/m^3	recommended air concentration limit over 8-hour work shift
NIOSH	REL (recommended exposure level)	0.5 mg/m^3	as barium in air, average over a 10-hour work shift. (recommended)
OSHA	PEL (permissible exposure limit)	0.5 mg/m^3	soluble barium compounds in air (as barium)
U.S. EPA	MCL (maximum contaminant level)	2 mg/L (ppm)	national drinking water standard
U.S. EPA	MCLG (maximum contaminant level goal)	2 mg/L (ppm)	goal, includes safety margin
U.S. EPA	DWEL (drinking water equivalent level	2 mg/L (ppm)	70 kg adult
U.S. EPA	Ten-day Health Advisory	2 mg/L (ppm)	10 kg child

Table adapted from ATSDR (1991), NIOSH (1994), U.S. EPA (1990), and U.S. EPA (2001).

State standards for barium in drinking water include MCLs of 1 mg/L in California, 1.5 mg/L in Arizona and Maine, and 2 mg/L in Minnesota (HSDB, 2002).

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