PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

BROMATE

December 2009

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Public Health Goal for
Bromate
in Drinking Water

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PREFACE

Drinking Water Public Health Goal
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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 (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 that may cause chronic disease shall be based solely on health effects 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 potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
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. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.

8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
9. 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.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once 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 Public Health (DPH) 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 or technical feasibility, drinking water standards adopted by DPH are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DPH 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 state and federal law, MCLs established by DPH must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DPH, 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 BROMATE IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 0.1 parts per billion (ppb) for bromate in drinking water, based on its carcinogenicity. Bromate can be found in drinking water as a byproduct of the ozonation disinfection process. Although bromate has a long history of use as a food additive [at levels up to 75 parts per million (ppm) in flour], it is largely converted to bromide in the baking process. Bromate is a strong oxidant and is chemically reactive. It is mutagenic and has caused cancer in multiple organs in rodent bioassays. The PHG is based on a study by DeAngelo *et al*. (1998) in which the authors related cancer in male F344 rats to lifetime exposure to bromate in their drinking water at daily doses from 1.1 to 28.7 mg/kg-day. A cancer potency estimate of 0.21 $(mg/kg\text{-}day)^{-1}$ is used, derived by a time-to-tumor multi-site approach based on the tumor data for mesothelioma, kidney tumors and thyroid tumors in the male rat, which was the sex and species observed to be most susceptible to the carcinogenic effects of bromate.

Non-cancer adverse effects were found in several studies, and OEHHA also selected the male rat data in the DeAngelo *et al.* (1998) study for determination of an acceptable daily dose (ADD). The noncancer No Observed Adverse Effect Level (NOAEL) is 1.1 mg/kg-day of bromate, based on renal pelvis urothelial hyperplasia in male rats. Using a relative source contribution (RSC) of 0.2, a total uncertainty factor (UF) of 100 for inter- and intra-species differences, and a daily water consumption rate of 0.044 L/kg-day, an ADD of 0.011 mg/kg-day and a health-protective value of 50 ppb are derived based on the noncancer endpoint.

The U.S. Environmental Protection Agency (U.S. EPA) Maximum Contaminant Level Goal (MCLG) for bromate is set at zero, based on carcinogenicity. The Maximum Contaminant Level (MCL) is set at 10 ppb, based on the practical quantification limit (U.S. EPA, 1998). The same level was designated as the California MCL in 2006 (DPH, 2008). Since May 31, 2002, bromate has been listed as a chemical known to the State of California to cause cancer. It was listed under Proposition 65 using the authoritative bodies mechanism. The listing was based on the U.S. EPA classification of bromate as a probable human carcinogen (Group B2) with sufficient evidence of carcinogenicity in experimental animals.

INTRODUCTION

Bromate (BrO_3^-) is a negatively charged polyatomic ion containing one bromine and three oxygen atoms. Typical salts of bromate are potassium bromate ($KBrO_3$) and sodium bromate ($NaBrO_3$). In 1998, the U.S. EPA published an MCL of 0.010 mg/L and an MCLG of zero mg/L for bromate in drinking water, based on a weight of evidence evaluation of both cancer (multiple sites, both sexes, rats) and noncancer effects. Bromate, as the potassium salt, is listed as a Group 2B possible human carcinogen by the International Agency for Research on Cancer (IARC). Bromate was shown to be

mutagenic via *in vitro* and *in vivo* studies. In rats, long-term exposure to bromate in drinking water yielded adverse thyroid and kidney effects and inhibited body weight gain.

Human exposure to bromate occurs in several ways. Bromate salts have been used as a food ingredient, being added to beer and cheese, and also used as a neutralizing agent for permanent wave hair styling products (Dupuis, 1997; IPCS, 2006). Bromate salts are currently permitted by the U.S. Food and Drug Administration (FDA) for use as bread dough conditioners (FDA, 2007a,b) at a maximum concentration of 75 ppm. Bromate is a quite unusual chemical in that although it is a Group 2B possible human carcinogen, its use as a food additive is still permitted. Importantly, it is permitted only in the raw flour and the baking process removes most of the chemical (WHO, 2005; IPCS, 2006).

The focus of this document is evaluation of risk from potential human exposure to bromate via drinking water. Bromate is not typically found in drinking water; however, the bromate ion can form as a disinfection byproduct from the ozonation disinfection process (WHO, 2005), when ozone reacts with relatively non-toxic amounts of bromide in the water to produce the more toxic bromate ion, or when chlorinated water is exposed to sunlight (Macalady *et al.*, 1977; Kemsley, 2008). Along with bromate, the U.S. EPA identified trihalomethanes, haloacetic acids, and chlorite as significant disinfection byproducts in drinking water (U.S. EPA, 2006).

CHEMICAL PROFILE

Chemical Identity

Bromate is a negatively charged ion containing one bromine and three oxygen atoms, with the chemical abbreviation of BrO_3^-. The acid form, bromic acid, is stable only in water. Many bromate salts are possible, but potassium bromate and sodium bromate are the most common. Table 1 describes these and some other available forms. The CAS number for bromate ion is 15541-45-4.

Table 1. Description of Bromic Acid and Common Salts

Parameter	**Property or Value**			
Chemical Name	**Bromic Acid**	**Calcium Bromate**	**Potassium Bromate**	**Sodium Bromate**
Synonyms	---	Bromic acid, calcium salt	Bromic acid, potassium salt	Bromic acid, sodium salt
Chemical formula	$HBrO_3$	$Ca(BrO_3)_2 \cdot H_2O$	$KBrO_3$	$NaBrO_3$
NIOSH RTECS	---	---	EF8725000	EF8750000
CAS Registry number	7789-31-3	10102-75-7	7758-01-2	7789-38-0

Sources: Merck, 1983; CRC, 1989; CDC, 2003, 2006.

Physical and Chemical Properties

Bromate is available as several different salts; the two most common forms are probably potassium and sodium bromate (WHO, 2005). Both salts take the form of colorless and odorless crystals, which can be a granular or powder form and have negligible vapor pressure. These bromate salts are soluble in water and dissociate in water to the metal and bromate ions (Merck, 1983; CDC, 2003; Health Canada, 1999). These salts are strong oxidizers and must be handled with care.

Figure 1. Bromate ion

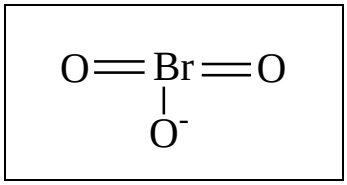

Table 2. Physical and Chemical Properties of Bromate Salts

Parameter	Property or Value		
Chemical Name	**Calcium Bromate**	**Potassium Bromate**	**Sodium Bromate**
Formula	$Ca(BrO_3)_2 \cdot H_20$	$KBrO_3$	$NaBrO_3$
Molecular weight	313.90	167.0	150.9
Color, form	Monoclinic crystals	Colorless crystals or white granules	Colorless crystals, granules, or crystalline powder
Physical state	Solid	Solid	Solid
Melting point	180ºC	350ºC	381ºC
Decomposition point	--	370ºC (decomp.)	381ºC (decomp. @ mp)
Density (g/cm^3)	3.33	3.27	3.34
Solubility in water	(very sol.)	75 g/L @25ºC	364 g/L @25ºC
Solubility in organics	--	Slightly sol. in alcohol, insol. in ether and acetone	Insol. in alcohol and ether

Sources: Merck, 1983; CRC, 1989; U.S. EPA, 2001; CDC, 2003.

Production and Uses

Bromate salts are produced intentionally for some commercial uses, and the bromate ion occurs as an unwanted byproduct of certain drinking water disinfection processes.

Both the potassium and sodium salts of bromate are currently in commerce worldwide. Potassium bromate, the more acutely toxic of the two, is used as a flour and bread dough

"improver" or maturing agent (Mack, 1988; Dupuis, 1997; WHO, 2004, 2006). Calcium bromate has also been used for this purpose. The maximum allowable level of potassium bromate in flour is 75 ppm (FDA, 2007a); however, as a result of a request from the FDA in 1991, most companies have omitted potassium bromate from their products on a voluntary basis (Dupuis, 1997). Potassium bromate was also used as a chemical component of neutralizer solutions in permanent wave hair care products (Mack, 1988; DeAngelo *et al.*, 1998; Health Canada, 1999). Potassium bromate was reportedly used in certain types of beer and cheese making, although OEHHA is not aware of any current use in the production of these commodities (DeAngelo *et al.*, 1998; WHO, 2005).

Similar to the potassium salt, sodium bromate has been used in neutralizer solutions for permanent wave and hair straightening products (WEEL, 2007). While the use of the potassium salt in these hair care preparations has significantly decreased (Mack, 1988), they remain permitted as commercial ingredients, with maximum limits as to their concentrations within the cosmetic product (FDA, 2006a).

The drinking water disinfection processes of ozonation, and to a lesser extent, chlorination, can yield the bromate ion as an unintentional byproduct of the disinfection reactions (DeAngelo *et al*., 1998; Weinberg *et al.*, 2003). Ozonation has the desirable advantage of being able to control *Cryptosporidium parvum* (Amy *et al.*, 2000). *Cryptosporidium* is a zoonotic parasitic protozoan, and its oocysts are refractory to most disinfectant chemicals (FDA, 2006b).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

OEHHA is not aware of an environmental scenario in which bromate enters the ambient air in significant quantities, although if it were present in dusts, it could become airborne. The physical properties of bromate salts (negligibly small vapor pressure and decomposition at the melting point) are such that they will not volatilize into the atmosphere (WHO, 2004, 2006).

Soil

Bromate only slightly adsorbs to soil, and its properties as a strong oxidant most likely lead to reactions with organic matter to form the bromide (Br^-) ion (WHO, 2004, 2006). Bromide similarly would only slightly adsorb to soil or sediment (Health Canada, 1999).

Water

Bromate is not commonly found in water, but it may be formed as a byproduct of ozonation disinfection of drinking water and also as a contaminant introduced from treatment of water with concentrated hypochlorite (Haag and Holgne, 1983; IPCS, 2000; Weinberg *et al.*, 2003; WHO, 2005; Fawell and Walker, 2006). Thus, ozonation treatment of drinking water represents an important potential pathway of bromate formation. In such conditions, drinking water is the primary route of exposure to

bromate. In the Netherlands, the exposure of humans to bromate in drinking water, relative to other pathways of exposure, has been reported as approaching 100 percent (Van Dijk-Looijaard and Van Genderen, 2000).

Amy and associates (2000) observed bromate formation in water under various ozonation conditions simulated and modeled to inactivate *Cryptosporidium*. The researchers reported that bromate formation was affected by such water quality conditions as bromide concentration, pH, temperature, carbonate alkalinity, ultraviolet light (UVA), disinfectant concentration and time (mg/L-min) and transferred ozone dose, among other factors. The authors note that even waters with lower concentrations of bromide can approach the U.S. EPA standard of 10 microgram/L (µg/L) for bromate (U.S. EPA, 2006) at sufficient ozone concentrations and disinfection times.

Formation of bromate and haloamines after exposure to sunlight had been reported earlier in seawater to which chlorinated wastewater had been discharged (Macalady *et al.*, 1977). Bromate was recently discovered at relatively high levels in two Los Angeles reservoirs used to store water already treated by chlorination (Kemsley, 2008). Water officials speculated that sunlight might have interacted with residual chlorine to oxidize bromide to bromate. The bromate levels in Silver Lake and Elysian reservoirs were reported as 68 and 106 ppb, respectively. High bromate levels were reportedly also found in two other reservoirs in San Diego County.

Bouland *et al*. (2005) described introduction of bromate into drinking water as a contaminant of sodium hypochlorite, which may be used in the disinfection process. Weinberg *et al.* (2003) examined the finished waters from forty treatment plants that use hypochlorite for disinfection, throughout the United States. They found bromate levels ranging from 0.02 to 3.19 µg/L in the post-treatment water (median 0.49 µg/L, with respective 25^{th} and 75^{th} percentile levels of 0.25 and 1.0 µg/L). The authors related the bromate levels to the amount of bromate contamination in the hypochlorite feedstocks before treatment use (Weinberg *et al.*, 2003).

The World Health Organization (WHO, 2005) reported that the annual mean concentration of bromate in finished drinking water from surface water sources in the United States was 2.9 µg/L with a range of <0.2-25 µg/L.

Bottled water is regulated as a food product in the United States (by FDA) rather than as an environmental issue (by U.S. EPA); however, it is useful to look at some historic high levels of bromate from bottled water sources. In the United States, as recently as 2006, the FDA recalled certain brands of bottled water having bromate concentrations of about 27 ppb, exceeding the FDA standard of 10 ppb (Mercer, 2006). This follows a widely publicized incident in 2003 in the United Kingdom in which a popular brand of bottled water was reported to have bromate levels of approximately 20 ppb (U.K. FSA, 2002).

Food

The primary food use for potassium bromate is that of a maturing agent in flour and as a dough conditioner and texture improver in bakery products such as bread, rolls, and blueberry muffins (Dupuis, 1997; IARC, 1999; WHO, 2005; Health Canada, 1999).

Potassium bromate has also been used in the malting process of barley for the brewing of beer and the production of distilled spirits (WHO, 2004, 2006; FDA, 2007b; IPCS, 2006).

The U.S. FDA standardized acceptable levels of potassium bromate in the treatment of flour and beer-making cereal as summarized in Table 3.

Table 3. U.S. FDA Acceptable Levels of Bromates in Food Ingredients

Salt Form	Allowed Level	Food Item	Ultimate Product
Potassium	< 75 ppm	Whole wheat flour	Bakery products
	< 50 ppm	White flour	Bakery products
	< 75 ppm	Malted cereal	Fermented malt beverages or distilled spirits
Calcium	< 75 ppm	Flour (unspecified)	Bakery products

Source: FDA, 2006c.

The U.S. FDA requested that bakers reduce potassium bromate use voluntarily, and furthermore, that package information must indicate any potassium bromate use (WHO, 2005).

Other Sources

Cosmetic Use

Sodium and potassium bromate are used in neutralizer solutions for home permanent wave cosmetic products (WHO, 2004, 2006). According to the U.S. FDA (FDA, 2006a), the Consumer Product Safety Commission responded to a number of cases of accidental ingestion by children of bromate neutralizer solutions by requiring in 1990 that "…permanent wave neutralizers, in liquid form, containing in a single container more than 600 mg of sodium bromate or more than 50 mg of potassium bromate be packaged in child-resistant packaging."

The Cosmetic Ingredient Review (CIR) Expert Panel (CIR, 2006) describes potassium and sodium bromate as "ingredients found safe with qualifications," with the qualifications in each case being that the concentration be less than or equal to 10.17 percent of the product (calculated as sodium bromate).

METABOLISM AND PHARMACOKINETICS

Absorption

Fujii and coworkers (Fujii *et al.*, 1984; U.S. EPA, 2001) studied the metabolism of potassium bromate in rats. The authors orally dosed four male Wistar rats each with a

single application (volume not given) of 50 mg/mL potassium bromate solution (as bromate) and detected approximately 30 percent of the dose in the urine after 24 hours.

Similarly, from a translated abstract of an oral administration study of potassium bromate in rats, Kawana and coworkers (1991) reported that potassium bromate was rapidly absorbed from the stomach as bromate and that about 95 percent of the potassium bromate disappeared from the stomach within 30 minutes. Twenty-four hours following administration, approximately 13 percent of the potassium bromate was found in the urine.

More recently, Keith and associates (2006) evaluated bromate ion reactions in synthetic and real gastric juices. For real gastric juices, the authors reported two separate bromate half-life findings on the same sample, with a half-life of 124 minutes for the first measurement and a half-life of 164 minutes determined a few days later. The authors suspected that the difference in half-lives was due to the loss of volatile H_2S in the sample between the measurement days.

Utilizing oxygen-18 (^{18}O) labeled bromate, Delker and coworkers (2006) measured the oral absorption of bromate in six- to eight-week old male F344 rats. Four to six animals/group received single doses of 2.5 μg/kg to 25 mg/kg ^{18}O-labeled potassium bromate (70 percent to 80 percent purity) via stomach tube. The rats were sacrificed at 1, 5, or 24 hours after dosing. Time-dependent and non-linear dose-dependent increases in ^{18}O levels were recorded in kidney, thyroid, liver, and testis; with the highest levels detected in kidney and liver. The detection of ^{18}O in multiple tissues provided evidence for uptake of potassium bromate from the digestive system to the systemic circulation.

