Screening Assessment for the Challenge

Bromic acid, potassium salt
(Potassium bromate)

Chemical Abstracts Service Registry Number
7758-01-2

Environment Canada
Health Canada

September 2010

Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of potassium bromate, Chemical Abstracts Service Registry Number 7758-01-2. The substance potassium bromate was indentified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Potassium bromate was identified as a high priority as it was considered to pose intermediate potential for exposure (IPE) of individuals in Canada and is classified by other agencies on the basis of carcinogenicity. This substance met the ecological categorization criteria for persistence and inherent toxicity to aquatic organisms, but not for bioaccumulation potential.

According to information submitted in response to a survey published under section 71 of CEPA 1999, less than 1000 kg of potassium bromate was imported into Canada in 2006. No Canadian companies reported manufacturing potassium bromate in 2006 and it was not reported to be released into the environment in 2006. In Canada, potassium bromate is used in primarily industrial and non consumer applications.

Based on available information from various sources and results from the aforementioned survey, exposure to the general population to potassium bromate in environmental media (e.g., drinking water) and in consumer products is considered to be negligible.

As potassium bromate was classified on the basis of carcinogenicity by international regulatory agencies, carcinogenicity was a key focus for this screening assessment. Kidney tumours, mesotheliomas (testes and peritoneal), and thyroid tumours were all observed after administration of potassium bromate in drinking water. No evidence was available to suggest a carcinogenic potential for potassium bromate via the inhalation or dermal routes. Data from a wide range of genotoxicity studies suggests that potassium bromate is genotoxic *in vitro* and *in vivo*. Although the mode of induction of tumours has not been fully elucidated, based on the genotoxicity of potassium bromate, it cannot be precluded that potassium bromate induces tumours via a mode of action involving direct interaction with genetic material.

Exposure to potassium bromate has also been associated with a variety of non-cancer effects in experimental animals. These include reproductive and immunological effects, as well as non -neoplastic effects in the kidney, thyroid, testes, and pituitary gland. Since exposure to potassium bromate is expected to be negligible and the most sensitive non-cancer effects occurred at a dose level at which pre-neoplastic lesions and tumours were also observed, margins of exposures were not calculated for non-cancer effects.

On the basis of the carcinogenic potential of potassium bromate, for which there may be a probability of harm at any exposure level, it is concluded that potassium bromate is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based on the information available (relatively low quantity in commerce, moderate aquatic toxicity), it is concluded that potassium bromate is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. Potassium bromate meets criteria for persistence in water but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Based on the information available, it is concluded that potassium bromate meets one or more of the criteria set out in section 64 of the *Canadian Environmental Protection Act, 1999*.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce in Canada; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance bromic acid, potassium salt (potassium bromate) was identified as a high priority for assessment of human health risk because it was considered to present IPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for this substance was published in the *Canada Gazette* on March 14, 2009 (Canada 2009). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although potassium bromate was determined to be a high priority for assessment with respect to human health it also met the ecological categorization criteria for persistence and inherent toxicity. This assessment therefore focuses on information relevant to both human health and the environment.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999. Screening assessments examine

scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution[1].

This final screening assessment includes consideration of information on substance properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents and stakeholder research reports and from recent literature searches, up to October 2009 for the exposure and health effects sections and November 2009 for the ecological sections. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of (non-occupational) exposure of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The final screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the proposed conclusion is based.

This final screening assessment was prepared by staff in the existing substances programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Dr. Bernard Gadagbui (TERA), Dr. Pam Williams (E Risk Sciences) and Dr. Harlee Strauss (Strauss Associates). Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada.

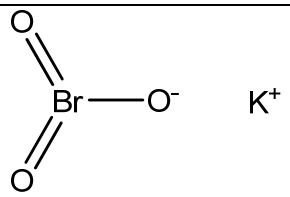
The critical information and considerations upon which the final assessment is based on are summarized below.

[1] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge Batches 1-12 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Controlled Products Regulations*, which is part of regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use

Substance Identity

For the purposes of this document, this substance will be referred to as potassium bromate. Information on the identity of potassium bromate is summarized in Table 1.

Table 1. Substance identity

CAS RN	7758-01-2
DSL name	Bromic acid, potassium salt
NCI names	Bromic acid, potassium salt (1:1) (TSCA) Bromic acid, potassium salt (AICS, ASIA-PAC, NZIoC, PICCS, SWISS) Potassium bromate (ECL, EINECS, ENCS, PICCS)
Other names	UN 1484; UN 1484 (DOT)
Chemical group (DSL stream)	Inorganics
Major chemical class or use	Inorganic salts
Major chemical subclass	Bromate-containing salts
Chemical formula	$KBrO_3$
Chemical structure	
SMILES	Not applicable
Molecular mass	167 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DOT, US Department of Transport; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; NZIoC, New Zealand Inventory of Chemicals; PICCS, Philippine Inventory of Chemicals and Chemical Substances; SMILES, simplified molecular input line entry specification; SWISS, Swiss Giftliste 1 and Inventory of Notified New Substances; TSCA, *Toxic Substances Control Act* Chemical Substance Inventory.
Source: NCI 2007

Physical and Chemical Properties

Table 2 contains experimental and calculated physical and chemical properties of potassium bromate that are relevant to its environmental fate. Quantitative structure–activity relationship (QSAR) model results are not generated for most inorganic compounds, including the present substance, because inorganic compounds fall outside of most QSAR application domains and their structures are not compatible with the estimation methods of these models. Therefore, Table 2 does not include any QSAR-based estimates, and the substance's SMILES sequence is not reported. All of the numerical values in Table 2 have been obtained from internationally recognized and credible sources (i.e., chemistry handbooks, peer-reviewed databases).

Table 2. Physical and chemical properties of potassium bromate

Property	Type	Value[1]	Temperature (°C)	Reference
Melting point (ºC)	Experimental	350	–	Clayton and Clayton 1993–1994
Boiling point (ºC)	Experimental	370 (decomposes)	–	Budavari 1996
Density (kg/m^3)	Experimental	3340 (3.34 g/cm^3)	Not indicated	Clayton and Clayton 1993–1994
Vapour pressure (Pa)	Professional judgement	Negligible	–	Neely and Blau 1985
Henry's Law constant (Pa·m^3/mol)	Professional judgement	Negligible	–	–
Log K_{ow} (dimensionless)	–	Not applicable	–	–
Log K_{oc} (dimensionless)	–	Not applicable	–	–
Water solubility (mg/L)	Experimental	1.33×10^5	20	Lide 1997–1998
	Experimental	6.9×10^4 (6.9 g/100 g)	20	HSDB 2009
	Experimental	7.53×10^4 (7.53 g/100 g)	25	HSDB 2009
	Experimental	3.1×10^4 (3.1 g/100 g)	0	HSDB 2009
pK_a (dimensionless)	–	Not applicable	–	–

Abbreviations: K_{oc}, organic carbon–water partition coefficient; K_{ow}, octanol–water partition coefficient; pK_a, acid dissociation constant.

[1] Values in parentheses represent the original ones as reported by the authors or as estimated by the models.

Sources

No natural sources of potassium bromate have been identified.

The Bromate (BrO_3^-) moiety also has not been reported to occur naturally in surface waters (Butler et al. 2005a). However, there is some evidence for the natural formation of bromate in certain environmental compartments. Hara et al. (2002), for example, detected the ion in bromine-rich particulate matter (sea salt sprays) in Arctic air and remote from anthropogenic sources of bromate. Hara et al. (2002) proposed that bromate is naturally synthesized via a gaseous production pathway involving oxy-brominated precursors and ozone, as per the following reactions:

$$2\ BrO + H_2O \rightarrow BrO^- + BrO_2^- + 2\ H^+ \quad [1]$$

$$BrO_2^- + O_3 \rightarrow BrO_3^- \quad [2]$$

Additionally, the bromate moiety may be formed in drinking water that has been treated with ozone or sodium hypochlorite for disinfection purposes (Health Canada 1999; IARC 1999; US EPA 2001a; Weinberg et al. 2003; WHO 2005). This formation occurs through the oxidation of bromide present in raw waters to bromate after treatment with ozone (see equations 3–5) (Krasner et al. 1993a, b; Bonacquisti 2006). Bromate may be present in drinking water that has been treated with sodium hypochlorite solution. This would occur because the bromate ion may be present in the sodium hypochlorite as a result of manufacturing and/or the conditions under which it is transported and stored (Asami et al 2009, Water Research Foundation, 2009).

$$O_3 + Br^- \rightarrow O_2 + OBr^- \quad [3]$$

$$O_3 + OBr^- \rightarrow 2O_2 + Br^- \quad [4]$$

$$2O_3 + OBr^- \rightarrow 2O_2 + BrO_3^- \quad [5]$$

Formation of bromate ion depends on oxidation of bromide present in some water sources when treated with ozone (a relatively uncommon method). Furthermore bromate contamination of hypochlorite stock solutions varies according to the source of the hypochlorite chemical feedstocks (Weinberg et al 2003).