Absorption of bromate via the skin is apparently poor. The CIR Expert Panel (CIR, 1994) cited an unpublished study in which excised guinea pig skin (1.77 cm^2) was exposed for 15 or 30 minutes to 0.2 mL hair neutralizing solution containing 16.5 mg bromate. Then the skin was exposed to buffer solution for 30, 60, 120, or 240 minutes, and the bromine uptake was determined via X-ray fluorescence. The researchers calculated that a maximum of about 0.1 percent of the bromate was absorbed in 30 minutes, and released after four hours into the buffer solution (CTFA, 1991).

The CIR Expert Panel (CIR, 1994) also reported two unpublished *in vivo* dermal bromate studies performed on guinea pigs. In the first study (BCL, 1992), bromate *in vivo* transdermal absorption from a hair neutralizer compound (10.17 percent sodium bromate, equivalent to 8.59 percent bromate**)** was evaluated by dermal dosing of 0.5 mL product over a 5 cm^2 area of 24 albino guinea pigs, and allowed to remain for 15 minutes. Twenty-four control animals were similarly exposed to physiological saline. The investigators reported no bromate in the blood of either active or control animals at 1, 2, 3, or 4 hours post-exposure.

While the above study by Bromine Compounds, Limited (BCL) evaluated guinea pigs for transdermally absorbed *bromate*, the companion study looked for *bromide* (BCL, 1992). The dosing protocols were identical; however, the researchers used X-ray fluorescence to measure bromide in the animal blood. The CIR report (1994) stated, “Elevated serum concentrations of Bromide were observed in some of the treated animals in one of the assays of one hair neutralizer, but not in the other. The investigators concluded that

Bromate does not penetrate through the guinea pig skin above the minimal limit of detection (76 ppb), and that the Bromide that was detected in serum is the nonoxidative form of Bromine."

Distribution

Fujii and coworkers (1984) studied the metabolism of potassium bromate in male Wistar rats. The researchers orally administered a 50 mg/mL potassium bromate solution (calculated as bromate) via stomach tube to groups of four rats for each dose (0, 0.625, 1.25, 5, 10, 20, 40, 60, 80, and 100 mg/kg, as bromate). Twenty-four hours post-exposure, several tissues were examined for both bromate and increases over control values of bromide. In the following tissues, bromate was not detected, however, bromide was significantly increased over control levels: plasma, red blood cell (RBC), spleen, kidney, liver, pancreas, stomach, and small intestine (Fujii *et al.*, 1984). Bromide is not readily taken up in tissues, and has been used as a marker for extracellular space (Pavelka *et al.*, 2000; Cousins *et al.*, 2002; Zdolsek *et al*., 2005).

Delker and associates (2006) examined the distribution of potassium bromate upon oral exposure to male F344 rats. The researchers orally administered a single dose each of 2.5 μg/kg to 25 mg/kg ^{18}O-labeled potassium bromate via stomach tube to four to six rats/group. After 1, 5, and 24 hours of exposure, time-dependent and non-linear dose-dependent increases in ^{18}O level were detected in kidney, thyroid, testis, and liver. The authors found the highest levels of ^{18}O in kidney and liver (more than 20 μg ^{18}O/g dry tissue weight at the highest dose), whereas ^{18}O deposition in the thyroid (less than 10 μg ^{18}O/g dry tissue weight at the highest dose) was approximately three-fold lower than that in the kidney. The differential deposition of ^{18}O in kidney and thyroid signaled differences in mode of action for bromate-induced carcinogenesis in these two organs. The high level of ^{18}O deposition in the liver could be indicative of first-pass metabolism of bromate prior to entering the systemic circulation.

Metabolism

Fujii and coworkers (1984) found that much of the orally administered bromate is rapidly absorbed and degraded within a short period; however, the authors were unable to conclude whether the increased bromide originated from metabolic degradation in specific organs, or from other origins (Fujii *et al.*, 1984). It is noteworthy that the contention that bromate is rapidly degraded is challenged by Kutom *et al*. (1990), inferring from data from several sources that "Bromates are very stable in the body and only small quantities are reduced to the less toxic bromide ion."

Excretion

As mentioned above, approximately 30 percent of the bromate was found unchanged in the urine (Fujii *et al.*, 1984; U.S. EPA, 2001). This differs from the observation of Kawana *et al*. (1991) of about 13 percent bromate in urine; however, many experimental specifics about the Kawana *et al*. (1991) study are not known, making comparison

difficult. Other animal studies suggest that bromide formed from bromate is also slowly excreted by the kidney (Trepanier and Babish, 1995; Pavelka *et al*., 2000).

Physiological/Nutritional Role

There is no known physiological or nutritional benefit to sodium or potassium bromate, nor for bromide.

TOXICOLOGY

Toxicological Effects in Animals and Plants

Acute Toxicity

Potassium bromate is more highly toxic than sodium bromate (Health Canada, 1999); and it follows that potassium bromate is more highly studied.

Kurokawa *et al*. (1990) determined the oral LD_{50} values in the F334 rat, the $B6C3F_1$ mouse, and the Syrian golden hamster. The authors concluded that potassium bromate should be classified as a "very toxic chemical" (see Table 4). Kurokawa *et al*. (1990) also cited a personal communication with a colleague obliquely reporting that for Wistar rats, the potassium bromate LD_{50} is significantly lower at "approximately 160–180 mg/kg body weight" for both sexes. Kawana *et al*. (1991) added validity to the above value by estimating (apparently independently) the oral LD_{50} for male and female Wistar rats to be 157 mg/kg potassium bromate. These authors administered 85, 159, 325, or 602 mg/kg potassium bromate orally to groups of male and female Wistar rats. Seventy-two hours post-dosing, the authors observed no deaths in the low-dose group, and about 20 percent survival in the 159 mg/kg group (sex not mentioned). Acute effects reported include a trace amount of methemoglobin in the blood of the rats and significant hemochromatosis in the kidney, spleen and liver; dose and sex not mentioned (Kawana *et al.*, 1991).

Table 4. Oral LD_{50} Values for Potassium Bromate

Species	Strain	LD_{50}, mg/kg	
		Male	Female
Rat	F344[a]	400	495
	Wistar[b]	157	
Mouse	$B6C3F_1$[a]	280	335
Hamster	Syrian golden[a]	388	460

Sources: Kurokawa *et al.* (1990)[a] and Kawana *et al.* (1991)[b].

Bromate toxicity includes kidney damage, hemolysis, and methemoglobinemia (Watanabe *et al.*, 2002). To evaluate the contribution of nitric oxide to bromate-induced methemoglobin elevation in five week-old male ddY mice, Watanabe *et al*. (2002) orally administered 1.2 mmol/kg of potassium bromate in dilute salt water 15 minutes following intraperitoneal (i.p.) administration of ebselen (an investigational anti-inflammatory antioxidant used as a mimic of glutathione peroxidase). Mice were terminated six hours following dosing; and blood and kidneys were removed for study. The authors observed that elevation of methemoglobin concentration was simultaneous with that of nitric oxide and also attenuation of glutathione peroxidase activity. Renal oxidative stress and renal damage were observed in potassium bromate-treated mice. The authors concluded that the evidence was suggestive that potassium bromate-induced methemoglobinemia resulted from the reduction of glutathione peroxidase activity due to increases in superoxide, nitric oxide, and peroxynitrite.

Sodium bromate is less well-studied. However, Sax (1979) reported a mouse i.p. LD_{50} of 140 mg/kg and a rabbit oral LD_{LO} of 250 mg/kg, and Merck (2004) reported a rat oral LD_{50} of 400 mg/kg.

Subchronic Toxicity

Kurokawa *et al*. (1990) cited an unpublished study in which male and female Wistar rats, at 10 rodents per group, were given potassium bromate in drinking water at concentrations of 150, 300, 600, 1,250, 5,000, or 10,000 ppm for 13 weeks. All animals at the three highest levels died within seven weeks; all animals at or below the 600 ppm level survived the 13-week treatment. At 600 ppm, the workers observed elevated glutamate oxaloacetate transaminase, glutamate pyruvate transaminase (GPT), lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen (BUN), sodium, and cholinesterase in the serum of rats of both sexes; also at this level serum potassium decreased significantly. Various-sized droplets, which stained strongly with eosin, were observed in the cytoplasm of the proximal tubules in treated males, along with extensive regenerative changes in the renal tubules, at unspecified dose levels.

Guo and associates (2001) assessed the immunotoxic potential of sodium bromate in a 28-day drinking water study in female $B6C3F_1$ mice. Drinking water concentrations were 20, 80, 400, 600 and 800 ppm of sodium bromate. The authors found no "overt toxicity" in any of the dose groups; and, they observed no significant differences between the treatment exposure groups and the tap water control group in body weight, weight gain, and such organ weights as thymus, liver, and lungs. Similarly, they observed no effects on erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, platelets or white blood cells, and they found no gross lesions. The authors did, however, observe a significant increase in relative spleen weights. This study is also described later in the Immunotoxicology section of this document.

Genetic Toxicity

Kurokawa and coworkers (1984) conducted studies on the promoting and complete carcinogenic activities of some oxidizing chemicals on skin carcinogenesis in six-week-old female Sencar mice. All the tested chemicals were dissolved in 0.2 mL acetone and

applied topically to the pre-shaved dorsal skin of the mice. In the first study, on tumor-promoting activity, groups of 15 to 20 mice each received a single application of 20 nmole dimethylbenzanthracene (DMBA). Beginning one week later, the mice were topically treated twice a week for 51 weeks with 0.2 mL of 40 mg/mL potassium bromate (19 mice), 0.2 mL of 10 μg/mL 12-O-tetradecanoly-phorbol-13-acetate (TPA, 20 mice as positive controls), or 0.2 mL acetone (15 mice as solvent controls). In the second study, on complete carcinogenic activity, groups of 15 to 20 mice topically received 0.2 mL of 40 mg/mL potassium bromate (20 mice), or 0.2 mL acetone (15 mice) twice a week for 51 weeks. The authors reported that all mice treated with TPA after initiation with DMBA developed skin tumors at 13, 26, 38, and 52 weeks, squamous cell carcinomas within 39 weeks, and epidermal hyperplasia (time not mentioned). In the presence or absence of DMBA initiation, mice treated with acetone or potassium bromate did not develop any skin tumors or epidermal hyperplasia. These results demonstrated the inertness of potassium bromate as a promoter or as a complete carcinogen for skin carcinogenesis in the Sencar mice.

In a two-stage renal tumorigenesis study, Kurokawa and associates (1985) further investigated the promoting activity of potassium bromate on renal tumorigenesis in six-week old male F344 rats. All chemicals were administered via drinking water. During the initiating phase, nine groups of 15 rats were administered 500 ppm N-ethyl-N-hydroxyethylnitrosamine (EHEN, a tumor initiator) in drinking water three times a week for two weeks, while three other groups of 15 rats were dosed with distilled water for two weeks. The two-week initiating phase was followed by a 24-week promoting phase in which groups exposed to the initiator in the first phase were treated with distilled water, potassium bromate (15, 30, 60, 125, 250, or 500 ppm), or potassium bromide (350 or 1,750 ppm). At the same time, groups exposed to distilled water in the initiation phase received distilled water, 500 ppm potassium bromate, or 1,750 ppm potassium bromide. The estimated daily intakes were 2.6 and 5.2 mg/kg-day potassium bromate, respectively, with the drinking water concentrations of 30 and 60 ppm potassium bromate. In the histopathological examination, the researchers classified both adenomas and adenocarcinomas of the kidney as renal cell tumors. They found no apparent morphological differences between renal cell tumors induced by initiator alone and those induced by EHEN followed by potassium bromate. Dysplastic foci (DF) were only observed in groups exposed to EHEN in the initiation phase. There was no statistically significant difference in the incidence of DF between the EHEN/bromate groups (dose dependently increased from 79 to 100 percent for the 15 ppm to 500 ppm potassium bromate groups) and the EHEN/distilled water group (80 percent), or between the EHEN/bromide groups (53 percent) and the EHEN/distilled water group. Similarly, there was no statistically significant difference in the incidence of renal cell tumors between the EHEN/bromate groups (dose dependently increased from 27 percent to 53 percent for the 15 ppm to 500 ppm potassium bromate groups) and the EHEN/distilled water group (20 percent), or between the EHEN/bromide groups (20 percent for low-dose group and 33 percent for high-dose group) and the EHEN/distilled water group. However, the mean numbers of DF per cm^2 in groups treated with EHEN followed by 30 ppm or higher concentrations of potassium bromate (dose dependently increased from 0.49 ±0.30 to 1.25 ± 0.76 DF/cm^2) were significantly different from that in the EHEN/distilled water

group (0.29 ± 0.16 DF/cm^2, $p<0.05$). Also, the mean number of renal cell tumors per cm^2 in the EHEN/distilled water group (0.04 ± 0.07 renal cell tumors/cm^2) was significantly different from that of the EHEN/highest-dose potassium bromate group (0.16 ± 0.16 renal cell tumors/cm^2, $p<0.05$). The authors concluded that potassium bromate, at concentration higher than 30 ppm, seemed to act as a promoter in the renal tumorigenesis initiated by EHEN. Potassium bromide, however, had no promoting activity under the conditions studied. Potassium bromate was hypothesized to promote tumorigenesis by inducing the expression of neoplastic characteristics in the initiated cell population, without affecting the growth rate and morphology of renal cell tumors.

According to a review conducted by the CIR Expert Panel (CIR, 1994), genotoxicity of potassium bromate is demonstrated in several *in vitro* bioassays. Potassium bromate is described as testing positive for mutagenicity in *Salmonella typhimurium* strains TA102 and TA104 in the presence of metabolic activation. Potassium bromate tested weakly positive in strain TA100 and negative in strains TA92, TA1535, TA1537, TA94, and TA98 with or without metabolic activation. Additionally, this chemical caused dose-dependent chromosomal aberrations in Chinese hamster fibroblast cells in the absence of metabolic activation.

Morgan and coworkers (2002) applied *in vitro* cDNA microarray technology to detect chemically-induced alterations of gene expression in HepG2 cells for a diverse group of chemicals examined at "equitoxic" concentrations. By noting gene expression differences, the authors deduced the levels of oxidative stress, for example, as a function of the GSH:GSSG ratio. For potassium bromate, the authors concluded, "observed changes include evidence of activation of p53 and cell cycle arrest, including down regulation of PCNA and [the gene] TOPO2A." As evidence of oxidative stress, they mentioned upregulation of genes HMOX1 and HSP 70 and down-regulation of gene CYO1A1.

Umemura and associates (2004) administered potassium bromate in drinking water for four weeks to groups of male and female F334 rats, with five rodents of each sex per group. Concentrations of bromate in drinking water were 0, 15, 30, 60, 125, 250, or 500 ppm. The authors observed that the potassium bromate in drinking water did not elevate thiobarbituric acid-reactive substances at any dose. However, at 250 ppm and above, 8-oxodeoxyguanosine (8-oxodG) levels in the kidney were significantly elevated. Additionally, bromodeoxyuridine-labeling index for proximal convoluted tubules was significantly increased at and above 30 ppm for males and at and above 250 ppm for females. Moreover, α2u-globulin accumulation in the male rat kidney was significantly increased at treatment levels of 250 ppm and above. The authors concluded that their subchronic results suggest that potassium bromate-induced DNA oxidation is independent of lipid peroxidation and that drinking water exposures exceeding 250 ppm can exert a carcinogenic effect in rats via oxidative stress (Umemura *et al*., 2004).

In a more recent review, Umemura and Kurokawa (2006) concluded that mechanisms for cancer induced in male rats were more complex than in female rats. Accumulation of 8-oxodG in the kidney provided supporting evidence for the contribution of oxidative stress and/or cytotoxic responses to the potassium bromate-induced carcinogenesis in female rats and potentially in humans.