Based on information submitted in response to a notice published under section 71 of CEPA 1999, <1000 kg of potassium bromate was imported into Canada in 2006; no manufacturing or usage of potassium bromate was reported in that year (Environment Canada 2009a).

Uses

Two of three uses of potassium bromate reported under section 71 of CEPA 1999 have been requested to be treated as confidential business information; however, these uses have predominantly industrial and commercial applications (Environment Canada 2009a), and are addressed in this assessment.

Potassium bromate used to be a permitted food additive in Canada, but it was delisted in 1994 and therefore is no longer permitted to be used as a food additive in foods offered for sale in Canada (2009 and 2010 personal communications from Food Directorate, Health Canada; unreferenced). It is, however, present as an impurity in a processing aid for paper food packaging (2009 personal communication from Food Directorate, Health Canada; unreferenced).

One company reported using potassium bromate as an oxidizer in flour milling; however, it also reported that all of the end product was exported to the United States (Environment Canada 2009a). The US Code of Federal Regulations permits potassium bromate to be used in various flours (US FDA 2009a, b) and in the malting of barley (US FDA 2009c).

Potassium bromate is not listed in the Drug Products Database, the Therapeutic Products Directorate's internal Non-Medicinal Ingredients Database, the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database as a medicinal or non-medicinal ingredient present in pharmaceuticals and natural health products and it is not used in veterinary drugs (DPD 2010, NHPID 2010, LNHPD 2010, 2009 personal communications from Therapeutic Products Directorate and Veterinary Drugs Directorate, Health Canada; unreferenced).

Potassium bromate has been used as an oxidizing reagent in laboratories and in the dyeing of textiles (sulphur dyes). The cosmetics industry has also used it as an oxidizer or neutralizer in permanent wave neutralizing solutions (IARC 1999; WHO 2005; HSDB 2009).

Releases to the Environment

No environmental releases of potassium bromate in 2006 were reported under section 71 of CEPA 1999 (Environment Canada 2009a). Environmental releases reported under the National Pollutant Release Inventory (NPRI) indicated that 21 kg of potassium bromate was released into air in 2007; however, no environmental releases were reported during the years 1994–2006 and for 2008 as well. In addition, the substance has not been reported to be released to water (NPRI 2009). In addition to environmental releases, information submitted under section 71 of CEPA 1999 revealed that less than 10 kg of potassium bromate was transferred to off-site waste management facilities (Environment Canada 2009a).

In 2006, the US Toxics Release Inventory (TRI) reported that 257 and 891 pounds of potassium bromate were released to air and transported to off-site disposal facilities, respectively. Additionally, between 1995 and 2005, 5 – 255 pounds of potassium bromate was released mainly to air, with the remainder being disposed of in landfills (TRI 2009).

Environmental Fate

Potassium bromate can be assumed to have a negligible vapour pressure, and it is therefore not expected to partition to air (Neely and Blau 1985). However, bromate may be associated with aerosols (Hara et al. 2002). Similar to many inorganic salts, potassium bromate is highly soluble in water and dissociates rapidly (primarily ionic bonds) to release the bromate ion, which is the moiety of interest in the ecological component of this assessment. As typified by many inorganic ions found primarily in anionic form in water (Garrett 2004), the bromate oxyanion is expected to have a high geochemical mobility in oxic waters (i.e., pH between 5 and 9; redox potential [E_h] between 0.5 and 1 V). As a possible consequence of this expected behaviour, there is a lack of impetus for researchers to study the speciation and bioavailability of bromate in solution. No studies have been found on interactions between bromate and colloidal organic matter, for example. However, available thermodynamic stability constants for bromate–inorganic ligand complexes suggest that this anion would be weakly complexed in natural waters (Smith and Martell 2004). The Windermere Humic Aqueous Model (WHAM 2001; Tipping 2002) was used to model the chemical speciation of bromate in 10% Lake Ontario water (diluted with deionized water), representing a very diluted Canadian surface water. The inorganic complexation of this ion was found to be negligible (<<1%). Appendix 1 provides the description of water type as well as details of the modelling with WHAM VI. Seawater and more mineralized waters are expected to also weakly complex bromate because of the tendency of chemical stability constants to decrease with increasing ionic strength (Smith and Martell 2004).

Considering its mobility in water, relatively little bromate is expected to partition to sediments and soils. Bromate ions found in sediments and soils are expected to be mobile in these compartments. For example, Butler et al. (2005a) reported a case in the United Kingdom of groundwater contamination by bromate in a chalk aquifer following an industrial spillage, indicating that bromate can, under some circumstances, pass through soil into groundwater.

Natural bromate reduction may occur in waters with low oxygen concentrations, according to the following reaction:

$$6\ CH_2O + 4\ BrO_3^- \rightarrow 6\ H_2O + 6\ CO_2 + 4\ Br^- \qquad [6]$$

Butler et al. (2005a) indicated that the rate of reduction may be slow, according to studies on these processes performed in laboratories.

Persistence and Bioaccumulation Potential

Environmental Persistence

Butler et al. (2005a) indicated that bromate is persistent in water even if this ion is thermodynamically unstable (e.g., Takeno 2005) and subject to slow biological reduction under natural conditions. In aqueous solution, bromate is highly stable at room temperature, does not volatilize and is not removed by boiling (Butler et al. 2005a). Furthermore, Grguric et al. (1994) observed that concentrations of the ion in a sample of salt water left in total darkness did not show any statistically significant change (±2%) over a period of more than 2 years.

A number of studies have demonstrated that bromate can be reduced to bromide in soil, using enriched microbial communities and an appropriate carbon source (Rodgers 1980; Butler et al. 2005b). Furthermore, Rodgers (1980) observed 60% to nearly 100% conversion of BrO_3^- to Br^- following 14-day incubation, at 25°C, of aerobic and anaerobic soils, both amended and unamended with glucose. These results suggest that natural attenuation of bromate in soil is possible.

Anaerobic degradation of bromate in sediment at depths at which anoxic conditions persist is theoretically possible (see equation 6 above), but no data relating to the rate of bromate reduction in sediments have been identified. However, the presence of bromate in deep sediments is not expected to present a high degree of exposure potential to most aquatic organisms and therefore is not likely to present an ecological concern.

Based on the lines of evidence provided by the above-described literature, potassium bromate is considered to meet the persistence criterion in water (half-life in water ≥182 days) but does not meet the criteria for air, soil or sediment (half-life in air ≥2 days, half-life in soil ≥182 days and half-life in sediment ≥365 days) as set out in the *Persistence and Bioaccumulation Regulations* of CEPA 1999 (Canada 2000).

Potential for Bioaccumulation

No studies were found with regards to the bioaccumulation potential (bioconcentration factor [BCF], bioaccumulation factor [BAF]) of bromate in plants and animals. However, toxicokinetic studies conducted in the laboratory strongly suggest that sulphydryl-containing compounds such as glutathione (GSH) contribute to the reduction of bromate to bromide in body tissues of mammals. Bromide (along with residual bromate) is subsequently excreted via urine and feces (Kurokawa et al. 1990; IPCS 2000; US EPA 2001a). Because GSH is also part of the cellular defence mechanism in aquatic animals (Di Giulio et al. 1995), it is anticipated that the physiological pathway described for mammals also operates in aquatic animals. This GSH-based pathway should generally result in low net accumulation of bromate and its metabolite Br^- in animal tissues. This conclusion is consistent with that of Hutchinson et al. (1997), who concluded that it is unlikely that bromate has the potential to accumulate significantly in aquatic species. It is noted that, at present, the element bromine has no known essential function in animals or

plants (Markert 1994) and that the bromide ion has a low to moderate potential for aquatic toxicity with short-term LC_{50}s greater than 30 mg/L (PAN Pesticide Database c2000-2010).

Considering published information and experimental evidence for metabolic transformation, potassium bromate does not meet the bioaccumulation criteria (BAF, BCF ≥5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

The approach taken in this assessment was to examine the available scientific information and develop conclusions based on a weight of evidence approach and using precaution as required under CEPA 1999. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on the persistence, bioaccumulation, toxicity, sources and fate of the substance.

Since potassium bromate is expected to be mainly discharged to freshwater systems (see exposure scenario below), effects on sensitive freshwater organisms were considered the critical endpoints. Given its persistence in water, chronic effects were of particular interest.

Ecotoxicological data of bromate toxicity to aquatic biota are available for a range of aquatic organisms including freshwater algae, invertebrates, fish and estuarine and marine crustaceans and bivalves. Hutchinson et al. (1997) summarized the results from seven studies which indicate that the median effective(lethal) concentrations ($E(L)C_{50}$ values) spanned over 4 orders of magnitude. The lowest reported values, ranging from 0.05 to - 100 mg/L in a 48-hour EC_{50} embryo study on the oyster, (*Crassostrea gigas*) were markedly lower than $E(L)C_{50}$ values obtained with the other species, which ranged from 31 to 100 mg/L bromate. In an attempt to reproduce the findings of the oyster study, Hutchinson et al. (1997) repeated twice the embryo development test using a similar protocol but was unable to reproduce the results and instead obtained a 24-hour EC_{50} of 170 mg/L as bromate for this endpoint. Given the lack of reproducibility of the test, the next most sensitive results were considered.

The National Water Research Institute (NWRI) of Environment Canada in Burlington, Ontario, performed a suite of acute toxicity tests on metallic and non-metallic elements using *Hyalella azteca* (Environment Canada 2007). The objective of this experiment was to compare the relative toxicity of a number of inorganic ions in a reasonable worst-case situation using water chemistry representative of the diluted waters of the Canadian Shield (10% Lake Ontario water with low ionic strength and low dissolved organic carbon). Exposure lasted 7 days, and temperature was maintained between 24°C and 25ºC. A 7-day LC_{50} of 1.093 mg/L was estimated for bromate based on nominal concentrations. Because bromate is stable in water, nominal concentrations can be considered a good estimate of exposure concentration. This study was determined to have

a high degree of reliability (see robust study summary in Appendix 2) and is therefore considered a key line of evidence.

These toxicity data indicate that potassium bromate generally has only a low to moderate potential for toxicity to aquatic organisms; however, it may be highly hazardous to some sensitive organisms (e.g., *Hyalella azteca*).

Due to requests for confidentiality, the quantity used at specific sites cannot be revealed (Environment Canada 2009a). The upper limit of the range of the quantity of potassium bromate imported in Canada, 1000 kg or 770 kg of bromate ion (the entity of concern), is therefore conservatively assumed to be used entirely at one industrial site. A generic scenario was used to estimate a conservative concentration of bromate ion resulting from this industrial discharge of 770 kg of bromate ion using Environment Canada's Industrial Generic Exposure Tool – Aquatic (IGETA: Environment Canada 2009b). The scenario assumed that 5 % of the mass of bromate is lost to wastewater over the course of a year, that there was no removal in a wastewater treatment plant and that the effluent is discharged to a small river flowing at a rate of 0.36 m^3/s. This yielded a predicted environmental concentration (PEC) of 4.5×10^{-3} mg/L (Environment Canada 2009c)..

A predicted no-effect concentration (PNEC) was derived from the lowest acceptable toxicity value identified for a freshwater organism—an acute LC_{50} for *Hyalella azteca* of 1.093 mg/L. This value was selected as the critical toxicity value (CTV) and divided by an assessment factor of 100 to account for uncertainties associated with extrapolation from a laboratory LC_{50} to a chronic no-effect value in the field and for inter-species and intra-species variablity. This calculation resulted in a PNEC of 0.011 mg/L.

The resulting highly conservative risk quotient (PEC/PNEC) of 4.1×10^{-1} indicates that exposure concentrations are unlikely to be high enough to cause harm to aquatic organisms. Significant exposure of organisms at other types of locations or in media other than water is considered to be unlikely. Soils and sediment would not be significant media of exposure based on uses and releases and the predicted partitioning behaviour of bromate.

Potassium bromate is thus unlikely to be causing ecological harm in Canada.

This conclusion was reached despite the conservative assumptions made in response to uncertainties encountered in the assessment. A key uncertainty relates to the lack of empirical data on environmental concentrations in Canada, which was addressed by predicting a conservative concentration in water using an industrial exposure scenario. There is also uncertainty associated with the PNEC, but there are a fair number of empirical data available (including algae, invertebrates and fish), and the *Hyalella* LC_{50} value that was selected as the CTV, is about 30 times lower than the next lowest acute value reported by Hutchinson et al. (1997). Therefore, this uncertainty was addressed by dividing the CTV by an assessment factor of 100, to account for uncertainties associated with inter- and intra-species variability and extrapolation from a laboratory LC_{50} to a chronic no-effect value in the field.

Potential to Cause Harm to Human Health in Canada

Exposure Assessment

Environmental Media and Food

Environmental concentrations of potassium bromate and the bromate ion are limited in scope, as no empirical data on their presence in air or soil are available. As potassium bromate is a salt with a relatively high melting point and negligible volatility, it is expected that exposure to the substance through air will be negligible. Additionally, as a consequence of its strong oxidizing capabilities, potassium bromate is expected to be reduced to bromide if released to soil (Butler et al. 2005a; WHO 2005). Therefore, intake estimates from these two sources were not calculated. Finally, as a salt with the ability to dissolve in water (water solubility 1.33×10^5 mg/L), potassium bromate is expected to dissociate readily into its component ions if released to water.

As stated in the section on sources, bromate ion may be present in drinking water treated with disinfection agents. However, the source of this bromate is naturally present bromide, not potassium bromate (see equations 3–5 in the sources section). Health Canada's *Guidelines for Canadian Drinking Water Quality* set a maximum acceptable concentration of 10 µg/L for bromate in drinking water (Health Canada 1998), although bromate has been detected above this limit in bottled drinking waters (Dabeka et al. 2002). Since bromate is not expected to be naturally present in water (Butler et al. 2005a), its presence in untreated waters would likely come from the environmental release of bromate salts. The presence of bromate, presumably from industrial releases, has been reported in 4 of 36 river samples in the Netherlands (range: 4–8 µg/L; Versteegh et al. 1993) and in contaminated groundwater near a chemical production plant in the United Kingdom (>2 mg/L; Butler et al. 2005a).

As mentioned in the section on releases to the environment, small quantities of potassium bromate are being released to the environment in Canada (Environment Canada 2009a; NPRI 2009). Additionally, data from the US Toxics Release Inventory indicate that this substance is also being released in small quantities in the United States (TRI 2009).

Estimates of daily intake from drinking water were calculated using Health Canada's maximum acceptable concentration (10 µg/L) for bromate. Maximum daily intake for all age groups including infants was estimated to be < 0.0011 mg/kg/day.

As of 1994, potassium bromate is no longer permitted to be used as a food additive in foods offered for sale in Canada (2009 and 2010 personal communications from Food Directorate, Health Canada; unreferenced). One company reported using potassium bromate as an oxidizing agent in flour milling; however, it also indicated that the entire final product is exported to the United States (Environment Canada 2009a). Additionally, its possible presence in food packaging materials will not lead to exposure, as the food packaging is coated with either a plastic or wax, and so no contact with food would be

expected (2009 personal communication from Food Directorate, Health Canada; unreferenced). As a result of the aforementioned considerations, the potential for exposure from food is expected to be negligible, and intake from this source was not calculated.

In light of its physical and chemical properties, the small quantities of environmental releases and the delisting of potassium bromate as a food additive, human exposure to potassium bromate from environmental media and food is expected to be negligible.

Consumer Products

Two out of three uses for potassium bromate reported under section 71 of CEPA 1999 are confidential. However, the reported uses of these products are predominately industrial and commercial.

Potassium bromate has been used as an oxidizer or neutralizer in permanent wave neutralizing solutions (hair product) and is currently listed on the Cosmetic Ingredient Hotlist as a restricted ingredient (Health Canada 2007). No companies reporting under section 71 of CEPA 1999 reported manufacturing or importing potassium bromate in these products in Canada (Environment Canada 2009a). There were no reports of potassium bromate use in personal care products in Health Canada's cosmetic notification system (CNS 2009). Furthermore, potassium bromate was not identified as an ingredient in products listed in the Household Products Database (HPD 2005).

Based upon information identified from various sources, there is high confidence that exposure to potassium bromate from use of consumer products is negligible.

Confidence in the exposure characterization for environmental media and food and consumer products is considered to be moderate. There is uncertainty due to limited information available with respect to the concentrations of potassium bromate in environmental media. However, based on the use patterns and limited amounts of releases, exposure to potassium bromate from environmental media and food would be expected to be negligible.

Health Effects Assessment

An overview of the toxicological database for potassium bromate is presented in Appendix 3. Since the toxicological effects are mediated primarily through the bromate ion, this assessment will incorporate data from the two major bromate salts (potassium bromate and sodium bromate).

On the basis of investigations in experimental animals, potassium bromate has been classified by the International Agency for Research on Cancer (IARC 1999) as "possibly carcinogenic to humans, based on inadequate evidence in humans and sufficient evidence in experimental animals" (Group 2B), while also being classified by the European Union

(EU) as a Category 2 carcinogen, "May cause cancer" (ESIS 2008). Similarly, Health Canada classified the bromate moiety as "probably carcinogenic to humans, based on sufficient evidence in animals and no data in humans" (Health Canada 1999). The US Environmental Protection Agency (EPA) also classified the bromate moiety as a "probable human carcinogen based on no evidence in humans, but adequate evidence of carcinogenicity in male and female rats" (Group B2 carcinogen) under previous guidelines and as a "likely human carcinogen by the oral route of exposure, insufficient data for evaluation by the inhalation route" under current guidelines (US EPA 2001a, b). Recently, the World Health Organization (WHO) evaluated the bromate moiety under the WHO Guidelines for Drinking-water Quality and stated that "the weight of evidence from rat bioassays clearly indicates that bromate has the potential to be a human carcinogen" (WHO 2005). Recently, the California EPA published a draft *Public Health Goal for Bromate in Drinking Water* document (Cal-EPA 2009).