Ballmaier and Epe (2006), as well as Kawanishi and Murata (2006), conducted a series of *in vitro* bioassays on the mechanisms for genotoxicity of potassium bromate in cultured human HL-60 and HL-100 cells and L1210 mouse leukemia cells. These studies showed potassium bromate inducing DNA breakage via generation of bromine radicals, or oxide radicals of bromine. These bromine radicals, which were formed in the presence of thiol compounds (glutathione or cysteine), oxidized DNA and induced the formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine (also known as 8-oxodeoxyguanosine, 8-oxodG). Accumulation of 8-oxodG was associated with the increase in mutations in both liver and kidney *in vivo* in mice and rats, probably via a GC to TA transversion and deletion mode of action (Ballmaier and Epe, 2006; Moore and Chen, 2006; Umemura *et al.*, 2006; Delker *et al.*, 2006).

Delker and coworkers (2006) conducted two mechanistic studies on carcinogenicity of potassium bromate in male F344 rats (number of animals not mentioned). Results on tumor development were discussed in detail in a separate publication (DeAngelo *et al.*, 1998). In the first gene expression study, six- to eight-week old male F344 rats were administered 0, 20, or 400 mg/L potassium bromate in drinking water for 52 weeks. Applying real-time polymerase chain reaction (PCR) analysis, the researchers found that multiple genes associated with glutathione metabolism were upregulated in kidney of the high-dose group, but not in kidney of the low-dose animals. The 8-oxodeoxyguanosine glycosylate (*Ogg*1), a DNA repair enzyme inducible in response to oxidative stress, was also upregulated in kidney of the high-dose animals, but not in the low-dose rats, nor in thyroid of the rats at both doses. The authors proposed that a carcinogenic dose of bromate might exhaust the extracellular antioxidant pools, which could result in the delivery of bromate to renal cells. Subsequently, a sulfhydryl-mediated DNA oxidation could be a mode of action for the bromate-induced renal carcinogenesis in male F344 rats.

In the second study (Delker *et al.*, 2006), a single gavage administration of ^{18}O-labeled potassium bromate (2.5 μg/kg to 25 mg/kg) to four to six male F344 rats per dose group resulted in a differential deposition of ^{18}O in kidney and thyroid. The authors observed a time-dependent and non-linear dose-dependent deposition of ^{18}O in kidney. Combining the results from the gene expression study and the deposition of ^{18}O in kidney, the authors surmised that oxidative DNA damage might be a mode of action for bromate-induced renal carcinogenesis in male F344 rats. A much lower level of ^{18}O was detected in thyroid, which paralleled the absence of upregulation in glutathione-metabolizing gene and *Ogg*1 gene in thyroid of the potassium bromate-treated rats, and a reduced bromate-mediated oxidation. The report concluded that bromate probably induced thyroid tumors in male F344 rats via a mode of action other than oxidative DNA damage.

According to the National Toxicology Program (NTP) report (NTP, 2007), potassium bromate-induced chromosomal aberrations, micronuclei, DNA strand breaks, oxidative DNA base damage, and hypoxanthine-guanine phosphoribosyltransferase gene mutations in cultured Chinese hamster fibroblast cells. Acute oral administration or i.p. injection of potassium bromate to rodents resulted in dose-dependent increases in frequencies of chromosomally aberrant metaphases in bone marrow cells of rats and induction of micronuclei in polychromatic erythrocytes of rats and mice.

Despite the extensive genotoxicity data on potassium bromate available in the literature, little information can be found about sodium bromate. Genotoxicity data on sodium bromate was limited to an abstract, which revealed the inactivity of sodium bromate in a *S. typhimurium* mutagenicity assay and a sex-linked recessive lethal assay in male *Drosophila melanogaster* (NTP, 2007).

In four separate NTP studies (NTP, 2007), researchers exposed groups of 15 male and 15 female Tg.AC hemizygous mice and also p53 haploinsufficient mice to sodium bromate concentrations of 0, 80, 400, or 800 ppm in drinking water for 27 weeks. In another two separate studies, they dermally exposed Tg.AC hemizygous mice (15 males and 15 females per group) to 0, 64, 128, or 256 mg/kg-day of sodium bromate in ethanol/water, five days per week for 26 weeks. The authors reported a clear dose response in all six micronucleus tests in both sexes of Tg.AC hemizygous mice and p53 haploinsufficient mice exposed via either pathway. Bromate exposures significantly increased frequencies of micronucleated erythrocytes in all treatment groups ($p \leq 0.008$). Furthermore, for Tg.AC hemizygous mice only, they reported increases in percentage of polychromatic erythrocytes among total erythrocytes in both males and females exposed via drinking water and also in dermally-dosed males. No significant changes in percentage of polychromatic erythrocytes were found in male or female p53 haploinsufficient mice. This NTP study on sodium bromate is discussed in greater detail in the Carcinogenicity section of this document.

Developmental and Reproductive Toxicity

In three 35-day NTP screening-level studies, Wolf and Kaiser (1996) evaluated the reproductive and developmental toxicity of sodium bromate in Sprague-Dawley rats. Animals were orally administered 0, 25, 80, or 250 mg/L sodium bromate in drinking water with respective estimated average daily intakes of 0, 2.2, 7.7, or 22 mg/kg-day bromate. In the first study, to examine effects on conception and early gestation, a group of 10 females was treated with sodium bromate from day 1 to 34. In another study, to investigate effects during late gestation and birth, a group of 13 females was exposed to sodium bromate from gestation day 6 to postnatal day 1 and allowed to litter. Pups were observed through postnatal day 5. In the last study, to determine adverse effects on males, 10 males were cohabited with females in the second study from day 1 to 5 (untreated) and were given sodium bromate from day 6 to 34/35. The report did not reveal any measurements on developmental endpoints in the pups or if any effects were observed. The authors observed no treatment-related effects on adult survival, organ weights, body weights, feed consumption, clinical observations, reproductive performance or histopathological changes in kidney, liver, spleen, testis, or epididymis in any group. Although there were no effects on male fertility, a statistically significant and concentration-related decrease in epididymal sperm density (approximately 18 percent) was detected in the highest-dose males. The authors concluded that sodium bromate did not have any general toxicity or adverse effects on female reproductive functions. The rat NOAEL is 7.7 mg/kg-day bromate, based on decrease in epididymal sperm density.

In an NTP (2001) follow-up study, reproductive toxicity of sodium bromate was assessed using a multigeneration, continuous-breeding paradigm. Groups of male and female

Sprague-Dawley rats received 0, 30, 100, or 300 mg/L sodium bromate in drinking water (number per group and average daily dose not mentioned). General toxicity was observed in both sexes at drinking water concentrations of 100 and 300 mg/L. Adverse effects included chronic progressive nephropathy and hyaline droplets in males, as well as renal cell proliferative changes in females. There were, however, no treatment-related changes in reproductive litter data and a non-significant decrease (eight percent) in sperm density in the F_1 generation, despite a 16 percent decrease in sperm density recorded in the F_0 generation. The authors decided that sodium bromate was a reproductive toxicant.

In a report on the workshop for Mechanisms of Cancer Induction organized by the American Water Works Association Research Foundation, an international non-profit professional organization, Bull and Cotruvo (2006) indicated the relative lack of information on reproductive and developmental toxicity of bromate. In the conclusion, the authors provided frameworks for several studies to further elucidate the auditory toxicity of bromate.

Crofton (2006) reviewed evidence on the developmental and reproductive toxicity of bromate and noted a need to examine bromate as a potential agent for developmental neurotoxicity, specifically ototoxicity to the developing organism due to transplacental and lactation routes of exposure. Crofton observed that current evidence for bromate neurotoxicity is confined to acute, high-dose animal studies and human overdose case reports. He concluded with a recommendation for long-term developmental neurotoxicological studies to reduce the uncertainty in this area.

Immunotoxicity

As described earlier, Guo and associates (2001) performed a 28-day sodium bromate drinking water study in female $B6C3F_1$ mice to assess the immunotoxic potential of sodium bromate. Drinking water sodium bromate concentrations were 0, 20, 80, 400, 600, or 800 ppm. Along with the earlier described observations that the exposures were not toxic to most organ systems (spleen weight was an exception) and blood values (a dose-related increase in reticulocytes was the exceptional observation), the authors observed no changes in the number of total T cells, $CD4^+CD8^-$ T cells, natural killer cells, or macrophages. The authors noticed a "slight" increase in the number of absolute B cells at the 600 ppm level. These, along with other observations of immunological parameters, led the authors to conclude that 80 to 800 ppm sodium bromate in drinking water produced "minimal toxicological and immunotoxic effects in female $B6C3F_1$ mice."

Neurotoxicity

It has been known for some time that bromate produces ototoxicity in animals and humans (Kamata *et al.*, 1983; Kutom *et al.*, 1990; Campbell, 2006; Crofton, 2006). Chuu *et al*. (2000) evaluated the mechanism of this effect by administering potassium bromate subcutaneously (50 mg/kg) alone or in combination with thioglycolate (15 mg/kg) dissolved in saline, or saline control to groups of six guinea pigs (sex not stated) once daily for two weeks. The authors evaluated the exposures for effects on auditory brainstem response, enzyme modifications, and brainstem changes. The authors

observed that bromate, especially in combination with thioglycolate, prolonged auditory wave I latency, suggesting a delayed auditory nerve conduction velocity. This observation contrasts with the lack of observed changes in the IV-V wave interval, suggesting to the authors that the potassium bromate exposure did not lead to conduction dysfunction in the brainstem, indicating that the exposure-related hearing loss was peripheral. The authors reported that their auditory observations compared favorably with a case study in which a 44-year old human intentionally ingested potassium bromate in a suicide attempt. He survived, but his peripheral auditory perception did not. The authors thus concluded that potassium bromate ototoxicity is mediated by peripheral auditory nerve dysfunction, as opposed to central brainstem intoxication (Chuu *et al.*, 2000).

Chronic Toxicity

Nakano and co-workers (1989) exposed respective groups of 12, 5, and 5 five-week old male SLC Wistar rats to 400 ppm potassium bromate in drinking water (roughly 30 mg/kg-day; U.S. EPA, 2001), 400 ppm potassium bromide in drinking water, and control for 15 months. The authors observed significantly decreased growth after one month of potassium bromate exposure; and karyopicnotic foci of the tubules of the renal medulla inner stripe occurring after 7-11 weeks of potassium bromate treatment. The authors observed increased BUN simultaneously with structural abnormalities of the renal cortical tubules after 15 months. They also observed atypical degeneration and regeneration and cystic changes in the renal cortex. Two of the nine potassium bromate-treated rats evidenced renal adenocarcinoma.

Ginocchio *et al*. (1979) evaluated mice fed potassium bromate-treated bread for long-term toxicity and carcinogenicity. Five groups of Theiller's Original strain mice, at 60 rodents/sex/group, were fed bread-based diets made up with flour containing 0 ppm bromate; 50 ppm bromate; 75 ppm bromate; 50 ppm bromate, 30 ppm ascorbic acid, and 50 ppm benzoyl peroxide; or 50 ppm bromate, 30 ppm ascorbic acid, 50 ppm benzoyl peroxide, and 15 ppm chlorine dioxide. Daily bromine intakes derived from potassium bromate were estimated as 0, 1.76, 2.64, 1.70, and 1.63 mg/kg-day in males and 0, 2.03, 2.99, 1.99, and 2.08 mg/kg-day in females. All the bread-based diets contained about 15 percent protein, six percent total fat, and 63 percent available carbohydrate, fiber, vitamins, and minerals (Fisher *et al*., 1979).

The concentrations of bromate in the diets referred to amounts added to flour, on a weight basis. Some bromate would be converted to bromide in baking, and perhaps the other additive levels could be altered as well. The diets administered were not assayed for bromate content.

Mice were maintained for 80 weeks on the diets. At 18 months, the authors observed anemia in all female mouse groups; and in all (including control) male mouse groups except the group treated with 50 ppm bromate and three of the four flour additives. They observed a dose-related significant reduction in the number of RBCs in males at three months (15 percent reduction in the high-dose group and 17 percent reduction in the 50 ppm bromate and two flour additives group), and a dose-related increase in neutrophil granulocytes in all male groups at 12 months and in bromate-treated male groups at 18

months. The authors additionally reported significant dose-related differences in weight of pituitary, brain, kidney, and thyroid organs, relative to body weight, in bromate-treated males at the end of the study. There were no pathological changes associated with differences in organ weight and no significant differences in mortality and mean body weight of the groups (Ginocchio *et al*., 1979).

Fisher *et al*. (1979) performed a long-term potassium bromate toxicity and carcinogenicity study in rats, similar to the Ginocchio *et al*. (1979) study in mice described above. Male and female Wistar-derived Porton rats were assigned to the same dose groups of bread-based diets as described above, at 60 rodents per sex per group. Rats were maintained for 104 weeks on the diets. The control group females had a higher death rate than any of the treatment groups. There were fewer deaths within the higher-dose group than in any of the other groups. The study reported no significant differences in mean body weight of all groups, except the low-dose male group at 12, 25, 36, 60, and 72 weeks, and the low-dose female group at 104 weeks. The authors reported no "definite" evidence of chronic toxicity which they could attribute to potassium bromate, and found no evidence of retention or accumulation of covalent bromine within the adipose tissues of the rats (Fisher, 1979).

Kurokawa *et al*. (1986b) studied long-term exposures to potassium bromate in rats exposed for 110 weeks via drinking water. Groups of male and female F334 rats (52 to 53 per group) were given 0, 250, or 500 ppm potassium bromate in drinking water. Daily intakes of potassium bromate were estimated as 0, 12.5, and 27.7 mg/kg-day in males and 0, 12.5, and 25.5 mg/kg-day in females. The authors observed significantly decreased values of GPT, the albumin/globulin ratio, serum potassium, and cholinesterase in female rodents at the high-dose level. The authors found no differences among the dose groups in RBC counts (Kurokawa *et al.*, 1990). At week 60, the high dosage level for males was reduced to 400 ppm because this dose inhibited growth of the rodents. Weight difference between the high-dose group and the controls at 60 weeks sustained until the end of the study, even after the reduction of bromate dosage in the high-dose group. The authors reported no apparent inhibition of weight gain in all other groups, up to 110 weeks. The rat NOAEL is 12.5 mg/kg-day potassium bromate on growth inhibition (Kurokawa *et al.*, 1986b). We provide further details on this study in the Carcinogenicity section below.

DeAngelo *et al.* (1998) evaluated the carcinogenic potential of potassium bromate administered via drinking water to male F344 rats and $B6C3F_1$ mice. The authors administered potassium bromate in drinking water to the groups of 50 rats (the more sensitive of the two rodent species tested) at doses of 0, 0.02, 0.1, 0.2, or 0.4 g/L (0, 1.5, 7.9, 16.9, or 37.5 mg/kg-day potassium bromate) for up to 100 weeks. The researchers observed treatment-related increases in hyperplasia of the transitional cells of the renal papilla and pelvis (which they termed urothelial hyperplasia), and described as a marked increase in the number of urothelial cell layers. The authors reported this effect at and above 7.9 mg/kg-day, with the NOAEL being 1.5 mg/kg-day. OEHHA selects this rat NOAEL for renal pelvis urothelial hyperplasia as the critical value for determining the non-cancer health-protective concentration.

Groups of 50 mice received potassium bromate in drinking water at doses of 0, 0.08, 0.4, or 0.8 g/L with respective estimated daily intake as 0, 9.1, 42.4, 77.8 mg/kg-day

potassium bromate (DeAngelo *et al.*, 1998). No significant alterations were observed in final body weight, absolute organ weights, and serum chemistry in all treatment groups. Histopathological examination also suggested no treatment-related increases in non-neoplastic lesions in any tissues studied. These rodent studies are described in greater detail later in this document with regard to carcinogenicity.

NTP (2007) studied the toxicity of sodium bromate in two species of genetically modified mice. The studies included 26- and 39-week dermal studies in Tg.AC hemizygous mice, 27- and 43-week drinking water studies in Tg.AC hemizygous mice, and 27- and 43-week drinking water studies in p53 haploinsufficient mice.