Multiple long-term bioassays have examined the effect of potassium bromate administered in drinking water on rodents. Administration of potassium bromate has induced renal cell tumours, thyroid follicular carcinomas and mesotheliomas, predominantly in rats. Renal cell tumours were observed in male mice and male Syrian hamsters; however, these effects were not as severe as those reported in rats.

Male and female F344 rats were administered potassium bromate at doses of 0, 250 or 500 mg/L in drinking water (equivalent to approximately 0, 9.6 and 21.2 mg kg-bw per day as bromate for males and 0, 9.6 and 19.5 mg/kg-bw per day as bromate for females) for 110 weeks. Percent survival and body weight gain were decreased in males, but not in females. Significantly increased incidences of renal cell tumours (adenomas and adenocarcinomas) were observed in all treated groups in both sexes. Male rats also showed significantly increased incidences of peritoneal mesotheliomas (Kurokawa et al. 1982, 1983a).

In a subsequent study, male F344 rats were administered potassium bromate at 0, 15, 30, 60, 125, 250 or 500 mg/L (equivalent to 0, 0.7, 1.3, 2.5, 5.6, 12.3 and 33 mg/kg-bw per day as bromate) in drinking water for 104 weeks. Dose-dependent increases in renal cell tumours (adenomas and adenocarcinomas) were observed starting at the 2.5 mg/kg-bw per day dose level, but significance was attained at 5.6 mg/kg-bw per day and higher. Preneoplastic lesions were also observed, with dose-dependent increases in frequency of dysplastic foci attaining significance at the 1.3 mg/kg-bw per day level and higher. Significant increases in incidences of peritoneal mesotheliomas and thyroid follicular adenomas and adenocarcinomas at the 33 mg/kg-bw per day level were also reported. At 33 mg/kg-bw per day, treated males showed decreased body weight gain and decreased survival (Kurokawa et al. 1986a).

Male F344 rats were administered potassium bromate doses of 0, 0.02, 0.1, 0.2 or 0.4 g/L in drinking water (corresponding to 0, 1.1, 6.1, 12.9 and 28.7 mg/kg-bw per day as bromate) for 100 weeks. The authors reported significant dose-dependent increased incidences of mesotheliomas, renal cell tumours (adenomas and carcinomas) and thyroid follicular tumours (adenomas and carcinomas). For mesotheliomas, significance was

attained at 6.1 mg/kg-bw per day and greater (increased at 1.1 mg/kg-bw per day, p = 0.06). For renal and thyroid tumours, significance was attained only in the 28.7 and the 12.9 and 28.7 mg/kg-bw per day dose levels respectively. Furthermore, the high-dose group also had significantly depressed body weight gain and average body weight. Significantly increased kidney and thyroid weights and increased relative liver, kidney, thyroid and spleen weights were also observed in the high-dose group (DeAngelo et al. 1998).

Long-term cancer bioassays were also performed on female B6C3F1 mice. Potassium bromate was administered at doses of 0, 500 or 1000 mg/L (corresponding to 0, 43.5 and 92.2 mg/kg-bw per day as bromate) in drinking water for 78 weeks, followed by 26 weeks of water administration. No significant increases in incidences of tumours were observed, although the number of tumour-bearing mice was greater in the high-dose group (effect did not attain significance). Body weight gain was inhibited in the high-dose group, but survival was not affected (Kurokawa et al. 1986b).

Male B6C3F1 mice were also administered potassium bromate doses of 0, 0.08, 0.4 or 0.8 g/L (corresponding to 0, 7, 32.6 and 59.9 mg/kg-bw per day as bromate) in drinking water for 100 weeks. The authors reported statistically significant, but not dose-related, increases in incidence of renal tumours (adenomas and carcinomas) after 100 weeks of exposure. Specifically, significantly increased renal cell tumour incidence was reported in the 7 mg/kg-bw per day group. Although renal tumours were also observed in the 32.6 and 59.9 mg/kg-bw per day groups, these incidences did not attain statistical significance. The authors stated that the historical incidence of renal tumours for B6C3F1 mice was <0.5%, thus making potassium bromate–induced increases in renal tumours a biologically relevant finding. Body weight, organ weights and survival were not affected in this study (DeAngelo et al. 1998).

A long-term bioassay was performed using male Syrian hamsters that were administered potassium bromate at doses of 0, 125, 250, 500 or 2000 mg/L (equivalent to 0, 20.1, 40.2, 80.4 and 321.6 mg/kg-bw per day as bromate) in drinking water for 89 weeks. Incidences of renal cell tumours were increased in the 80.4 and 321.6 mg/kg-bw per day groups, but this effect was not dose dependent or significant. The authors stated that the spontaneous incidence of renal cell tumours in Syrian hamsters is very low (less than 1 in 1000); therefore, this finding may be biologically significant. No difference in mean survival times between treated groups and controls was observed, although the high-dose group had significantly lower mean body weights and significantly higher mean absolute and relative kidney weights (Takamura et al. 1985).

Potassium bromate has also been administered to rats and mice in their diet (bread made with added potassium bromate). No significant pathological findings were reported by the authors, although low levels of bromide were detected in adipose tissue (Fisher et al. 1979; Ginocchio et al. 1979). The absence of tumour induction through the dietary route may be explained by the reduction of potassium bromate to bromide in the baking process (Cunningham and Warner 2000).

The tumour-initiating and tumour-promoting potentials of potassium bromate have also been examined. No progression to renal cancer was observed with continuous treatment of sodium barbital after a single dose of potassium bromate, indicating that a single dose of potassium bromate does not initiate renal tumour growth (Kurata et al. 1992). Potassium bromate, on the other hand, has been shown to have promoting and enhancing activity in the induction of renal tumours in rats after being administered following *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) dosing (Kurokawa et al. 1983b, 1985). It does not, however, show promoting or enhancing activity in liver and skin tumorigenesis when given after EHEN and 7,12-dimethylbenzanthracene (DMBA) administration, respectively (Kurokawa et al. 1983b, 1984).

The genotoxicity of potassium bromate has been well characterized both *in vitro* and *in vivo*. *In vitro*, potassium bromate has induced mixed results for mutagenicity in bacteria and silk worms (Kawachi et al. 1980; Ishidate et al 1981; Ishidate et al. 1984; Zeiger et al. 1992; Akintonwa et al. 2007). However, in mammalian cell lines, potassium bromate has increased mutation frequency (Speit et al. 1999; Harrington-Brock et al. 2003; Luan et al. 2007). Overall, while potassium bromate has induced mixed results in bacteria, it has produced predominantly positive mutagenic results in mammalian cell lines.

Potassium bromate induced deoxyribonucleic acid (DNA) damage in cultured mammalian cells and primary human thyroid, white blood and kidney cells as measured by the *in vitro* comet assay (Robbiano et al. 1999; Speit et al. 1999; Parsons and Chipman 2000; Plewa et al. 2002; Poul et al. 2004; Mattioli et al. 2006; Smith et al. 2006; Luan et al. 2007). Predominantly positive induction of micronuclei was also observed in cultured mammalian cells and primary human lymphocytes and kidney cells (Matsuoka et al. 1992; Robbiano et al. 1999; Speit et al. 1999; Poul et al. 2004; Ballmaier and Epe 2006; Kaya and Topaktaş 2007; Luan et al. 2007; Fellows et al. 2008; Platel et al. 2009). Potassium bromate also induces chromosomal aberrations, DNA repair, Sister Chromatid Exchange, and DNA modifications (increased oxidation of DNA) in mammalian cell lines, primary human cultured cells and cell-free systems (Kawachi et al. 1980; Sasaki et al 1980; Ishidate et al 1981; Ishidate et al. 1984; Matsuoka et al. 1992; Sai et al. 1994; Ballmaier and Epe 1995; Chipman et al. 1998; Speit et al. 1999; Parsons and Chipman 2000; Murata et al. 2001; Ballmaier and Epe 2006; Mattioli et al. 2006; Kaya and Topaktaş 2007). A weak chromosomal aberration induction was also observed in cultured mammalian cells (Speit et al. 1999).

No induction of oxidative DNA modifications in isolated perfused kidneys or calf thymus DNA was observed after potassium bromate administration (Sai et al. 1994; Chipman et al. 1998).

Potassium bromate and sodium bromate also induced micronuclei *in vivo* in multiple organs in rats and mice (Hayashi et al. 1982; CSGMT 1986; Nakajima et al. 1989; Awogi et al. 1992; Sai et al. 1992 a; Robbiano et al. 1999; Allen et al. 2000; Hamada et al. 2001; NTP 2007). In addition, potassium bromate induced DNA damage (as measured by the DNA comet assay) in the rat kidney, liver and thyroid (McLaren et al. 1994; Robbiano et al. 1999; Mattioli et al. 2006). DNA damage was also induced in the mouse kidney, liver,

colon, stomach, bladder, lung, brain and bone marrow (Sasaki et al. 1997; Sekihashi et al. 2001). Potassium bromate has also been observed to induce chromosomal aberrations in rat bone marrow cells after oral administration (Kawachi et al. 1980; Fujie et al. 1988). Additionally, it induced *in vivo* mutagenicity in the kidneys of mice and rats (Arai et al 2002; Umemura et al. 2006; Yamaguchi et al. 2008). Increases in DNA oxidative modifications have also been observed in kidneys and livers of rats and mice treated with potassium bromate (Kasai et al. 1987; Sai et al. 1991, 1992 b; Cho et al. 1993; Umemura et al. 1995, 1998, 2004, 2006, 2009; Chipman et al. 1998; Cadenas and Barja 1999; Arai et al. 2002, 2003, 2006; McDorman et al. 2005; Yamaguchi et al. 2008).

Negative results in *in vivo* genotoxicity assays have also been reported for potassium bromate. No induction of micronuclei was observed in spermatids, and no induction of DNA damage was observed in the lung, spleen or bone marrow of mice treated with potassium bromate (Allen et al. 2000; Sasaki et al. 1997). Furthermore, inductions of oxidative and apurinic/apyrimidinic modifications were not observed in rat liver or kidney, respectively (Kasai et al. 1987; Umemura et al. 1995; McDorman et al. 2005). Results of a test for induction of DNA damage in rat kidneys were also inconclusive (Nesslany et al. 2007). Tests for *in vivo* mutagenicity in rat kidneys and mice livers, as measured by the *gpt* and *red/gam* mutation assays, were inconclusive and negative, respectively (Arai et al 2003; Umemura et al. 2006; Umemura et al 2009).

A fully elucidated mode of action for induction of tumours has not been developed. Oxidative stress may play a role in the formation of kidney tumours, as evidenced by the detection of 8 – hydroxydeoxyguanine in kidneys of rodents (US EPA 2001a). Evidence that cell proliferation also plays a role in bromate-mediated renal carcinogenicity also exists; however, this mechanism remains to be further elucidated (US EPA 2001a). The US EPA concluded that "observation of tumours at relatively early time points and the positive response of bromate in a variety of genotoxicity assays suggest that the predominant mode of action at low doses is DNA reactivity" (US EPA 2001a). Furthermore, WHO has stated that "bromate should be considered a mutagenic disinfection by-product" (WHO 2005).

Non-cancer effects have also been reported in numerous studies. Degenerative, necrotic, nephropathic and regenerative changes in kidneys were reported in F344 rats that were administered potassium bromate in drinking water (Kurokawa et al. 1983a, 1986a, b). However, information as to the incidence or statistical significance of these findings was not reported. Significant non-neoplastic observations were reported in the renal pelvis, where a dose-dependent increase in urothelial hyperplasia was observed, of F344 rats (DeAngelo et al. 1998). Based on these effects, a no-observed-adverse-effect level (NOAEL) of 1.1 mg/kg-bw per day as bromate and a lowest-observed-adverse-effect level (LOAEL) of 6.1 mg/kg-bw per day as bromate is derived. Additionally, hyaline degeneration of epithelial cells, dilatation of tubules, tubular regeneration, fibrosis and inflammatory cell infiltration were all observed in kidneys when potassium bromate was administered in drinking water to male Big Blue® rats (five per group) for 16 weeks (Yamaguchi et al. 2008). Based on degeneration of epithelial cells, a LOAEL of 1.3

mg/kg-bw per day as bromate is derived, although the low number of rats reduces confidence in this determination.

Oral administration of sodium bromate in drinking water for 27 and 43 weeks to male and female Tg.AC hemizygous mice also induced significant non-neoplastic effects. Increased follicular cell hypertrophy, follicular depletion and lymphocyte infiltration were observed in the thyroid. Increased nephropathy, renal tubule degeneration and hypertrophy were also observed in the kidneys of treated mice. Hypertrophy of the pituitary gland and degeneration of the germinal epithelium in the testes were also observed. Based on significant increases in follicular cell hypertrophy in males, a LOAEL of 8.4 mg/kg-bw per day as bromate is derived. None of the aforementioned non-neoplastic lesions were reported in p53 haploinsufficient mice treated with sodium bromate in drinking water for 27 and 43 weeks (NTP 2007).

Significant non-cancer effects were observed after dermal application (26 and 39 weeks) of sodium bromate to Tg.AC hemizygous mice. Thyroid follicular cell hypertrophy (all dosage groups), secretory depletion and lymphocyte infiltration were observed. Non-neoplastic effects in the kidneys were also observed; specifically, relative kidney weights and nephropathy were increased (NTP 2007). Based on significant thyroid hypertrophic effects in males and females, a LOAEL of 54.2 mg/kg-bw per day as bromate is derived.

Non-cancer effects have also been reported in an immunotoxicity study in which drinking water containing sodium bromate was administered to mice for 28 days. Significantly increased spleen weights, increases in reticulocytes and decreased macrophage activities were observed (Guo et al. 2001). Although a lack of a clear dose–response relationship for the increase in absolute spleen weights was observed, a lowest-observed-effect level (LOEL) of 10.6 mg/kg-bw per day as bromate is derived.

Sodium bromate was also administered (via drinking water for 35 days) to male and female Sprague-Dawley rats in a short-term reproductive and developmental toxicity assay. Sodium bromate was deduced to be a selective male toxicant; specifically, males showed a significant decrease in epididymal sperm density (NTP 1996). Based on this effect, a LOAEL of 16.1 mg/kg-bw per day as bromate and a NOAEL of 5.5 mg/kg-bw per day as bromate are derived.

Potassium bromate, when injected subcutaneously for 2 weeks, can induce alterations in the auditory system (increased threshold of hearing) and vestibular system (reduced equilibrium performance and spontaneous locomotor activity) in guinea pigs (Chuu et al. 2000; Young et al. 2001). These findings are of importance, since ototoxicity has been observed after acute exposure in humans.

Data on bromate toxicity in humans are limited to acute toxicity case reports and one case–control study. Acute toxicity, through either voluntary or accidental ingestion of large quantities of bromate salt–containing home permanent wave solutions, involves reversible effects, such as gastrointestinal effects, central nervous system depression, hemolytic anemia and pulmonary edema. Irreversible effects include kidney failure and

ototoxicity (summarized in Appendix 3). No robust epidemiological studies of human health effects associated with potassium bromate were found in the literature.

No data are available regarding the absorption of bromate from the respiratory tract. In the gastrointestinal tract, bromate is adequately absorbed (Fujii et al. 1984; Lichtenberg et al. 1989), and its detection in various organs indicates that ingestion of bromate may lead to widespread distribution (Fujii et al. 1984). Bromate may be reduced to bromide when ingested at low doses, as increased levels of bromide were detected in various organs (Fujii et al. 1984). The excretion of bromate occurs primarily through urine, although some bromate may also be excreted through feces (Fujii et al. 1984).

The confidence in the toxicity database is moderate to high, as data on acute and repeated-dose toxicity, carcinogenicity, genotoxicity, immunotoxicity and reproductive and developmental toxicity are available. There is some uncertainty associated with the lack of robust reproductive and multigenerational developmental toxicity studies. Additionally, toxicity data and data pertinent to the critical effect of cancer have been studied primarily through the oral route, as dermal and inhalation routes have not been fully characterized. Also, rat testicular mesotheliomas may have limited relevance to humans because of anatomical differences between rats and humans with respect to the scrotal cavity (Haber et al. 2009). However, both the US EPA and WHO used the incidence of these tumours to quantify cancer risk for humans. Finally, there is uncertainty associated with the lack of epidemiological studies specific to exposure of humans to potassium bromate.

Risk Characterization

As potassium bromate has been classified on the basis of carcinogenicity by other national and international agencies, carcinogenicity is the main focus of this assessment. Increased incidences of tumours were reported in the kidney, thyroid and mesothelium (testes and peritoneal cavity) of rats treated with potassium bromate in drinking water. Potassium bromate has also induced significant increased incidences of renal tumours in one mouse bioassay. Furthermore, it has been found to be genotoxic *in vitro* and *in vivo*. Although recent evidence links the genotoxicity of potassium bromate to oxidative stress, this potential mode of action has not been fully elucidated. Therefore, based on the genotoxicity of potassium bromate, it cannot be precluded that the tumours observed in experimental animals have resulted from direct interaction with genetic material.