NTP Dermal Study in Tg.AC Hemizygous Mice (NTP, 2007)

The researchers dermally applied 0, 64, 128, or 256 mg/kg-day sodium bromate in ethanol/water five days per week for 26 weeks to groups of 15 male and 15 female Tg.AC hemizygous mice. They similarly dosed additional groups of 10 male and 10 female Tg.AC hemizygous mice for 39 weeks.

The researchers noted significantly increased reticulocyte counts in the 128 mg/kg-day females and 256 mg/kg-day male and female dose groups at 26 weeks. There were significant increases in relative kidney weights at 26 weeks in males at the high dose and in all male dose groups at 39 weeks. Absolute testis weights in 256 mg/kg-day males and absolute kidney weights in 256 mg/kg-day females were decreased at 39 weeks. Nephropathy occurred in 14 of 15 males receiving 128 and 256 mg/kg-day at 26 weeks and in all 256 mg/kg-day females in both studies. In the thyroid gland, significant increases in the incidence of follicular cell hypertrophy were observed in all dosed groups of males and females in both studies, follicular secretory depletion in 128 and 256 mg/kg-day females in both studies, and lymphocytic cellular infiltration in 64 and 256 mg/kg-day females at 26 weeks and 128 and 256 mg/kg-day females at 39 weeks.

NTP Drinking Water Studies in Tg.AC Hemizygous Mice (NTP, 2007)

Groups of 15 Tg.AC hemizygous mice of each sex were exposed to sodium bromate concentrations of 0, 80, 400, or 800 ppm in drinking water for 27 weeks. NTP calculated that the concentrations were equivalent to average daily doses of approximately 0, 13, 63, and 129 mg/kg-day to male mice and 0, 15, 72, and 148 mg/kg-day to female mice. Additionally, groups of 10 mice of each sex were exposed to drinking water concentrations of sodium bromate of 0, 80, 400, or 800 ppm for 43 weeks; daily doses of 0, 11, 52, and 131 mg/kg-day to male mice and 0, 15, 65, and 152 mg/kg-day to female mice were estimated. The report shows decreased survival in 400 ppm females and 800 ppm males and females at 43 weeks; and lower mean body weights within the 400 ppm males and 800 ppm male and female groups, compared with controls, in both studies.

Absolute kidney weights were decreased in 800 ppm females and relative kidney weights were increased in 400 and 800 ppm males at 27 weeks. Absolute testis weights were significantly decreased in 800 ppm males at 43 weeks. Additional toxic effects were reported for kidney and thyroid.

NTP Drinking Water Studies in p53 Haploinsufficient Mice (NTP, 2007)

Groups of 15 p53 haploinsufficient mice of each sex were exposed to sodium bromate concentrations of 0, 80, 400, or 800 ppm in drinking water for 27 weeks. NTP calculated that the concentrations were equivalent to average daily doses of approximately 0, 8, 39, and 74 mg/kg to males and 0, 13, 72, and 136 mg/kg-day to female mice. Additionally, groups of 10 mice of each sex were exposed to drinking water sodium bromate concentrations of 0, 80, 400, or 800 ppm for 43 weeks, with approximate daily doses of 0, 7, 37, and 65 mg/kg to males and 0, 11, 58, and 107 mg/kg-day to female mice. NTP reported that survival of exposed groups was similar to that of controls. Mean body weights of 400 and 800 ppm females were generally lower, but not significantly less than those of the control groups during most of the studies (NTP, 2007).

Carcinogenicity

There are several scientific studies that describe the carcinogenic properties of potassium bromate exposure via drinking water in animals. The chemical has been shown to be a multisite carcinogen in multiple studies, inducing mesothelioma, kidney tumors, and thyroid tumors. Conversely, sodium bromate was recently studied in non-standard bioassays using transgenic mouse models and no clear indications of carcinogenicity were found (NTP, 2007; Pritchard *et al.*, 2003). These NTP studies were part of a method development initiative using non-standard and shorter-term bioassay approaches (NTP, 2007).

Kurokawa and associates (1983) examined orally administered potassium bromate for carcinogenicity in F344 rats. Male and female rats (53 per sex per group) were exposed to 250 or 500 ppm potassium bromate in drinking water, or a distilled water control, for 110 weeks. The researchers reported shortened mean survival times for the male rats in the high-dose group (88.1 ± 18.1 wk in high-dose group versus 104.5 ± 11.3 wk in controls); however, the percentage of survival in week 104 was relatively high for all female groups (61.5 to 66.0 percent) and the male controls (77.4 percent in controls versus 20.8 percent in the high-dose group). The authors observed significantly high incidences of renal cell tumors for both males and females for both dose groups, and mesotheliomas of the peritoneum for high-dose males. They concluded that potassium bromate was carcinogenic to F344 rats under their oral dosing conditions.

Kurokawa and coworkers (1986a) performed a study to further characterize the dose-response relationship of potassium bromate in male F344 rats. The researchers exposed groups of 20 to 24 rats orally to potassium bromate via drinking water at concentrations of 0, 15, 30, 60, 125, 250, or 500 ppm for 104 weeks. They observed significantly shortened survival times and decreased body weight gain at the highest dose. The researchers noted that renal cell tumors and renal adenomas, but not renal adenocarcinomas, significantly increased over controls in a dose-dependent manner at exposure concentrations of 125, 250, and 500 ppm potassium bromate. They reported a significant increase in incidence of renal dysplastic foci at concentrations of 30 ppm and higher, in a dose-dependent manner. The authors observed peritoneal mesotheliomas at 30 ppm and higher, with a significant increase in incidence at 500 ppm. Further, the combined incidence of thyroid follicular adenomas and adenocarcinomas was significantly increased at the 500 ppm level.

Kurokawa and coworkers (1986b) examined the carcinogenic effects of potassium bromate in groups of 52 to 53 male and 52 female F344 rats. The authors administered potassium bromate orally via drinking water at concentrations of 0, 250, or 500 ppm for 110 weeks. They reported significant inhibition in weight gain and lower survival rate in the 500 ppm males. The authors observed significant increases in renal cell tumors, renal adenocarcinomas, and renal adenomas at both dose levels for both sexes. Additionally, they observed significant increases in the combined incidence of follicular adenocarcinomas and adenomas of the thyroid in the high-dose males, and in the incidence of peritoneal mesothelioma in all exposed males.

To study the relationship between duration of treatment and incidence of tumors induced by potassium bromate, Kurokawa and coworkers (1987) conducted a drinking water study in six-week old male F344 rats. In the first continued treatment study, 10 groups of 8 to 20 rats were given distilled water or 500 ppm potassium bromate for 13, 26, 39, 52, or 104 weeks before sacrifice. The average daily consumption was 41.9 ± 3.2 mg/kg-day potassium bromate. The mean survival time of rats receiving potassium bromate continuously for 104 weeks was significantly shorter than that of the distilled water controls (84.1 ± 12.0 weeks for potassium bromate-treated rats versus 103.6 ± 3.5 weeks for the controls, $p<0.001$). Compared to the distilled water controls, significant inhibition of body weight gain was detected in rats with the longest potassium bromate exposure duration (358.7 ± 84.1 g for the controls versus 330.0 ± 64.5 g for the 104-week potassium bromate treatment group, $p<0.001$). Histopathological examination of the tissues showed no renal preneoplastic or neoplastic lesions in any rats treated with distilled water only. Renal dysplastic foci and renal adenomas were detected in rats exposed to potassium bromate continuously for 26 weeks or longer (incidences of tumor were 5 to 95 percent for 26- to 104-week exposure). Additionally, renal adenomas and adenocarcinomas were detected, respectively, in three and six of 20 rats after 104 weeks of continuous potassium bromate exposure. The researchers reported that no tumors were observed in the thyroid of rats administered only distilled water, but follicular adenomas of the thyroid developed in rats exposed to potassium bromate and sacrificed at weeks 26, 39, or 52. Follicular adenomas and adenocarcinomas of the thyroid developed, respectively, in five and two of 20 rats after 104 weeks of continuous potassium bromate exposure. Non-neoplastic lesions of the kidney (e.g., eosinophilic bodies) were found in rats treated continuously with potassium bromate for 13 to 104 weeks.

Kurokawa and coworkers (1987) also exposed another four groups of 14 to 20 rats to 500 ppm potassium bromate for 13, 26, 39, or 52 weeks, followed by distilled water until sacrifice at week 104 (discontinued treatment). The authors reported that the mean survival times of rats treated with potassium bromate were significantly shorter than that of the controls (96.5 ± 10.1 to 84.8 ± 19.6 weeks for 13-week to 52-week of potassium exposure versus 103.6 ± 3.5 weeks for controls, $p<0.05$). Histopathological examination of tissues revealed that all potassium bromate-treated rats developed renal adenomas and adenocarcinomas by the end of the experiment. The combined incidences of renal adenomas and adenocarcinomas in potassium bromate treatment groups were significantly higher than in the distilled water controls (47 percent to 64 percent in potassium bromate treatment groups versus 0 percent in controls, $p<0.001$). The incidences of renal dysplastic foci or combined incidences of renal adenomas and

adenocarcinomas were generally increased with the length of potassium bromate exposure. In the thyroid, combined incidences of follicular adenomas and adenocarcinomas were significantly higher in rats exposed to potassium bromate for 26 weeks (32 percent) or 52 weeks (36 percent), than in controls (0 percent, p values not shown). In the peritoneum, significant increases in incidence of mesotheliomas were identified in all discontinued potassium bromate treatment groups (30 to 42 percent in potassium bromate treatment groups versus 0 percent in controls, $p<0.01$). In the testis, irrespective of the chemical treatments and durations of exposure, almost all rats developed interstitial cell tumors by the end of the experiment. This result suggested that development of interstitial cell tumors was independent of potassium bromate treatment. Calcification at the renal pelvis was noted in all rats with continued or discontinued potassium bromate treatments. Considering all the results, the authors concluded that a higher dose of potassium bromate within a shorter period of time was more effective in producing tumors than a lower dose over a longer period. These studies demonstrated that potassium bromate acted as a complete carcinogen in inducing renal cell tumors. The authors derived a TD_{50} of 6 mg/kg-day potassium bromate and a virtually safe dose (VSD) of 0.038 mg/kg-day potassium bromate, with a corresponding drinking water level of 0.95 ppm potassium bromate at a risk level of one in a million.

DeAngelo *et al.* (1998) studied male rats and male mice to verify the results of earlier bioassays and further investigate the carcinogenicity of bromate. Potassium bromate was administered to five groups of 78 male F344/N rats with target drinking water concentrations of 0, 20, 100, 200, or 400 ppm for up to 100 weeks (DeAngelo *et al.*, 1998; DeAngelo, pers. comm., 2006). There were at most three rats to a cage and they had unlimited access to the water. DeAngelo *et al.* (1998) calculated the mean daily doses from the volume of water that was consumed and the measured water concentrations, reporting estimated daily potassium bromate consumption levels of 0, 1.5, 7.9, 16.9, or 37.5 mg/kg-day. Correcting for the molecular weight ratio of $BrO_3^-/KBrO_3$ (127.9/167.0), this is equivalent to bromate doses of 0, 1.1, 6.1, 12.9, or 28.7 mg/kg-day.

DeAngelo *et al.* (1998) describes a subset of the full data set from the bromate bioassay. The full data set with all available individual animal data was obtained from DeAngelo (pers. comm., 2006). The published subset consisted of 270 rats that were scheduled to be sacrificed at 100 weeks. The 120 rats not included in this subset were scheduled for sacrifice at 12, 26, 52 and 77 weeks (six at each time per non-zero dose group).

Dose-related increases in the incidence of mesothelioma, thyroid tumors, and kidney tumors were observed in male rats (DeAngelo *et al.*, 1998; Crosby *et al.*, 2000). A treatment-related decrease in survival time was reported, which appeared to be related to tumor development in male rats. DeAngelo *et al.* (1998) also reported a statistically significant increase in the incidence of renal tumors in low-dose male mice, but the effect was not dose-related. Our analyses focus on the study by DeAngelo in the male rat, the most sensitive sex and species, as described in detail in the Dose-Response Assessment section below.

Takamura and coworkers (1985) supplemented drinking water of groups of 20 male Syrian golden hamsters with potassium bromate at concentrations of 125, 250, 500, or 2,000 ppm for 89 weeks. The mean final body weights of the high-dose group were

significantly lower than the controls, and mean absolute and relative kidney weights were significantly higher in the two highest-dose groups than the controls. The authors noticed no apparent differences in survival times among the groups. Seven of the 75 treated rodents developed renal adenomas; this was dose-related at 1, 2, and 4 renal adenomas, respectively, in the 250, 500, and 2,000 ppm groups. The authors opined that it was highly likely that the adenomas were induced by the exposure to potassium bromate, especially in light of the typically low incidence of these lesions in this species of laboratory animal.

Kurata and coworkers (1992) tested potassium bromate for single-dose tumor initiating properties. The researchers dosed six-week-old F344/NCr male rats intragastrically with a single 300 mg/kg dose of potassium bromate, which is the maximum tolerated dose. Beginning at two weeks post-exposure, groups of 39 treatment and control rats were given either a basic diet or a basic diet containing 4,000 ppm barbital sodium, a promoting agent. Animals were terminated at weeks 30, 52, 104, or when found in poor condition. At week 30, the authors observed nephropathy in all rats treated with potassium bromate followed by barbital sodium and in rats receiving barbital sodium alone, but not in rats exposed to potassium bromate alone. From week 47 to the end of the study, in rats exposed to potassium bromate followed by barbital sodium and in rats exposed to barbital sodium alone, the researchers noticed dysplastic renal tubular cell foci, which they described as putative preneoplastic renal tubular cell lesions associated with nephropathy. The authors surmised that the single potassium bromate dose of 300 mg/kg did not initiate renal carcinogenesis (Kurata *et al.*, 1992).

NTP (2007) released its final report on the toxicology, including carcinogenicity, of sodium bromate in two species of genetically modified mice. These studies were part of a special method development initiative to evaluate the use of transgenic animal models for detecting the carcinogenesis of disinfection byproducts and other environmental contaminants. Highlights of the studies include 26- and 39-week dermal studies in Tg.AC hemizygous mice, 27- and 43-week drinking water studies in Tg.AC hemizygous mice, and 27- and 43-week drinking water studies in p53 haploinsufficient mice. The report concluded that no evidence of carcinogenicity for sodium bromate was observed. Details are provided below.

NTP Dermal Studies in Tg.AC Hemizygous Mice (NTP, 2007)

The NTP-sponsored researchers dermally applied 0, 64, 128, or 256 mg/kg-day sodium bromate in ethanol/water five days per week for 26 weeks to groups of 15 male and 15 female Tg.AC hemizygous mice. They similarly dosed additional groups of 10 male and 10 female Tg.AC hemizygous mice for 39 weeks. The researchers observed no increased incidence of neoplasia in male or female Tg.AC hemizygous mice dermally exposed to sodium bromate.

NTP Drinking Water Studies in Tg.AC Hemizygous Mice (NTP, 2007)

Groups of 15 Tg.AC hemizygous mice of each sex were exposed to sodium bromate concentrations of 0, 80, 400, or 800 ppm in drinking water for 27 weeks. NTP calculated that the concentrations were equivalent to average daily doses of approximately 0, 13, 63, and 129 mg/kg-day to male mice and 0, 15, 72, and 148 mg/kg-day to female mice.

Additionally, groups of 10 mice of each sex were exposed to drinking water concentrations of sodium bromate of 0, 80, 400, or 800 ppm for 43 weeks; average daily doses of 0, 11, 52, and 131 mg/kg-day sodium bromate to male mice and 0, 15, 65, and 152 mg/kg-day sodium bromate to female mice were estimated. Absolute kidney weights were decreased in 800 ppm females and relative kidney weights were increased in 400 and 800 ppm males at 27 weeks. Absolute testis weights were significantly decreased in 800 ppm males at 43 weeks. Other toxic effects were reported for kidney and thyroid. No increases in neoplasia were observed among either males or females.