Exposure to bromate salts has induced a range of non-cancer effects in experimental animals. Non–cancer effects after bromate salt administration include non-cancer effects in multiple organs, reproductive and developmental toxicity and immunotoxicity. The lowest effect level that has induced non-cancer effects has been in the induction of non-cancer effects in the kidney (LOAEL of 1.3 mg/kg-bw per day) in a subchronic study. At this dose level, preneoplastic lesions (dysplastic foci, kidney) and mesotheliomas (p = 0.06) were increased in long-term assays. A margin of exposure was not calculated for non-cancer effects, as exposure of the general population is considered to be negligible.

Furthermore, preneoplastic lesions and tumours are observed at the same effect level as the non-cancer lesions.

Uncertainties in Evaluation of Risk to Human Health

There is some uncertainty with regard to exposure to potassium bromate from consumer products due to limited available information. However, the diminished use of potassium bromate in recent years suggests that exposure to products containing potassium bromate is unlikely. There is uncertainty due to limited information available with respect to the concentrations of potassium bromate in environmental media; however, based on limited use and releases of potassium bromate, exposure to potassium bromate from environmental media and food would be expected to be negligible.

There is some uncertainty associated with the limited characterization of human health effects through the dermal and inhalation routes. Also, since no epidemiological studies on the human health effects of exposure to bromate are available, there is uncertainty regarding its potential toxicity in humans. Finally, there is some uncertainty regarding the relevance of rat testicular mesotheliomas to humans; however, other organizations have used the incidence of these tumours in their cancer risk estimations for humans.

Conclusion

Based on the information presented in this screening assessment, it is concluded that potassium bromate is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. Additionally, potassium bromate meets the persistence criterion in water but does not meet the criteria for air, soil or sediment, and it does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

On the basis of the carcinogenicity of potassium bromate, for which there may be a probability of harm at any level of exposure, it is concluded that potassium bromate is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that potassium bromate meets one or more of the criteria set out in section 64 of CEPA 1999.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment

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Appendix 1: Details of the modelling with WHAM VI and descriptions of water types used

Speciation of bromate in the dissolved phase was determined with the help of the Windermere Humic Aqueous Model (WHAM 2001; Tipping 2002). The conditions for running the model are described below:

- Thermodynamic constants for metal–inorganic ligand interactions were obtained from the National Institute of Standards and Technology Standard Reference database 46 (Smith and Martell 2004).
- Constants were available for complexes with silver, iron, barium, lithium, sodium, potassium and calcium.
- The constants were corrected for an ionic strength of 0 using the Dubye–Huckel equation in order to produce a thermodynamic database usable by WHAM.
- All chemical concentrations were converted to moles per litre before entering them in the WHAM spreadsheet.
- Dissolved inorganic carbon concentrations were entered in the spreadsheet as CO_3^{2-} concentrations (Table A1.1).

Table A1.1. Physicochemical characteristics of surface water used to model speciation of bromate in solution[a]

Water type	***N***	**Dissolved inorganic carbon**	**Cl^- [b]**	**SO_4^{2-} [b]**	**pH[b]**	**Ca[b]**	**Mg[b]**
		Mean concentration (mol/L)					
Lake Ontario 10%	Variable 17–85	1.71×10^{-4}	7.02×10^{-5}	3.21×10^{-5}	7.3	9.22×10^{-5}	3.55×10^{-5}
Na[b]	**K[b]**	**Ag[c]**	**Fe[c]**	**Ba[c]**	**Li[c]**	**BrO_3^- [d]**	**DOC[b] (mg/L)**
Mean concentration (mol/L)							
5.7×10^{-5}	4.22×10^{-6}	6.67×10^{-13}	8.06×10^{-10}	1.13×10^{-8}	2.88×10^{-8}	8.55×10^{-6}	~1

Abbreviation: DOC, dissolved organic carbon.

[a] All values are for the dissolved phase.

[b] Borgmann et al. (2005).

[c] Rossman and Barres (1988).

[d] Environment Canada (2007). The bromate concentration is the LC_{50} obtained from an acute 7-day toxicity test with the amphipod *Hyalella azteca* exposed to bromate in 10% Lake Ontario water.

Appendix 2: Robust study summary

Robust study summary for aquatic toxicity				
No	**Item**	**Weight**	**Yes/No**	**Specify**
1	Reference: Environment Canada 2007			
2	Substance identity: CAS RN	n/a	Y	7789 38 0
3	Substance identity: chemical name(s)	n/a	Y	Sodium bromate
4	Chemical composition of the substance	2	Y	$NaBrO_3$
5	Chemical purity	1	Y	Reagent grade
6	Persistence/stability of test substance in aquatic solution reported?	1	Y	Stable
Method				
7	Reference	1	Y	Borgmann et al. 2005
8	OECD, EU, national, or other standard method?	3	N	
9	Justification of the method/protocol if a standard method was not used	2	Y	Developed specifically to allow testing a large number of compounds in a short time period
10	GLP (Good Laboratory Practice)	3	Y	
Test organism				
11	Organism identity: name	n/a		*Hyalella azteca*
12	Latin or both Latin & common names reported?	1	Y	
13	Life cycle age / stage of test organism	1	Y	24 h old *Hyalella*
14	Length and/or weight	1		N/A
15	Sex	1		N/A
16	Number of organisms per replicate	1	Y	15 individuals
17	Organism loading rate	1	Y	15 in 400 mL test water
18	Food type and feeding periods during the acclimation period	1	Y	
Test design / conditions				
19	Test type (acute or chronic)	n/a	Y	Acute
20	Experiment type (laboratory or field)	n/a	Y	Lab
21	Exposure pathways (food, water, both)	n/a	Y	Water & food
22	Exposure duration	n/a	Y	7 day
23	Negative or positive controls (specify)	1	Y	Negative
24	Number of replicates (including controls)	1	Y	Two
25	Nominal concentrations reported?	1	Y	
26	Measured concentrations reported?	3	N	
27	Food type and feeding periods during the long-term tests	1	Y	2.5 mg TetraMin fish food flake
28	Were concentrations measured periodically (especially in the chronic test)?	1	N	
29	Were the exposure media conditions relevant to the particular chemical reported? (e.g., for the metal toxicity - pH, DOC/TOC, water hardness, temperature)	3	Y	10% Lake Ontario water; pH: 7.37; DOC: <1 mg/L; Ca: 3.6 mg/L; T: 25°C
30	Photoperiod and light intensity	1	Y	16:8 h L/D
31	Stock and test solution preparation	1	Y	
32	Was solubilizer/emulsifier used, if the chemical was poorly soluble or unstable?	1		N/A
33	If solubilizer/emulsifier was used, was its concentration reported?	1		N/A
34	If solubilizer/emulsifier was used, was its ecotoxicity reported?	1		N/A
35	Analytical monitoring intervals	1	N	
36	Statistical methods used	1	Y	Trimmed Spearman-Karber method
Information relevant to the data quality				
37	Was the endpoint directly caused by the chemical's	n/a	Y	Survival in the control

Robust study summary for aquatic toxicity				
No	**Item**	**Weight**	**Yes/No**	**Specify**
	toxicity, not by organism's health (e.g., when mortality in the control >10%) or physical effects (e.g., "shading effect")?			was very good
38	Was the test organism relevant to the Canadian environment?	3	Y	Widely distributed in Canada
39	Were the test conditions (pH, temperature, DO, etc.) typical for the test organism?	1	Y	Can be found in very diluted water of Canada
40	Does system type and design (static, semi-static, flow-through; sealed or open; etc.) correspond to the substance's properties and organism's nature/habits?	2	Y	Substance very soluble
41	Was pH of the test water within the range typical for the Canadian environment (6–9)?	1	Y	
42	Was temperature of the test water within the range typical for the Canadian environment (5–27°C)?	1	Y	
43	Was toxicity value below the chemical's water solubility?	3	Y	Solubility of $NaBrO_3$ is 420 g/L
Results				
44	Toxicity values (specify endpoint and value)	n/a	n/a	7-day LC_{50} = 0.683 mg/L based on Br (1.093 mg/L as BrO_3)
45	Other endpoints reported - e.g., BCF/BAF, LOEC/NOEC (specify)?	n/a	N	
46	Other adverse effects (e.g. carcinogenicity, mutagenicity) reported?	n/a	N	
47	***Score*: ... %**			***81.8***
48	***EC Reliability code*:**			***1***
49	***Reliability category (high, satisfactory, low)*:**			***High Confidence***
50	***Comments***	*This is a toxicity testing program with* Hyalella azteca *conducted by Dr Uwe Borgmann of the National Water Research Institute, Environment Canada, Burlington, Ontario. This program provided a key line of evidence to determine the inherent toxicity of substances during DSL categorization.* *The 7-day test is not a standard method as such. It uses many standard techniques, but it was developed specifically to allow testing a large number of compounds in a short time period. Good lab practices were followed.*		

Abbreviations: BAF, bioaccumulation factor; BCF, bioconcentration factor; DO, dissolved oxygen; DOC, dissolved organic carbon; DSL, Domestic Substances List; EU, European Union; GLP, Good Laboratory Practice; LC_{50}, median lethal concentration; L/D, light/dark; LOEC, lowest-observed-effect concentration; N, no; n/a, not applicable; NOEC, no-observed-effect concentration; OECD, Organisation for Economic Co-operation and Development; T, temperature; TOC, total organic carbon; Y, yes.