NTP Drinking Water Studies in p53 Haploinsufficient Mice (NTP, 2007)

Groups of 15 p53 haploinsufficient mice of each sex were exposed to sodium bromate concentrations of 0, 80, 400, or 800 ppm in drinking water for 27 weeks. NTP calculated that the concentrations were equivalent to average daily doses of approximately 0, 8, 39, and 74 mg/kg-day sodium bromate to males and 0, 13, 72, and 136 mg/kg-day sodium bromate to female mice. Additionally, groups of 10 mice of each sex were exposed to drinking water sodium bromate concentrations of 0, 80, 400, or 800 ppm for 43 weeks, with approximate daily doses of 0, 7, 37, and 65 mg/kg-day sodium bromate to males and 0, 11, 58, and 107 mg/kg-day sodium bromate to female mice. NTP reported that survival of exposed groups was similar to that of controls. Mean body weights of 400 and 800 ppm females were less than those of the control groups during most of the studies. No neoplasms or non-neoplastic lesions were reported in either males or females that could be attributed to sodium bromate exposure.

In summary, the NTP (2007) studies using non-standard transgenic mouse models did not report any neoplastic effects from sodium bromate. NTP concluded, “These studies provide evidence that these transgenic mouse models are not a sensitive and rapid means of assessing potential toxicity and carcinogenicity of sodium bromate.”

Toxicological Effects in Humans

Acute Toxicity

Most of the information regarding toxic effects of bromate to humans rises from acute poisonings. Acute symptoms include nausea, vomiting, diarrhea, and epigastric pain followed by anuria, oliguria, central nervous system depression, tinnitus, deafness, and renal failure (Gosselin, 1976; Kurokawa *et al*., 1990). Kurokawa *et al.* (1990) described numerous case reports of acute human poisonings due to accidental or intentional ingestion of potassium bromate. Over the 31 cases cited, the accidental intoxications were typically children ingesting bromate-containing hair care products; the adult ingestions were mostly suicides or suicide attempts by hairdressers. The authors reported a range of 12 to 50 grams ingested (with no reference to body weights), and that of the 24 adult cases, nine were fatal.

Genetic toxicity

Kaya and Topaktas (2007) conducted *in vitro* bioassays on genotoxicity and cytotoxicity of potassium bromate in cultured human peripheral lymphocytes. Sister chromatid exchange (SCE), chromosomal aberrations (CA), proliferation index (PI), mitotic index (MI), and micronuclei were evaluated in cells treated with 400, 450, 500, or 550 μg/mL potassium bromate for 24 or 48 hours. Mitomycin-C was used as a positive control. Potassium bromate at concentrations of 400 to 550 μg/mL induced a statistically significant increase in SCE and a statistically significant decrease in PI after 48 hour of incubation. It also caused a statistically significant increase in CA and a significant decrease in MI in both the 24-hour and 48-hour incubation periods. Potassium bromate caused statistically significant increases in micronucleus formation at concentrations of 500 and 550 μg/mL in the 24-hour incubation and at all concentrations for the 48-hour incubation. The authors concluded that this study further demonstrated the induction of tumor formation by potassium bromate via DNA strand breaks. Chromatid and chromosome breaks (structural CA), and to a less extent numerical CA, were found to be the predominant potassium bromate-induced genotoxicity mechanisms of action in the tested human system.

Similarly, Luan and associates (2007) conducted an *in vitro* genotoxicity study on potassium bromate in human lymphoblastoid TK6 cells. Acute exposure to the chemical resulted in DNA double-strand breaks. Potassium bromate was also shown to be positive in a micronucleus test and a thymidine kinase gene mutation assay, in a dose-dependent manner. Results from a gene chip assay further associated treatment with potassium bromate with upregulation of stress, apoptosis, and DNA repair genes. It is hypothesized that potassium bromate caused large DNA deletions in human cells (Luan *et al.*, 2007; Moore and Chen, 2006), instead of the previously proposed GC>TA transversion mediated by accumulation of 8-hydroxydeoxyguanosine (Ballmaier and Epe, 2006).

Chronic Toxicity

OEHHA found no epidemiological information describing either noncancer or carcinogenic toxicological consequences of long-term human exposure to bromate compounds.

Neurotoxicity

OEHHA found no human reports on neurotoxicity induced by chronic exposure to bromate. However, the association of acute exposure to high doses of bromate with hearing loss in humans has been well documented (Kutom *et al.*, 1990; Matsumoto *et al.*, 1980). Campbell (2006) presents a scholarly review of bromate-induced ototoxicity. The author cited multiple references establishing several key issues, including:

- Hearing loss due to high dose bromate ingestion manifests rapidly.
- The actual incidence of bromate-induced hearing loss is unknown, leaving the presumption of many cases diagnosed simply as idiopathic.

- Bromate-caused hearing loss appears to be refractory; however tinnitus due to bromate exposure may be reversible (dizziness and tinnitus can precede actual hearing loss).
- The primary site for the toxic lesion appears to be in the cochlea; potential effects on the VIIIth nerve and the central auditory system have not, as yet, been thoroughly evaluated.
- The mechanisms of bromate-induced ototoxicity have not been thoroughly investigated, however reduced cochlear oxygen might be one possibility.
- No available data link long-term, low-dose bromate exposure with ototoxicity, although if such a connection existed, it could go undetected due to the high rate of idiopathic hearing loss in the general public.

The lowest doses associated with ototoxicity have not been determined, and this information is especially lacking for longer-term and lower-dose exposure (Campbell, 2006; Crofton, 2006).

Other Toxic Effects in Humans

OEHHA found no information related to human exposure to bromate compounds and immunological, developmental, or reproductive toxicity.

DOSE-RESPONSE ASSESSMENT

Noncancer Effects

As discussed earlier, DeAngelo *et al.* (1998) evaluated the chronic effects and carcinogenic potential of potassium bromate administered via drinking water to male F344 rats and $B6C3F_1$ mice. Potassium bromate was administered to rats (the more sensitive of the two rodent species) at concentrations of 0, 20, 100, 200, or 400 ppm (0, 1.1, 6.1, 12.9, or 28.7 mg/kg-day bromate) for up to 100 weeks. The researchers observed non-neoplastic pathology of treatment-related increases in hyperplasia of the transitional cells of the renal papilla and pelvis (which they termed urothelial hyperplasia), and described as a marked increase in the number of urothelial cell layers. The authors reported this effect at and above 6.1 mg/kg-day bromate, with the NOAEL being 1.1 mg/kg-day of bromate. This report provides the lowest effect level of the available toxicity studies. OEHHA therefore selects this rat NOAEL of renal pelvis urothelial hyperplasia as the critical value for determining a non-cancer health-protective value for bromate in drinking water.

Carcinogenic Effects

Overview of Time-to-Tumor and Multi-Site Analyses

Animal cancer bioassays of bromate that are potentially useful for dose-response analysis were carried out in two laboratories: Kurokawa *et al.* (1983, 1986a,b, 1987), and

DeAngelo *et al*. (1998; Crosby *et al.*, 2000, Wolf *et al.*, 1998). The DeAngelo *et al*. bioassays used more animals per dose group and included more dose groups in the low-dose region compared to the bioassays of Kurokawa *et al.* In addition, individual animal tumor data were available only for the DeAngelo *et al.* bioassays. Therefore, the DeAngelo *et al.* bioassays were chosen as the most appropriate for the cancer dose-response assessment of bromate, which is consistent with the approach of U.S. EPA (2001, 2007).

Dose-related increases in the incidence of mesothelioma, thyroid tumors, and kidney tumors were observed in male rats exposed to potassium bromate via drinking water (DeAngelo *et al.*, 1998; Wolf *et al.*, 1998; Crosby *et al.*, 2000). DeAngelo *et al.* also reported a statistically significant increase in the incidence of renal tumors in low-dose male mice; although the effect was not dose-related. The analyses discussed below focus on the male rat, the most sensitive sex and species.

The DeAngelo *et al.* (1998) male rat study included multiple sacrifice times; in addition there was an increase in mortality with increasing dose. Time-to-tumor analyses were therefore performed to derive potency estimates for each site affected by bromate. The analyses took into account the early deaths of the animals in the study. Statistical distributions of cancer potency were generated for each site. A composite cancer potency estimate was derived to give an overall measure of carcinogenic activity of the compound by statistically summing the cancer potency distributions for individual tumor sites.

DeAngelo Data Set

Dose-response analysis was carried out on the data in male rats because they were the most sensitive sex/species (DeAngelo *et al*., 1998). Potassium bromate was administered to five groups of 78 male F344/N rats with target drinking water concentrations of 0, 20, 100, 200, or 400 ppm for up to 100 weeks (DeAngelo *et al.*, 1998; DeAngelo, pers. comm., 2006). There were at most three rats to a cage and they had unlimited access to the water. DeAngelo *et al.* (1998) calculated the mean daily doses from the volume of water that was consumed and the measured water concentrations, estimating mean daily potassium bromate consumption levels of 0, 1.5, 7.9, 16.9, or 37.5 mg/kg-day. OEHHA converted these potassium bromate doses to bromate doses of 0, 1.1, 6.1, 12.9, or 28.7 mg/kg-day from the molecular weight ratio of these chemicals.

DeAngelo *et al.* (1998) described a subset of the full data set from the bromate bioassay. The full data set with all available individual animal data was obtained from DeAngelo (pers. comm., 2006). The published subset consisted of 270 rats that were scheduled to be sacrificed at 100 weeks. The 120 rats not included in this subset were scheduled for sacrifice at 12, 26, 52 and 77 weeks (six at each time per non-zero dose group) (DeAngelo, pers. comm., 2006). U.S. EPA (2001) reported on a dose-response analysis of the DeAngelo *et al.* male rat bioassay. In that analysis, U.S. EPA included all of the rats in the full data set, regardless of sacrifice time, except it appears that they excluded from the analysis all rats without autopsy or site-specific pathology information. OEHHA conducted the dose-response analysis using the same inclusion criteria as U.S. EPA (2001) (i.e., for a given tumor site, all autopsied animals in the full data set with

site-specific pathology information). The male rat data file obtained from DeAngelo is provided in the Appendix.

The tumor types analyzed were mesothelioma, thyroid adenoma or carcinoma, and kidney adenoma or carcinoma. Mesotheliomas primarily originated at the tunica vaginalis testis or the spleen and then spread to the peritoneum (DeAngleo *et al.*, 1998). All of the mesotheliomas were malignant (DeAngelo, pers. comm., 2007). Some other sites where mesotheliomas were found included mesentery, jejunum and colon, pancreas, urinary bladder, stomach, liver, caecum, rectum, and kidney (DeAngelo *et al*., 1998).

DeAngelo *et al.* (1998) only discussed cause of death for the highest-dose group, where there was a "significant depression of the body weight gain." Without detailed information about the suspected causes of death for the studied rats, for each site, tumor context was set to "incidental" when only a benign tumor was present, "fatal" if a malignant tumor was present, or "censored" if no tumor was present. In the case of mesotheliomas, all were assumed to be malignant and were set to "fatal." Animals were removed from the analysis if there was no site-specific pathology available. Out of the 387 rats, 50 animals had mesotheliomas and 37 were missing site-specific pathology for mesothelioma. Twenty-eight animals had either type of thyroid tumor and 83 were missing site-specific pathology for thyroid tumors. Twenty-nine animals had either type of kidney tumor and 64 were missing site-specific pathology for kidney tumors. The animals missing site-specific pathology data are summarized by dose in Table 5. The tumor incidence data for animals in all scheduled sacrifice groups, after excluding animals with missing site-specific pathology, are shown in Table 6.

Table 5. Number of Male Rats per Dose Group Missing Tumor Pathology (DeAngelo, pers. comm., 2006)

Bromate Dose (mg/kg-day)	Number Missing Tumor Pathology		
	Mesothelioma	Kidney	Thyroid
0	7/78	9/78	18/78
1.1	5/78	11/78	14/78
6.1	6/78	7/78	12/78
12.9	8/78	15/78	17/78
28.7	11/77	22/77	22/77
Total Missing	37	64	83
Total Studied	389	389	389

Table 6. Tumor Incidence in Male Rats Exposed via Drinking Water to Bromate (DeAngelo, pers. comm., 2006)[a]

Bromate Dose (mg/kg-day)	Tumor Incidence		
	Mesothelioma	Kidney Adenoma or Carcinoma	Thyroid Adenoma or Carcinoma
0	0/71	1/69	0/60
1.1	4/73	1/67	4/64
6.1	5/72	6/71	2/66
12.9	10/70	3/63	5/61
28.7	31/67	18/56	17/56

[a]The animals missing site-specific pathology have been removed from the denominators.

Methods

The lifetime probability of dying with a tumor induced by an average daily dose (*d*) is often assumed to be described by the multistage model:

$$P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \cdots + q_j d^j)] \quad (1)$$

with constraints, $q_i \geq 0$ for all i. The q_i parameters are estimated from the animal cancer bioassay data using maximum likelihood techniques. The parameter q_0 provides an estimate of the background lifetime incidence of the tumor. The parameter q_1 is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received.

Because survival of male rats in the DeAngelo *et al.* (1998; Wolf *et al*., 1998; Crosby *et al*., 2000) study was poor, the multistage model may not provide an accurate basis for estimating the risk of cancer. Therefore, a time-dependent analysis was performed using the multistage-in-dose Weibull-in-time model. This model is an extension of the form given above (Eqn. 1), with the probability of tumor by time t given as:

$$P(t,d) = 1 - \exp[-(q_0 + q_1 d + ... + q_j d^j)(t - t_0)^k] \quad (2)$$

with

$$q_i \geq 0, \text{ for all i, and } 0 \leq t_0 < t$$

where t_0 is commonly interpreted as the latency period, and k is the age exponent. In this case, carcinogenic potency for animals is derived by applying a maximum likelihood modeling approach to estimate the parameters (q_i, t_0, and k) and generate the distribution of q_1. The animal cancer potency, q_{animal}, is defined as the upper 95 percent confidence bound on q_1 estimated at 104 weeks, the assumed standard lifetime for rats.

In fitting the multistage Weibull model (Eqn. 2), the maximum number of dose parameters is equal to the number of dose groups (i.e., j+1). The corresponding degree of

the multistage-in-dose component of the polynomial varies from 1 to j. The most parsimonious multistage Weibull model, i.e., the model of lowest order (with regard to the dose polynomial in Eqn. 2), is selected in the following way. First the fit of a model to the data was assessed, and deemed appropriate, using a χ^2 goodness-of-fit test criterion p-value greater than or equal to 0.05. If the model fit was adequate, then a test was performed to determine whether a higher order model provided a significantly better fit. To do this, the likelihood ratio test (LRT) was calculated, with the test statistic being equal to -2(log likelihood$_{\text{sub-model}}$ - log likelihood$_{\text{full model}}$), where the "sub-model" is nested and has fewer parameters than the "full model." The p-value for the test statistic was calculated using the χ_{df}^2 distribution, where the degrees of freedom (df) are equal to the difference in the number of parameters between the two models. A p-value of less than 0.05 for the LRT was considered to provide enough evidence that the full model (the model with more parameters) should be used in favor of the more parsimonious model.

The two-stage Weibull model ($q_3 = 0$) was chosen as the most parsimonious for modeling mesothelioma and thyroid time-to-tumor. The most parsimonious kidney time-to-tumor model was one-stage, where $q_3 = q_2 = 0$. The likelihood was calculated with a Microsoft Excel Visual Basic function.[1] Using this function, distributions of the q_1 estimates were generated for each tumor site. The likelihood was maximized using the Microsoft Excel Solver Add-In for parameters q_0, q_1, q_2 (except for kidney, as noted above) and k, and varied by tumor site. The profile likelihood distribution of the potency was traced for each site using a Microsoft Excel Visual Basic procedure.

To take into account multi-site tumorigenicity and to provide the basis for estimating the cumulative risk of any bromate treatment-related tumor, a multi-site cancer potency estimate was derived using a Monte Carlo procedure. The multistage Weibull model parameters were first estimated for each of the treatment-related tumors observed in the male rat bioassay of DeAngelo *et al.* (1998). Statistical distributions, rather than point estimates, were generated for q_1 at each site by tracing the profile likelihood distribution. The q_1 distributions for each of the treatment-related sites were then statistically summed using random sampling with 100,000 Monte Carlo trials and assuming independence of the tumor sites. The upper 95 percent confidence bound on the combined distribution was taken as the animal cancer potency (q_{animal}).