Appendix 3: Summary of toxicological effects information for potassium bromate

Endpoint	Lowest effect levels[1]/results
Laboratory animals and *in vitro* studies	
Acute toxicity	**Lowest oral (intragastric) LD_{50}** (mice) = 214.4 mg/kg-bw as bromate (Kurokawa et al. 1990). [additional studies: Nakajima et al. 1989; Kurata et al. 1992] **Lowest oral (intragastric) LOAEL** (rats) = 229.8 mg/kg-bw as bromate based on basophilic regenerative tubules and focal accumulation of eosinophilic droplets in proximal tubules in surviving male rats (one of five male rats died at day 6) after dosing (Kurata et al. 1992). [additional studies: Kurokawa et al. 1987; Fujie et al. 1988; Umemura et al. 2004]
Short-term repeated-dose toxicity	**Lowest oral LOAEL** (rats) = 6.4 mg/kg-bw per day as bromate based on dose-dependent degeneration of proximal tubules in male rats. Potassium bromate was administered at doses of 0, 15, 30, 60, 125, 250 or 500 mg/L (corresponding to 0, 1.6, 3.2, 6.4, 13.4, 26.8 and 53.6 mg/kg-bw per day as bromate; Health Canada 1994) in drinking water to male and female F344 rats (five per sex per group) for 4 weeks. The authors stated that a dose-dependent degeneration of proximal tubules was observed in male rats at the 60 mg/L level and above. No overt nephrotoxicity was observed in females. Increased cell proliferation in the proximal convoluted tubules was observed at 30 mg/L and above in males and at 125 mg/L and above in females. Increased α2u-globulin was increased in males only at 125 mg/L and above, while serum creatinine levels were also increased only in males at the 250 mg/L level and above (Umemura et al. 2004). [additional studies: Matsushima et al. 1986; Kurokawa et al. 1990; Kawana et al. 1991; Umemura et al. 1993; Chuu et al. 2000; Young et al. 2001; McDorman et al. 2005]
Subchronic toxicity	**Oral LAOEL** (rats) = 1.3 mg/kg-bw per day as bromate, based on significant hyaline degeneration of epithelial cells in kidneys. Potassium bromate was administered at doses of 0, 0.02, 0.2, 2, 8, 30, 125 or 500 mg/L in drinking water (corresponding to doses of 0.00019, 0.0010, 0.0090, 0.10, 0.41, 1.3, 5.6 or 33.4 mg/kg-bw per day as bromate) to male Big Blue® rats (five per group) for 16 weeks. Body weights were decreased and relative kidney weights were increased in the high-dose group. Hyaline degeneration of epithelial cells in the kidney (control, 0/5; 30 mg/L, 5/5, $p < 0.01$; 125 mg/L, 5/5, $p < 0.01$; 500 mg/L, 5/5, $p < 0.01$) was observed at doses of 30 mg/L and higher. Dilatation of tubules, tubular regeneration and fibrosis, and inflammatory cell infiltration were all observed at doses of 125 mg/L and higher. The low number of animals reduces confidence in this LOAEL determination (Yamaguchi et al. 2008). **Oral LOAEL** (mice): 8.4 mg/kg-bw per day as bromate, based on significant increases in incidence of follicular cell hypertrophy in males after 43 weeks of treatment with sodium bromate in drinking water. Sodium bromate was administered to male and female Tg.AC hemizygous mice (15 per sex per group) at doses of 0, 80, 400 or 800 mg/L in drinking water, corresponding to 0, 10/11.5, 48.2/55.1 and 98.8/113.3 mg/kg-bw per day as bromate for male/female mice, for 27 weeks. Lowered mean body weights in 400 and 800 mg/L dose males and high-dose females were observed. Increased

Endpoint	Lowest effect levels[1]/results
	incidences of follicular cell and secretory depletion were observed in 400 and 800 mg/L dose groups of males and females. Increased lymphocyte infiltration in the thyroid was observed in females of those two groups as well. In the kidney, significantly increased incidences of nephropathy were observed in all dose groups in males and in the 400 and 800 mg/L dose groups in females. Furthermore, increased incidences of renal tubule degeneration were observed in both high-dose groups of males and females, with females also showing increased incidences of renal tubule hypertrophy. Significantly increased incidences of pituitary gland hypertrophy were also observed in females in the high-dose group. An increased incidence of lymphoid hyperplasia was also observed in the 80 and 800 mg/L female groups. Hematological parameters were altered in males and females, but the authors deemed most of these effects to be minimal (less than or equal to 10%). However, significant increases in reticulocytes were observed and deemed to be biologically relevant. *Kidney*: Nephropathy: Males: control, 1/15; 80 mg/L, 7/15, $p < 0.05$; 400 mg/L, 10/15, $p < 0.01$; 800 mg/L, 14/15, $p < 0.01$ Females: control, 2/15; 400 mg/L, 10/15, $p < 0.01$; 800 mg/L, 13/15, $p < 0.01$ Renal tubule degeneration: Males: control, 0/15; 800 mg/L, 10/15, $p < 0.01$ Females: control, 0/15; 800 mg/L, 8/15, $p < 0.01$ Renal tubule hypertrophy: Females: control, 0/15; 400 mg/L, 5/15, $p < 0.05$; 800 mg/L, 12/15, $p < 0.01$ *Thyroid* Follicular cell hypertrophy: Males: control, 1/15; 400 mg/L, 12/15, $p < 0.01$; 800 mg/L, 15/15, $p < 0.01$ Females: control, 2/15; 400 mg/L, 11/13, $p < 0.01$; 800 mg/L, 13/15, $p < 0.01$ Follicular secretory depletion: Males: control, 4/15; 400 mg/L, 15/15, $p < 0.01$; 800 mg/L, 15/15, $p < 0.01$ Females: control, 7/15; 400 mg/L, 11/13, $p < 0.05$; 800 mg/L, 14/15, $p < 0.01$ Lymphocyte infiltration: Females: control, 0/15; 400 mg/L, 5/13, $p < 0.05$; 800 mg/L, 11/15, $p < 0.01$ *Pituitary gland* Pituitary gland hypertrophy: Females: control, 0/15; 800 mg/L, 6/15, $p < 0.01$ Sodium bromate was administered to male and female Tg.AC hemizygous mice (10 per sex per group) at doses of 0, 80, 400 or 800 mg/L in drinking water, corresponding to 0, 8.4/11.5, 39.8/49.8 and 100.3/116.4 mg/kg-bw per day as bromate for males/females, for 43 weeks. Mean body weights were affected in the 400 and 800 mg/L dose groups in males and in the 80 and 800 mg/L dose groups in females. Significant increases in incidence in follicular cell hypertrophy were observed in all male and female dose groups. Incidences of lymphocyte infiltration in the thyroid were also observed in high-dose males and 400 and 800 mg/L group females. Finally, incidences of follicle secretory depletion were also observed in all dose groups in females. Significantly increased incidences of renal tubule degeneration were observed in males and females in the high-dose groups.

Endpoint	Lowest effect levels[1]/results
	Significant degeneration of the germinal epithelium and epididymis of the testes was also observed in males in the high-dose group. High-dose females showed increased incidences of hypertrophic effects in the pituitary gland and hyperkeratosis in the epithelium of the forestomach (NTP 2007). *Thyroid* Follicular cell hypertrophy: Males: control, 0/10; 80 mg/L, 6/10, $p < 0.01$; 400 mg/L, 8/10, $p < 0.01$; 800 mg/L, 8/9, $p < 0.01$ Females: control, 0/10; 80 mg/L, 8/9, $p < 0.01$; 400 mg/L, 10/10, $p < 0.01$; 800 mg/L, 10/10, $p < 0.01$ Follicle secretory depletion: Females: control, 1/10; 80 mg/L, 8/9, $p < 0.01$; 400 mg/L, 9/10, $p < 0.01$; 800 mg/L, 10/10, $p < 0.01$ Lymphocyte infiltration: Males: control, 0/10; 800 mg/L, 4/9, $p < 0.05$ Females: control, 0/10; 400 mg/L, 7/10, $p < 0.01$; 800 mg/L, 8/10, $p < 0.01$ *Kidney* Renal tubule degeneration: Males: control, 0/10; 800 mg/L, 8/10, $p < 0.01$ Females: control, 0/10; 800 mg/L, 7/10, $p < 0.01$ Renal tubule hypertrophy: Males: control, 0/10; 800 mg/L, 6/10, $p < 0.01$ Females: control, 0/10; 800 mg/L, 5/10, $p < 0.05$ *Testes* Germinal epithelium degeneration: Males: control, 0/10; 800 mg/L, 8/10, $p < 0.01$ Epididymis: Males: control, 0/10; 800 mg/L, 7/10, $p < 0.01$ *Pituitary gland* Pituitary gland hypertrophy: Females: control, 0/10; 800 mg/L, 6/10, $p < 0.01$ Sodium bromate was also administered to male and female p53 haploinsufficient mice (10–15 per sex per group) at doses of 0, 80, 400 or 800 mg/L in drinking water, corresponding to 0, 6.8/11.0, 33.1/61.0 and 62.7/115.3 mg/kg-bw per day as bromate for males/females, for 27 and 43 weeks. Survival of all groups was similar in both studies. Mean body weights were generally higher in treated females in both studies; however, treated male body weights were similar to controls. No neoplastic or non-neoplastic lesions were observed in either study (NTP 2007). **Dermal LOAEL** (mice) = 54.2 mg/kg-bw per day as bromate, based on significant increases in incidence of follicular cell hypertrophy in males and females in both 26- and 39-week studies. Sodium bromate was administered dermally at doses of 0, 64, 128 or 256 mg/kg-bw per day (corresponding to 0, 54.2, 108.4 and 216.8 mg/kg-bw per day as