In deriving the human cancer potency from animal data it was assumed that dose, when expressed in terms of amount (e.g., milligrams) per body weight scaled to the ¾ power, produces the same cancer incidence, regardless of species. This ¾ scaling approach leads to the following equation for extrapolating animal cancer slope factors to humans:

$$q_{\text{human}} = q_{\text{animal}} \times (bw_{\text{human}} / bw_{\text{animal}})^{1/4} \qquad (2)$$

where the bw_{human} is the human body weight (assumed to be 70 kg) and bw_{animal} is the animal body weight in kilograms (kg). OEHHA estimated the control male rat body

[1] OEHHA thanks Dr. Edmund Crouch for providing us with an Excel spreadsheet containing a Visual Basic macro and likelihood function to model the probability of tumor using the multistage-in-dose Weibull-in-time model.

weight based on Figure 1 in DeAngelo *et al.* (1998) to be approximately 0.4 kg, which is consistent with the male rat body weight reported by U.S. EPA (2001).

Results

Estimates of the cancer slope factor (q_{human}) derived from the different tumor sites are reported in Table 7 (derived by OEHHA) and Table 8 (derived by U.S. EPA, 2001). The median and upper 95th percentile cancer slope factor estimates are provided for the individual tumor sites and for the combined sites. The corresponding LED_{10} values are also provided. The LED_{10} is the lower-bound estimate of the average lifetime dose associated with a ten percent cancer risk and was calculated using the approximation $LED_{10} = - \ln(0.9)/q_{human}$ where q_{human} represents the upper 95 percent confidence bound on q_1, after correcting for differences in size between test animals and humans.

Table 7. Human Cancer Potency and LED_{10} Values for Bromate

Tumor Type	q_{human} $(mg/kg\text{-}day)^{-1}$		LED_{10} (mg/kg-day)
	Median	**95th Percentile**	**Lower 95th Percentile**
Mesothelioma	0.017	0.13	1.1
Kidney adenoma or carcinoma	0.074	0.11	0.96
Thyroid adenoma or carcinoma	~0	0.054	2.0
Multi-site	0.11	**0.21**	0.55

Bolding indicates basis for estimating human cancer potency.

Table 8. Human Cancer Potency and LED_{10} Values for Bromate as Reported by U.S. EPA (2001)

Tumor Type	q_{human} $(mg/kg\text{-}day)^{-1}$		LED_{10} (mg/kg-day)
	Median	**95th Percentile**	**Lower 95th Percentile**
Mesothelioma	0.27	0.54	0.20
Kidney adenoma or carcinoma	0.08	0.18	0.59
Thyroid adenoma or carcinoma	0.05	0.10	1.1
Multi-site [a]	0.41	0.70	0.15

[a]Multi-site values for q_{human} were reported by U.S. EPA (2001). Multi-site LED_{10} value was calculated by OEHHA.

Discussion

In the multistage Weibull time-to-tumor model, it is necessary to designate the tumors as either "fatal," "incidental," "censored," or "unknown." Most of the records where no autopsy data was available were in rats that were found dead or were moribund sacrificed. Since the coding of tumors can affect the maximum likelihood model that is fit to the data, a sensitivity analysis was performed with many combinations of tumor designations and inclusion criteria to determine how various tumor coding schemes affect the cancer potency estimates.

Four scenarios were used for the sensitivity analysis and provide evidence that the current inclusion criteria and tumor coding schemes are appropriate. First, all tumors were considered "incidental" and rats missing pathology information were coded as "censored" (assumed to have tumor incidence at some point beyond death). For this case, the upper bound human cancer potencies were within 0.7 to 1.0-fold of the upper bound values for the individual tumor sites displayed in Table 7. Second, rats with unknown site-specific pathology were excluded from the analysis and all benign and malignant tumors were coded as "incidental," resulting in upper bound estimates within 0.8 to 1.0-fold of the Table 7 values. Third, malignant tumors were coded "fatal," benign tumors were coded "incidental" and the animals without site-specific pathology were coded as "unknown." In this case, the upper bound estimates on human cancer potency were within 0.9 to 1.5-fold of the values provided in Table 7. Lastly, all benign tumors were coded "incidental," malignant tumors coded "fatal," and animals without autopsy information coded "incidental," under the assumption that these unknowns could have had a tumor. Including these missing records and coding them as "incidental" resulted in upper bound potency values within 0.9 to 1.1-fold of the values reported in Table 7. In all sensitivity analyses, the upper bound human cancer potencies were within 0.7 to 1.5-fold of those reported for the individual tumor sites in Table 7, providing evidence of adequate inclusion criteria and tumor coding.

The results reported in Table 7 differ from those reported by U.S. EPA (2001, 2007) and reproduced in Table 8. Some differences between the OEHHA and U.S. EPA analyses that could account for the different results are:

(1) The site-specific tumor incidence counts used by OEHHA do not match the counts in the U.S. EPA 2001 document; however, they are quite close. OEHHA obtained a recently updated data file directly from Dr. DeAngelo and established counts based on that data file (see Appendix).

(2) For mesothelioma and thyroid tumors, the model that best fit the data according to the likelihood ratio test was two-stage (which included a linear and a squared term in dose) whereas U.S. EPA chose the one-stage model for all three sites.

(3) U.S. EPA coded all tumors as incidental, whereas OEHHA coded malignant tumors as "fatal" and benign tumors as "incidental."

(4) Tox_Risk allows the user to specify the natural lifespan at which cancer potency is estimated (typically 104 weeks for rodents). It is unclear what lifespan U.S. EPA used in their computation of animal potency. In the OEHHA analysis, animal

potencies were calculated using an assumed rat lifetime of 728 days (104 weeks). Using a lifespan of more than 104 weeks would increase the potency estimates.

The cancer potency estimate of 0.21 $(mg/kg\text{-}day)^{-1}$ based on the multi-site analysis in male rats is chosen as the most appropriate cancer potency for bromate. This estimate was derived using the time-to-tumor multi-site approach based on the tumor data for mesothelioma, kidney tumors and thyroid tumors in the male rat, which was the sex and species observed to be most susceptible to the carcinogenic effects of bromate.

CALCULATION OF PHG

Noncancer Effects

For estimation of a health-protective concentration of a chemical in drinking water, an acceptable daily dose of the chemical from all sources will first be calculated. This involves incorporation of appropriate estimates of uncertainty in the extrapolation of the critical toxic dose from human or animal studies to the estimation of a lifetime daily dose for that is unlikely to result in any toxic effects. For this purpose, the following equation will be used:

$$ADD = \frac{\text{NOAEL/LOAEL in mg/kg-day}}{UF}$$

where,

ADD = acceptable daily dose, an estimated maximum daily dose that can be consumed by humans for an entire lifetime without toxic effects;

NOAEL/LOAEL = no-observed-adverse-effect level or lowest-observed-adverse-effect level in the critical study;

UF = combined uncertainty factor.

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water incorporates the ADD in the following equation for noncarcinogenic endpoints:

$$C = \frac{\text{ADD mg/kg-day x RSC}}{\text{L/kg-day}}$$

where,

RSC = relative source contribution (usually 20 to 80 percent, expressed as 0.20 to 0.80);

L/kg-day = upper 95^{th} percentile of the daily tap water consumption of the critical population for this case.

From DeAngelo *et al.* (1998), the noncancer NOAEL = 1.1 mg/kg-day of bromate, based on renal pelvis urothelial hyperplasia in male rats. The combined UF should be 100, based on 10 for intraspecies variation and 10 for interspecies variation. Thus, the recommended acceptable daily dose is:

$$\text{ADD} = \frac{1.1 \text{ mg/kg-day}}{100} = 0.011 \text{ mg/kg-day}$$

Bromate exposure from food could be significant, and concentrations found in water are commonly small; thus it is clear that multiple exposure sources are relevant. However, data are inadequate to accurately estimate a RSC from food versus drinking water, so the default value of 0.2 (20 percent) is considered the most appropriate for drinking water exposure.

Because the critical toxic effect is from chronic exposure, a long-term, general population drinking water consumption rate seems most defensible. OEHHA utilizes the upper 95th percentile of municipal water consumption for the general population, 0.044 L/kg-day, from the U.S. EPA (2004) analysis, to ensure that high-end water consumers are accounted for. A public health-protective concentration (C, in mg/L) for non-cancer effects of bromate in drinking water is then calculated as:

$$C = \frac{0.011 \text{ mg/kg-day} \times 0.2}{0.044 \text{ L/kg-day}} = 0.05 \text{ mg/L} \times \frac{1000 \text{ ppb}}{\text{mg/L}} = 50 \text{ ppb}$$

Carcinogenic Effects

OEHHA estimates a health-protective concentration in drinking water for protection against potential carcinogenic effects from the calculated cancer slope factor q_{human} in the following expression:

$$C = \frac{R}{q_{human} \times \text{L/kg-day}} = \text{mg/L}$$

where,

R = the *de minimis* level for lifetime excess individual cancer risk (a default of one in one million, or 10^{-6});

q_{human} = cancer slope factor, the upper 95 percent confidence limit of the cancer potency slope (q_1*) converted to human equivalents;

L/kg-day = the upper 95th percentile of consumption of municipal water for the general population, or 0.044 L/kg-day (U.S. EPA, 2004).

Thus, the estimated drinking water concentration corresponding to a one in one million cancer risk, utilizing the cancer potency for potassium bromate, is:

$$C = \frac{1x10^{-6}}{0.21\ (mg/kg\text{-}day)^{-1} \times 0.044\ L/kg\text{-}day} = 0.00011\ mg/L$$

$$C = \mathbf{0.0001\ mg/L\ (rounded)\ x\ \frac{1000\ ppb}{mg/L} = 0.1\ ppb}$$

In order to protect the entire population from carcinogenic risk from exposure to bromate in drinking water, the above estimated health-protective concentration of 0.1 ppb (rounded to one significant figure), is utilized as the PHG for bromate in drinking water. Because this value is much lower than the non-cancer value, the population will also be protected against non-cancer effects at this exposure level. The PHG is judged to be adequately protective against potential effects in any known sensitive subpopulation, including pregnant women, neonates, infants, children, and the elderly. Risks of 10^{-5} and 10^{-4} are associated with lifetime exposure to concentrations of 1 ppb and 10 ppb, respectively.

RISK CHARACTERIZATION

The noncancer PHG calculation is based on the study of DeAngelo *et al.* (1998), which demonstrated adverse kidney effects in male F344 rats chronically exposed to potassium bromate via drinking water. The DeAngelo *et al.* values present a valid NOAEL for chronic, noncancer exposure.

OEHHA bases the calculation of the PHG on carcinogenic effects in the DeAngelo *et al*. bioassays because these studies used more animals per dose group and included more dose groups in the low-dose region than in the bioassays of Kurokawa *et al.* (1986a,b). In addition, individual animal tumor data were available only for the DeAngelo *et al.* bioassays. Selection of the DeAngelo *et al.* bioassays as the most appropriate for the cancer dose-response assessment of bromate is consistent with the approach of U.S. EPA (2001, 2007).

U.S. EPA (2007) estimated a reference dose for bromate of 0.004 mg/kg-day based on the DeAngelo *et al.* (1998) study, with a NOAEL of 1.5 mg/kg-day potassium bromate (1.1 mg/kg-day of bromate) and a combined UF of 300. Similar to this PHG document, U.S. EPA has applied a UF of 10 to account for extrapolation from animals to humans, and another UF of 10 for protection of sensitive subpopulations and potential differences between adults and children. The extra factor of three used by U.S. EPA is to account for deficiencies in the database, specifically developmental studies in two species and a multigeneration study.

OEHHA selects the *de minimis* cancer risk value of 0.1 ppb over the noncancer value of 50 ppb for the PHG as a matter of public health prudence, to protect against all health risks.

OEHHA is aware of the uncertainty in bioavailability of bromate in humans, based on the lack of information on pharmacokinetics in humans and no epidemiological data available on chronic exposure to bromate in humans. Continued research on bromate, including development of a PBPK model, would provide a better understanding of pharmacokinetics and toxicity of the chemical and further improve the risk assessment.

OEHHA notes that bromate is an unusual chemical in that although it is a Group B2 probable human carcinogen (as classified by U.S. EPA in 2001 based on the 1996 cancer guidelines), its use as a food additive is still permitted. Importantly, it is permitted only in the raw ingredients (flour) and the baking process removes most of the chemical (WHO, 2005; IPCS, 2006). The continued use of bromate in the food industry does not diminish the importance of potential health effects from exposure to bromate in drinking water.

The OEHHA PHG value is most comparable to the U.S. EPA MCLG. For carcinogens, the U.S. EPA sets all MCLGs at zero, as a matter of policy, while OEHHA provides a specific *de minimis* risk level for reference by the California Department of Public Health in developing an MCL. For bromate, the 0.1 ppb PHG value OEHHA proposed is much lower than the U.S. EPA and California MCL of 10 ppb. U.S. EPA based their MCL on a $1x10^{-4}$ risk level (U.S. EPA, 1998), and the value actually calculated for bromate was apparently 5 ppb. This was then modified to 10 ppb to account for available analytical methods, and the resulting U.S. EPA regulatory level was based on the practical quantification limit (PQL). The California MCL was simply based on the U.S. EPA MCL. Differences in modeling approaches account for the remainder of the dissimilarity between the U.S. EPA risk assessment and the value of the proposed PHG.

OTHER REGULATORY STANDARDS

The U.S. EPA MCLG for bromate in drinking water is set at zero, based on carcinogenicity. The MCL is set at 10 ppb, based on the PQL (U.S. EPA, 1998). Bromate was listed on May 31, 2002, as a chemical known to the State of California to cause cancer under Proposition 65 using the authoritative bodies mechanism. The Proposition 65 cancer listing was based on the U.S. EPA classification of bromate as a probable human carcinogen (Group B2) with sufficient evidence of carcinogenicity in experimental animals. The Agency for Toxic Substances and Disease Registry has no evaluation or toxicological profile for bromate or its salts. IARC concluded in Volume 73 (1999) that "There is inadequate evidence in humans for the carcinogenicity of potassium bromate. There is sufficient evidence in experimental animals for the carcinogenicity of potassium bromate. Overall evaluation: Potassium bromate is possibly carcinogenic to humans (Group 2B)" (IARC, 1999). The available regulatory standards are summarized in Table 9.

Table 9. Regulatory Standards for Bromate

Agency	Standard or Criterion	Level	Comment
U.S. EPA	MCL	10 ppb	Based on PQL
U.S. EPA	MCLG	0 ppb	Goal, based on carcinogenicity
California DPH	MCL	10 ppb	Based on U.S. EPA MCL
FDA		50 ppm	$KBrO_3$ in white flour and cereal flours
FDA		75 ppm	$KBrO_3$ in whole wheat flour and in malt for production of fermented malt beverages or distilled spirits $Ca(BrO_3)_2$ in flour (unspecified)
FDA	MRDL[a]	10 ppb	Bromate in bottled water
Health Canada	IMAC[b]	10 ppb	Based on PQL

[a]MRDL stands for maximum residual disinfectant level.
[b]IMAC stands for interim maximum acceptable concentrations.
Sources: Health Canada, 1999; FDA, 2006c; U.S. EPA, 2006; DPH, 2008.

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APPENDIX

Original data file on individual male rat tumor pathology from DeAngelo (personal communication, 2006); copied from Excel with notes added by OEHHA (italicized).

STUDY 9302 IH Pathology/Animal Correlation/Cancer QA **F344 Rat KBrO3**

START DATE: JULY 16, 1992 OCTOBER 8, 1993

	1 Control	**ED: Early Death**	Transcribe: 1-(6-9)98 MHGeorge	***OEHHA Notes:***
FILE: 9302wqa	**2 0.4 g/L KBrO3**	**AA: Advanced Autolysis**	**2nd Check:**	***SS: Scheduled Sacrifice***
Mortality and Cancer	**3 0.2 g/L KBrO3**	**NTS: No Tissue Saved**		***FD: Found Dead***
	4 0.1 g/L KBrO3			***MS: Moribund Sacrifice***
	5 0.02 g/L KBrO3			

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
1 CONTROL	1	092886	6JAN94	12	SS	+	0	0		0	0	0	
1 CONTROL	1	375003	6JAN94	12	SS	+	0	0		0	0	0	
1 CONTROL	1	369543	6JAN94	12	SS	+	0	0		0	0	0	
1 CONTROL	2	306021	6JAN94	12	SS	+	0	0		0	0	0	
1 CONTROL	2	638536	6JAN94	12	SS	+	0	0		0	0	0	
1 CONTROL	2	373768	6JAN94	12	SS	+	0	0		0	0	0	
1 CONTROL	3	110820	8APR94	26	SS	+	0	0		0	0	0	
1 CONTROL	3	041032	8APR94	26	SS	+	0	0		0	0	0	
1 CONTROL	3	106776	8APR94	26	SS	+	0	0		0	0	0	
1 CONTROL	4	612623	8APR94	26	SS	+	0	0		0	0	0	

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
1 CONTROL	4	032558	8APR94	26	SS	+	0	0		0	0	0	
1 CONTROL	4	825023	8APR94	26	SS	+	0	0		0	0	0	
1 CONTROL	5	638873	7OCT94	52	SS	+	0	0		0	0	0	
1 CONTROL	5	369051	7OCT94	52	SS	+	0	0		0	0	0	
1 CONTROL	5	008610	7OCT94	52	SS	+	0	0		0	0	0	
1 CONTROL	6	831843	7OCT94	52	SS	+	0	0		0	0	0	
1 CONTROL	6	040540	7OCT94	52	SS	+	0	0		0	0	0	
1 CONTROL	6	608608	7OCT94	52	SS	+	0	0		0	0	0	
1 CONTROL	7	362591	5APR95	77	SS	+	0	0		0	0	0	
1 CONTROL	7	565332	5APR95	77	SS	+	0	0		0	0	0	
1 CONTROL	7	610040	5APR95	77	SS	+	0	0		0	0	0	
1 CONTROL	8	362811	5APR95	77	SS	+	0	0		0	0	0	
1 CONTROL	8	036258	5APR95	77	SS	+	0	0		0	0	0	
1 CONTROL	8	776520	5APR95	77	SS	+	0	0		0	0	0	
1 CONTROL	9	366607	9MAY95	82	MS	+	0	0	0	0			
1 CONTROL	9	611056	28AUG95	98	MS	+	0	0	0	0	0	0	
1 CONTROL	9	824283	20SEP95	100	SS	+	0	0	1	0	0	0	
1 CONTROL	10	615007	22MAY95	84	FD	AA							
1 CONTROL	10	639272	20SEP95	100	SS	+	0	0	0	0	0	0	
1 CONTROL	10	368563	17AUG95	96	MS	+	0	0	0	0	0	0	
1 CONTROL	11	039586	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	11	368307	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	11	029379	20SEP95	100	SS	+	0	0		0	0	0	
						+							

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
1 CONTROL	12	365631	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	12	609596	18AUG95	96	FD	+	0	0		0			
1 CONTROL	12	639780	20SEP95	100	SS	+	0	0	1	0	0	0	
1 CONTROL	13	035362	14AUG95	96	FD	+	0	0		0			
1 CONTROL	13	105277	28AUG95	98	MS	+	0	0	1	0			
1 CONTROL	13	615884	20SEP95	100	SS	+	0	0	1	0	0	0	
1 CONTROL	14	032286	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	14	871006	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	14	036822	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	15	293826	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	15	037518	20SEP95	100	SS	+	0	0		0	0	0	
1 CONTROL	15	612020	4MAY95	81	MS	+	0	0		0			
1 CONTROL	16	827623	9MAR95	73	MS	ED							
1 CONTROL	16	037038	20SEP95	100	SS	+	0	0	1	0	0	0	
1 CONTROL	16	610576	20SEP95	100	SS	+	0	0	1	0	0	0	
1 CONTROL	17	367119	6JUN95	86	**FD**	+				0			
1 CONTROL	17	036514	20SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	17	826831	20SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	18	892268	27MAR95	76	MS	ED							
1 CONTROL	18	866801	3MAY95	81	MS	+	0	0		0			
1 CONTROL	18	893090	3MAY95	81	**MS**	+				0			
1 CONTROL	19	004068	11JAN94	13	MS	MISSING							
1 CONTROL	19	118118	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	19	375617	21SEP95	100	SS	+	1	0		0	0	0	0

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
1 CONTROL	20	009108	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	20	007040	10FEB95	70	FD	ED							
1 CONTROL	20	017308	12SEP95	100	FD	AA							
1 CONTROL	21	122327	21SEP95	100	SS	+	0	0		0			
1 CONTROL	21	121807	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	21	109801	21SEP95	100	SS	+	0	0	1	0	0	0	0
1 CONTROL	22	375562	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	22	016788	21SEP95	100	SS	+	0	0	1	0	0	0	0
1 CONTROL	22	852606	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	23	000296	14JUN95	87	MS	+	0	0		0			
1 CONTROL	23	067837	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	23	791623	21SEP95	100	SS	+	0	0	1	0	0	0	0
1 CONTROL	24	104809	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	24	775595	2FEB95	68	FD	NTS							
1 CONTROL	24	892382	21SEP95	100	SS	+	0	0	1	0	0	0	0
1 CONTROL	25	022772	28AUG95	98	MS	+	0	0		0			
1 CONTROL	25	836362	21SEP95	100	SS	+	0	0	1	0	0	0	0
1 CONTROL	126	369559	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	126	828051	21SEP95	100	SS	+	0	0	1	0	0	0	0
1 CONTROL	127	828015	21SEP95	100	SS	+	0	0		0	0	0	0
1 CONTROL	127	632372	21SEP95	100	SS	+	0	0	1	0	0	0	0
2 0.4KBRO3	26	065561	6JAN94	12	SS	+	0	0		0	0	0	

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
2 0.4KBRO3	26	374073	6JAN94	12	SS	+	0	0		0	0	0	
2 0.4KBRO3	26	022512	6JAN94	12	SS	+	0	0		0	0	0	
2 0.4KBRO3	27	020556	6JAN94	12	SS	+	0	0		0	0	0	
2 0.4KBRO3	27	773123	6JAN94	12	SS	+	0	0		0	0	0	
2 0.4KBRO3	27	786339	6JAN94	12	SS	+	0	0		0	0	0	
2 0.4KBRO3	28	007092	8APR94	26	SS	+	0	0		0	0	0	
2 0.4KBRO3	28	358027	8APR94	26	SS	+	0	0		0	0	0	
2 0.4KBRO3	28	613861	8APR94	26	SS	+	0	0		0	0	0	
2 0.4KBRO3	29	264117	8APR94	26	SS	+	0	0		0	0	0	
2 0.4KBRO3	29	625035	8APR94	26	SS	+	0	0		0	0	0	
2 0.4KBRO3	29	573619	8APR94	26	SS	+	0	0		0	0	0	
2 0.4KBRO3	30	820631	7OCT94	52	SS	+	0	0		0	0	0	
2 0.4KBRO3	30	022279	7OCT94	52	SS	+	0	0		0	0	0	
2 0.4KBRO3	30	333302	7OCT94	52	SS	+	1	0		0	0	0	
2 0.4KBRO3	31	335030	7OCT94	52	SS	+	0	0		0	0	0	
2 0.4KBRO3	31	635587	7OCT94	52	SS	+	1	0		0	0	0	
2 0.4KBRO3	31	772344	7OCT94	52	SS	+	0	0		0	0	0	
2 0.4KBRO3	32	545317	5APR95	77	SS	+	1	0		0	0	0	
2 0.4KBRO3	32	541869	5APR95	77	SS	+	1	0		1	0	1	
2 0.4KBRO3	32	569283	5APR95	77	SS	+	0	0		1	1	0	
2 0.4KBRO3	33	607029	5APR95	77	SS	+	1	0		0	0	0	
2 0.4KBRO3	33	301264	20OCT94	53	FD	ED							
2 0.4KBRO3	33	330514	5APR95	77	SS	+	1	0		1	0	1	

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
2 0.4KBRO3	34	311066	13MAR95	74	FD	NTS							
2 0.4KBRO3	34	032120	13FEB95	70	MS	ED							
2 0.4KBRO3	34	122608	5APR95	77	SS	+	0	0		1	0	0	
2 0.4KBRO3	35	028034	18JUN95	88	FD	+				1			
2 0.4KBRO3	35	365016	11AUG95	96	SS	+	1	0	0	1	0	0	0
2 0.4KBRO3	35	268566	11AUG95	96	SS	+	1	0	1	0	1	0	1
2 0.4KBRO3	36	082568	11AUG95	96	SS	+	0	0	1	0	0	0	0
2 0.4KBRO3	36	339048	4AUG95	95	FD	**AA?**				0			
2 0.4KBRO3	36	364060	11AUG95	96	SS	+	1	0	1	1	1	0	0
2 0.4KBRO3	37	638091	13APR95	78	MS	+	0	0	0	1	0	1	0
2 0.4KBRO3	37	801357	11AUG95	96	SS	+	0	0	0	1	1	0	0
2 0.4KBRO3	37	568599	2MAY95	81	FD	+				1			
2 0.4KBRO3	38	780337	11AUG95	96	SS	+	0	1	1	1	0	1	0
2 0.4KBRO3	38	031106	11AUG95	96	SS	+	0	0	1	1	0	0	0
2 0.4KBRO3	38	537769	18JUL95	92	FD	AA							
2 0.4KBRO3	39	303292	11AUG95	96	SS	+	0	0	0	1	0	1	0
2 0.4KBRO3	39	363276	11AUG95	96	SS	+	0	0	0	0	0	0	0
2 0.4KBRO3	39	300552	11AUG95	96	SS	+	1	0	1	1	1	0	1
2 0.4KBRO3	40	027070	11AUG95	96	SS	+	1	0	1	0	0	0	
2 0.4KBRO3	40	633311	25JUL95	93	FD	AA				0			
2 0.4KBRO3	40	777281	9MAY95	82	MS	+	1	0	1	0	NT	NT	
2 0.4KBRO3	41	260820	14JUN95	87	FD	AA							
2 0.4KBRO3	41	773628	6FEB95	69	FD	NTS							
2 0.4KBRO3	41	633287	11AUG95	96	SS	+	0	0	1	1	0	0	0

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
2 0.4KBRO3	42	631127	11AUG95	96	SS	+	0	0	1	1	0	0	0
2 0.4KBRO3	42	816315	7AUG95	95	FD	+				1			
2 0.4KBRO3	42	305350	11AUG95	96	SS	+	0	1		0	1	0	0
2 0.4KBRO3	43	030082	9MAR95	73	FD	ED							
2 0.4KBRO3	43	634571	2JUL95	90	FD	+				0			
2 0.4KBRO3	43	779517	11AUG95	96	SS	+	0	1	0	1	0	1	0
2 0.4KBRO3	44	549333	8JUL95	91	FD	**AA?**				0			
2 0.4KBRO3	44	033892	11AUG95	96	SS	+	0	0	0	1	0	0	0
2 0.4KBRO3	44	771532	11AUG95	96	SS	+	0	0	0	1	1	0	0
2 0.4KBRO3	45	341308	5AUG95	95	FD	+	0	0	0	1	NT	NT	1-29-98ABD/mhg
2 0.4KBRO3	45	535883	21MAY95	84	MS	+	0	0	1	1	0	0	0
2 0.4KBRO3	45	806033	13MAR95	74	FD	ED							
2 0.4KBRO3	46	296092	11AUG95	96	SS	+	1	0	0	0	0	0	0
2 0.4KBRO3	46	637527	20DEC94	62	FD	NTS							
2 0.4KBRO3	46	361264	14JUN95	87	MS	+	1	0	1	1	0	1	0
2 0.4KBRO3	47	040877	29MAY95	85	FD	+				1			
2 0.4KBRO3	47	634123	12APR95	78	FD	AA							
2 0.4KBRO3	47	024022	22JUN95	88	FD	+				1			
2 0.4KBRO3	48	805113	11AUG95	96	SS	+	0	0	0	1	0	1	0
2 0.4KBRO3	48	304094	11AUG95	96	SS	+	1	1	1	0	0	0	0
2 0.4KBRO3	48	816099	9APR95	78	FD	AA				0			
2 0.4KBRO3	49	777085	11AUG95	96	SS	+	0	0	1	0	0	0	0

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
2 0.4KBRO3	49	541077	11AUG95	96	SS	+	0	0	0	1	0	0	0
2 0.4KBRO3	49	630819	11AUG95	96	SS	+	0	0	1	1	0	0	0
2 0.4KBRO3	50	569259	11AUG95	96	SS	+	0	0	0	1	1	0	0
2 0.4KBRO3	50	627627	4AUG95	95	MS	+	0	0	1	0	0	0	0
2 0.4KBRO3	128	039606	MISSING			MISSING							
2 0.4KBRO3	128	363587	11AUG95	96	SS	+	0	0	0	1	0	0	0
2 0.4KBRO3	129	038346	23MAY95	84	MS	+	0	0	0	0	1	0	0
2 0.4KBRO3	129	632800	23MAY95	84	FD	+				1			
3 0.2KBRO3	51	627547	6JAN94	12	SS	+	0	0		0	0	0	
3 0.2KBRO3	51	829546	6JAN94	12	SS	+	0	0		0	0	0	
3 O.2KBRO3	51	630863	6JAN94	12	SS	+	0	0		0	0	0	
3 0.2KBRO3	52	807025	6JAN94	12	SS	+	0	0		0	0	0	
3 0.2KBRO3	52	038356	6JAN94	12	SS	+	0	0		0	0	0	
3 O.2KBRO3	52	631091	6JAN94	12	SS	+	0	0		0	0	0	
3 0.2KBRO3	53	821771	8APR94	26	SS	+	0	0		0	0	0	
3 0.2KBRO3	53	806005	8APR94	26	SS	+	0	0		0	0	0	
3 O.2KBRO3	53	341036	8APR94	26	SS	+	0	0		0	0	0	
3 0.2KBRO3	54	357792	8APR94	26	SS	+	0	0		0	1	0	
3 0.2KBRO3	54	801041	8APR94	26	SS	+	0	0		0	0	0	
3 O.2KBRO3	54	045073	8APR94	26	SS	+	0	0		0	0	0	
3 0.2KBRO3	55	122010	7OCT94	52	SS	+	0	0		1	0	0	
3 0.2KBRO3	55	805281	7OCT94	52	SS	+	0	0		0	0	0	
3 O.2KBRO3	55	355344	7OCT94	52	SS	+	0	0		0	0	0	

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
3 0.2KBRO3	56	363124	7OCT94	52	SS	+	0	0		0	0	0	
3 0.2KBRO3	56	364312	7OCT94	52	SS	+	0	0		0	0	0	
3 O.2KBRO3	56	055322	7OCT94	52	SS	+	0	0		0	0	0	
3 0.2KBRO3	57	121084	5APR95	77	SS	+	0	0		0	0	0	
3 0.2KBRO3	57	818827	5APR95	77	SS	+	0	0		0	0	0	
3 O.2KBRO3	57	805629	5APR95	77	SS	+	0	0		0	0	0	
3 0.2KBRO3	58	352036	5APR95	77	SS	+	0	0		0	0	0	
3 0.2KBRO3	58	082808	5APR95	77	SS	+	0	0		0	0	0	
3 O.2KBRO3	58	264846	23FEB95	71	FD	ED	0	0		0	0	0	
3 0.2KBRO3	59	301320	5APR95	77	SS	+							
3 0.2KBRO3	59	838555	18SEP95	100	SS	+	0	0	1	0	0	0	1
3 O.2KBRO3	59	303604	10JUL95	91	MS	+	0	0	0	0	0	0	
3 0.2KBRO3	60	771552	18SEP95	100	SS	+	0	0	0	0	1	0	0
3 0.2KBRO3	60	026774	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 O.2KBRO3	60	363800	18SEP95	100	SS	+	0	0	0	1	1	0	0
3 0.2KBRO3	61	548353	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 0.2KBRO3	61	605381	18SEP95	100	SS	+	0	0	0	0	0	0	0
3 O.2KBRO3	61	783785	18SEP95	100	SS	+	0	0	0	1	0	0	0
3 0.2KBRO3	62	359892	8SEP95	100	FD	+	0	1	0	0	0	0	0
3 0.2KBRO3	62	082588	15MAR95	74	FD	ED							
3 O.2KBRO3	62	352624	18SEP95	100	SS	+	0	0	0	1	0	0	0
3 0.2KBRO3	63	026090	18SEP95	100	SS	+	0	0	0	0	0	0	1
3 0.2KBRO3	63	367860	27FEB95	72	FD	ED							

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
3 O.2KBRO3	63	358024	18SEP95	100	SS	+	0	0	0	0	0	0	0
3 0.2KBRO3	64	638375	18SEP95	100	SS	+	1	0	0	0	0	0	0
3 0.2KBRO3	64	334598	21JUL95	93	FD	+				0			
3 O.2KBRO3	64	307614	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 0.2KBRO3	65	302616	4AUG95	95	FD	+	1	0	1	1			
3 0.2KBRO3	65	777605	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 O.2KBRO3	65	782037	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 0.2KBRO3	66	297028	9MAR95	73	MS	ED							
3 0.2KBRO3	66	829322	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 O.2KBRO3	66	553083	18SEP95	100	SS	+	0	0	0	0	0	0	0
3 0.2KBRO3	67	256356	18SEP95	100	SS	+	0	0	0	1	0	0	0
3 0.2KBRO3	67	029094	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 O.2KBRO3	67	300560	18SEP95	100	SS	+	0	0	0	0	0	0	0
3 0.2KBRO3	68	031802	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 0.2KBRO3	68	268014	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 O.2KBRO3	68	634891	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 0.2KBRO3	69	081576	8JUN95	86	FD	+	0	0	0	1			
3 0.2KBRO3	69	264562	3JUL95	90	MS	+	0	0	1	0	0	0	0
3 O.2KBRO3	69	822011	13APR95	78	MS	+	0	0	0	0	0	0	0
3 0.2KBRO3	70	121552	18SEP95	100	SS	+	0	0	0	0	0	0	0
3 0.2KBRO3	70	300584	1AUG95	94	MS	+	0	0	0	0	0	0	0
3 O.2KBRO3	70	367808	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 0.2KBRO3	71	030022	19MAR95	75	FD	ED							

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
3 0.2KBRO3	71	343292	4AUG95	95	FD	+	0	0	1	0	0	1	0
3 O.2KBRO3	71	126788	1AUG95	94	FD	+				0			
3 0.2KBRO3	72	362576	9MAY95	82	MS	+	0	0	1	0			
3 0.2KBRO3	72	296564	31AUG95	99	MS	+	0	0	0	1			
3 O.2KBRO3	72	804333	2JUN95	86	FD	+				0			
3 0.2KBRO3	73	630567	18SEP95	100	SS	+	0	0	0	0	0	0	0
3 0.2KBRO3	73	026594	18SEP95	100	SS	+	0	0	0	1	0	0	
3 O.2KBRO3	73	541017	23JUL95	93	FD	+				1	0	0	0
3 0.2KBRO3	74	539593	9SEP95	100	FD	AA							
3 0.2KBRO3	74	530047	26MAY95	85	FD	**AA?**				0			
3 O.2KBRO3	74	801313	18SEP95	100	SS	+	0	0	1	0	0	0	0
3 0.2KBRO3	75	029118	18SEP95	100	SS	+	0	0	0	0	0	0	0
3 0.2KBRO3	75	546293	6JUN95	86	FD	+				0	0	0	
3 0.2KBRO3	130	035794	2JUN95	86	FD	+				0			
3 0.2KBRO3	**130**	**036338**	**2JUL95**	**90**	**FD**	**+**							
3 0.2KBRO3	131	632316	4AUG95	95	FD	+	0	0	0	0	0	1	0
3 0.2KBRO3	131	034622	19FEB95	71	FD	ED							
4 0.1KBRO3	76	537001	6JAN94	12	SS	+	0	0		0	0	0	
4 0.1KBRO3	76	354856	6JAN94	12	SS	+	0	0		0	0	0	
4 0.1KBRO3	76	332330	6JAN94	12	SS	+	0	0		0	0	0	
4 0.1KBRO3	77	627023	6JAN94	12	SS	+	0	0		0	0	0	
4 0.1KBRO3	77	543861	6JAN94	12	SS	+	0	0		0	0	0	
4 0.1KBRO3	77	824838	6JAN94	12	SS	+	0	0		0	0	0	

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
4 0.1KBRO3	78	055286	8APR94	26	SS	+	0	0		0	0	0	
4 0.1KBRO3	78	125616	8APR94	26	SS	+	0	0		0	0	0	
4 0.1KBRO3	78	257016	8APR94	26	SS	+	0	0		0	0	0	
4 0.1KBRO3	79	774856	8APR94	26	SS	+	0	0		0	1	0	
4 0.1KBRO3	79	122016	8APR94	26	SS	+	0	0		0	0	0	
4 0.1KBRO3	79	878315	8APR94	26	SS	+	0	0		0	0	0	
4 0.1KBRO3	80	039620	7OCT94	52	SS	+	0	0		0	0	0	
4 0.1KBRO3	80	538557	7OCT94	52	SS	+	0	0		0	0	0	
4 0.1KBRO3	80	353324	7OCT94	52	SS	+	0	0		0	0	0	
4 0.1KBRO3	81	629335	7OCT94	52	SS	+	0	0		0	0	0	
4 0.1KBRO3	81	631551	7OCT94	52	SS	+	0	0		0	0	0	
4 0.1KBRO3	81	363004	7OCT94	52	SS	+	0	0		0	0	0	
4 0.1KBRO3	82	120072	5APR95	77	SS	+	0	0		0	0	0	
4 0.1KBRO3	82	265110	5APR95	77	SS	+	0	0		0	0	0	
4 0.1KBRO3	82	039796	5APR95	77	SS	+	0	0		0	0	0	
4 0.1KBRO3	83	635607	5APR95	77	SS	+	0	0		0	0	0	
4 0.1KBRO3	83	625607	5APR95	77	SS	+	0	0		0	0	0	
4 0.1KBRO3	83	872885	5APR95	77	SS	+	0	0		0	0	0	
4 0.1KBRO3	84	334262	18SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	84	033008	18SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	84	032060	18SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	85	827570	18SEP95	100	SS	+	0	1	0	0	0	0	0
4 0.1KBRO3	85	546853	18SEP95	100	SS	+	0	0	1	0	1	0	0

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
4 0.1KBRO3	85	631815	8JUN95	86	FD	AA							
4 0.1KBRO3	86	626623	7AUG95	95	MS	+	0	0	1	0	0	0	0
4 0.1KBRO3	86	045361	18SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	86	257512	4AUG95	95	MS	+	0	0	0	0	0	0	0
4 0.1KBRO3	87	806629	18SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	87	770844	18SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	87	634547	18SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	88	807121	9APR95	78	MS	+	0	0	0	0			
4 0.1KBRO3	88	633003	18SEP95	100	SS	+	0	1	0	0	0	0	0
4 0.1KBRO3	88	297256	20AUG95	97	FD	AA							
4 0.1KBRO3	89	818543	18SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	89	637319	18SEP95	100	SS	+	1	0	0	0	0	0	0
4 0.1KBRO3	89	358884	18SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	90	**805841**	24AUG95	97	FD	+	0	0	1				
4 0.1KBRO3	90	333266	19SEP95	100	SS	+	1	0	0	0	0	0	0
4 0.1KBRO3	90	258620	19SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	91	258572	24AUG95	97	FD	+	0	0	0	0	0	0	0
4 0.1KBRO3	91	357024	19SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	91	540837	01SEP95	99	FD	AA							
4 0.1KBRO3	92	367636	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	92	303352	19SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	92	636851	9MAY95	82	MS	+	0	0	0	0			
4 0.1KBRO3	93	626007	7APR94	25	MS	ED							

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
4 0.1KBRO3	93	044853	27OCT94	54	MS	ED							
4 0.1KBRO3	93	355884	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	94	334770	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	94	299080	19SEP95	100	SS	+	0	0	0	0	0	0	
4 0.1KBRO3	94	352804	2JUN95	86	FD	AA				0			
4 0.1KBRO3	95	805077	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	95	780853	19SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	95	771104	19SEP95	100	SS	+	0	0	1	0	0	0	0
4 0.1KBRO3	96	570007	19SEP95	100	SS	+	1	0	0	0	0	0	0
4 0.1KBRO3	96	551533	19SEP95	100	SS	+	1	0	1	1	0	0	0
4 0.1KBRO3	96	120118	13SEP95	100	FD	+	0	0	0	0	0	0	1
4 0.1KBRO3	97	830310	04SEP95	99	FD	+	0	0	0	1	0	0	0
4 0.1KBRO3	97	624811	19SEP95	100	SS	+	0	0	0	1	0	0	0
4 0.1KBRO3	97	536085	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	98	635815	19SEP95	100	SS	+	0	0	0	1	0	0	1
4 0.1KBRO3	98	125884	30AUG95	98	MS	+	0	0	0	0			
4 0.1KBRO3	98	017083	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	99	606261	22JUN95	88	MS	+	0	0	0	0	0	0	0
4 0.1KBRO3	99	055098	19SEP95	100	SS	+	0	0	1	1	0	0	0
4 0.1KBRO3	99	541797	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	100	579335	3JUL95	90	MS	+	0	0	0	0	0	0	0
4 0.1KBRO3	100	361864	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	132	611892	14SEP95	100	FD	+	0	0	0	0			

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
4 0.1KBRO3	132	369851	27APR95	80	FD	+				0			
4 0.1KBRO3	133	375095	19SEP95	100	SS	+	0	0	0	0	0	0	0
4 0.1KBRO3	133	636024	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	101	311338	6JAN94	12	SS	+	0	0		0	0	0	
5 0.02KBRO3	101	570319	6JAN94	12	SS	+	0	0		0	0	0	
5 0.02KBRO3	101	781069	6JAN94	12	SS	+	0	0		0	0	0	
5 0.02KBRO3	102	366800	6JAN94	12	SS	+	0	0		0	0	0	
5 0.02KBRO3	102	120876	6JAN94	12	SS	+	0	0		0	0	0	
5 0.02KBRO3	102	304842	6JAN94	12	SS	+	0	0		0	0	0	
5 0.02KBRO3	103	121350	8APR94	26	SS	+	0	0		0	0	0	
5 0.02KBRO3	103	777537	8APR94	26	SS	+	0	0		0	0	0	
5 0.02KBRO3	103	054774	8APR94	26	SS	+	0	0		0	0	0	
5 0.02KBRO3	104	340632	8APR94	26	SS	+	0	0		0	0	0	
5 0.02KBRO3	104	296624	8APR94	26	SS	+	0	0		0	0	0	
5 0.02KBRO3	104	875043	8APR94	26	SS	+	0	0		0	0	0	
5 0.02KBRO3	105	364544	7OCT94	52	SS	+	0	0		0	0	0	
5 0.02KBRO3	105	036064	7OCT94	52	SS	+	0	0		0	0	0	
5 0.02KBRO3	105	831034	7OCT94	52	SS	+	0	0		0	0	0	
5 0.02KBRO3	106	264858	7OCT94	52	SS	+	0	0		0	0	0	
5 0.02KBRO3	106	537829	7OCT94	52	SS	+	0	0		0	0	0	
5 0.02KBRO3	106	540109	7OCT94	52	SS	+	0	0		0	0	0	
5 0.02KBRO3	107	301288	5APR95	77	SS	+	0	0		0	0	0	
5 0.02KBRO3	107	606517	5APR95	77	SS	+	0	0		0	0	0	

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
5 0.02KBRO3	107	329278	5APR95	77	SS	+	0	0		0	0	0	
5 0.02KBRO3	108	354772	5APR95	77	SS	+	0	0		0	0	0	
5 0.02KBRO3	108	551017	5APR95	77	SS	+	0	0		0	0	0	
5 0.02KBRO3	108	818895	5APR95	77	SS	+	0	0		0	0	0	
5 0.02KBRO3	109	328002	11JUN95	87	FD	AA				0			
5 0.02KBRO3	109	016583	1AUG95	94	MS	+				0			
5 0.02KBRO3	109	034348	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	110	589331	19SEP95	100	SS	+	0	0	0	0	0	1	0
5 0.02KBRO3	110	034844	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	110	298352	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	111	824890	18SEP95	100	FD	AA	0	0	0	0	0	0	
5 0.02KBRO3	111	121536	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	111	**530330**	26MAY95	84	FD	+				0			
5 0.02KBRO3	112	630887	19SEP95	100	SS	+	0	0	1	0	1	0	0
5 0.02KBRO3	112	081616	19SEP95	100	SS	+	0	0	0	1	0	0	0
5 0.02KBRO3	112	263832	6AUG95	95	FD	+	0	0	0	0			
5 0.02KBRO3	113	360580	11JUL95	91	FD	+				0			
5 0.02KBRO3	113	639627	19SEP95	100	SS	+	0	0	0	0	0	1	0
5 0.02KBRO3	113	043889	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	114	337032	25AUG95	97	FD	AA							
5 0.02KBRO3	114	549069	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	114	018315	3JAN95	64	MS	**ED**							
5 0.02KBRO3	115	307062	19SEP95	100	SS	+	0	0	0	0	0	0	0

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
5 0.02KBRO3	115	780773	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	115	636023	19SEP95	100	SS	+	0	0	1	0	0	0	0
5 0.02KBRO3	116	364616	19SEP95	100	SS	+	0	0	1	0	0	0	0
5 0.02KBRO3	116	777869	19SEP95	100	SS	+	0	0	0	0			
5 0.02KBRO3	116	335521	19SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	117	310082	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	117	353336	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	117	366892	20SEP95	100	SS	+	0	0	1	0	0	0	0
5 0.02KBRO3	118	638035	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	118	550081	20SEP95	100	SS	+	0	0	0	1	0	0	0
5 0.02KBRO3	118	629615	29JUN95	89	FD	+				0			
5 0.02KBRO3	119	049334	11JUL95	91	FD	+				1			
5 0.02KBRO3	119	803057	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	119	536777	20SEP95	100	SS	+	0	0	1	0	0	0	0
5 0.02KBRO3	120	539609	17AUG95	96	MS	+	0	0	0	0			
5 0.02KBRO3	120	028298	11JUN95	87	FD	+				1			
5 0.02KBRO3	120	816519	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	121	632295	20SEP95	100	SS	+	0	0	1	0	0	0	1
5 0.02KBRO3	121	352568	20SEP95	100	SS	+	0	0	1	0	0	0	0
5 0.02KBRO3	121	001552	10APR95	78	MS	+	0	0	0	0	0	0	0
5 0.02KBRO3	122	300084	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	122	807789	20SEP95	100	SS	+	0	0	1	0	0	0	0
5 0.02KBRO3	**122**	**540877**	**20SEP95**	**100**	**SS**	**+**	0	0	0		0	0	0

GROUP	CAGE	ANIMAL NO.	DAY OF DEATH	WEEKS	CAUSE OF DEATH	Pathology +Yes/No	Kidney Adenoma	Kidney Carcinoma	Kidney HyP	Mesoth	Thyroid Adenoma	Thyroid Carcinoma	Thyroid HYP
5 0.02KBRO3	123	875027	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	123	625367	20SEP95	100	SS	+	0	0	1	0	0	0	0
5 0.02KBRO3	123	779117	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	124	538121	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	124	600109	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	124	333334	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	125	541593	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	125	545269	12AUG94	44	MS	ED							
5 0.02KBRO3	134	826267	20SEP95	100	SS	+	0	0	0	0	0	0	0
5 0.02KBRO3	134	368555	28MAR95	76	FD	ED							
5 0.02KBRO3	135	033378	20SEP95	100	SS	+	1	0	0	0	1	0	0
5 0.02KBRO3	135	119841	20SEP95	100	SS	+	0	0	0	0	0	0	0

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Acknowledgement

OEHHA thanks Dr. Edmund Crouch for providing us with an Excel spreadsheet containing a Visual Basic macro and likelihood function to model the probability of tumor using the multistage-in-dose Weibull-in-time model.