Endpoint	Lowest effect levels[1]/results
	bromate) to male and female Tg.AC hemizygous mice (15 per sex per group) for 26 weeks. Mean body weights of males were lower in the high-dose group. Incidences of follicular cell hypertrophy were significantly increased in all dosed groups of males and females. Females also showed significantly increased incidences of follicular secretory depletion and lymphocyte infiltration in the two high-dose groups and the 64 and 256 mg/kg-bw per day groups, respectively. A significant increase in incidence of nephropathy was observed in the 128 and 256 mg/kg-bw per day dose groups in males and in the high-dose group in females. Relative kidney weights were also increased in high-dose males. Hematopoietic cell proliferation was significantly increased in the 128 and 256 mg/kg-bw per day female dose groups. Minimal alterations in hematological parameters were also reported. *Kidney* Nephropathy: Males: control, 8/15; 128 mg/kg-bw per day, 14/15, $p < 0.05$; 256 mg/kg-bw per day, 14/15, $p < 0.05$ Females: control, 8/15; 256 mg/kg-bw per day, 15/15, $p < 0.01$ *Thyroid* Follicular cell hypertrophy: Males: control, 0/15; 64 mg/kg-bw per day, 7/15, $p < 0.01$; 128 mg/kg-bw per day, 10/15, $p < 0.01$; 256 mg/kg-bw per day, 14/15, $p < 0.01$ Females: control, 1/15; 64 mg/kg-bw per day, 9/15, $p < 0.01$; 128 mg/kg-bw per day, 12/15, $p < 0.01$; 256 mg/kg-bw per day, 13/15, $p < 0.01$ Follicular secretory depletion: Females: control, 6/15; 128 mg/kg-bw per day, 13/15, $p < 0.01$; 256 mg/kg-bw per day, 14/15, $p < 0.01$ Lymphocyte infiltration Females: control, 0/15; 64 mg/kg-bw per day, 6/15, $p < 0.01$; 128 mg/kg-bw per day, 3/15, not significant; 256 mg/kg-bw per day, 12/15, $p < 0.01$ Sodium bromate was administered dermally at doses of 0, 64, 128 or 256 mg/kg-bw per day (corresponding to 0, 54.2, 108.4 and 216.8 mg/kg-bw per day as bromate) to male and female Tg.AC hemizygous mice (10 per sex per group) for 39 weeks. Mean body weights were lower in the 128 and 256 mg/kg-bw per day groups in males and in all dose groups in females. As with the 26-week study, increased incidences of follicular cell hypertrophy were significantly increased in all dosed groups of males and females. Increased incidences of follicular secretory depletion and lymphocyte infiltration were also observed in the 128 and 256 mg/kg-bw per day dose group females. In the males, significant increases in relative kidney weights were observed in all dose groups, while the females showed increased absolute kidney weights and nephropathy in the high-dose groups. Finally, in males, absolute testis weights and incidences of germinal epithelium degeneration were significantly increased (NTP 2007). *Kidney* Females: control, 5/9; 256 mg/kg-bw per day, 10/10, $p < 0.05$ *Thyroid* Follicular cell hypertrophy: Males: control, 0/10; 64 mg/kg-bw per day, 9/10, $p < 0.01$; 128 mg/kg-bw per day, 8/10, $p < 0.01$; 256 mg/kg-bw per day, 8/10, $p < 0.01$

Endpoint	Lowest effect levels[1]/results
	Females: control, 1/9; 64 mg/kg-bw per day, 9/10, $p < 0.01$; 128 mg/kg-bw per day, 9/10, $p < 0.01$; 256 mg/kg-bw per day, 10/10, $p < 0.01$ Follicular secretory depletion: Males: control, 5/9; 128 mg/kg-bw per day, 10/10, $p < 0.05$; 256 mg/kg-bw per day, 10/10, $p < 0.05$ Females: control, 0/9; 128 mg/kg-bw per day, 5/10, $p < 0.05$; 256 mg/kg-bw per day, 10/10, $p < 0.01$ Lymphocyte infiltration: Females: control, 0/9; 128 mg/kg-bw per day, 5/10, $p < 0.05$; 256 mg/kg-bw per day, 10/10, $p < 0.01$ *Testes* Germinal epithelium degeneration: Males: control, 1/10; 256 mg/kg-bw per day, 6/10, $p < 0.05$ Potassium bromate was administered at 0, 0.02 or 0.4 g/L in drinking water (corresponds to 0, 2.1 and 42.9 mg/kg-bw per day as bromate; Health Canada 1994) to Tsc2 mutant Long-Evans rats (8–10 per group) for 4 and 10 months. Significantly increased preneoplastic lesions (per rat) were observed at 4 months in both male treatment groups. These effects were increased but non-significant after 10 months of treatment in males. Adenomas and carcinomas were increased but not significantly in males after 10 months of treatment in both dose groups. For females, atypical tubule formation and hyperplasia were significantly increased in the high-dose group after 4 months of treatment. Both these parameters were increased but did not achieve significance in the 0.02 g/L dose group. At 10 months, atypical tubule formation was significantly increased in both treatment groups, while atypical hyperplasia was increased in the 0.4 g/L group only. Adenomas and carcinomas were increased in both treatment groups but did not achieve significance after 10 months of treatment in females. The absence of progression of preneoplastic lesions to neoplastic lesions reduces confidence in these results (McDorman et al. 2003a). [additional studies: Kurokawa et al. 1990; McDorman et al. 2003b; Arai et al. 2006]
Chronic toxicity/ carcinogenicity	**Oral (drinking water) carcinogenicity bioassay in rats** Male and female F344 rats (53 per sex per group) were administered potassium bromate doses of 0, 250 or 500 mg/L (equivalent to approximately 0, 9.6 and 21.2 mg/kg-bw per day as bromate for males and 0, 9.6 and 19.5 mg/kg-bw per day as bromate) for 110 weeks. Body weight gain was inhibited in the high-dose male group; percent survival was decreased in both dose groups in males, although it occurred earlier in the high-dose group (week 60). No effect on survival or body weight inhibition was seen in females. Significantly increased incidences of renal cell tumours (males: control, 3/53; 250 mg/L, 32/53, $p < 0.001$; 500 mg/L, 46/52, $p < 0.001$; females: control, 0/57; 250 mg/L, 28/50, $p < 0.001$; 500 mg/L, 39/49, $p < 0.001$) were observed in all treatment groups. In male rats, significantly increased incidences of peritoneal mesotheliomas (males: control, 6/53; 250 mg/L, 17/52, $p < 0.05$; 500 mg/L, 28/46, $p < 0.001$) were also reported. Incidences of tumours were increased but not significantly in the thyroid (male and female) (Kurokawa et al. 1982, 1983a). Male F344 rats (20 or 24 rats per group) were administered potassium bromate doses of 0, 15, 30, 60, 125, 250 or 500 mg/L (equivalent to 0, 0.7, 1.3, 2.5, 5.6,

Endpoint	Lowest effect levels[1]/results
	12.3 or 33 mg/kg-bw per day as bromate) in drinking water for 104 weeks. The high-dose group showed decreased body weight gain and decreased survival. For doses lower than 250 mg/L, survival was comparable to controls. Dose-dependent increases in renal cell tumours (control, 0/19; 125 mg/L, 5/24, $p < 0.05$; 250 mg/L, 5/20, $p < 0.05$; 500 mg/L, 9/20, $p < 0.001$) were observed, predominantly adenomas, as adenocarcinomas were seen only in the high-dose group. A dose-dependent increase in number of rats with dysplastic foci was also reported (significant at the 30 mg/L dose level). Mean numbers of renal cell tumours per square centimetre of kidney were also increased dose dependently (significant at the 125 mg/L level). Increases in incidences of peritoneal mesotheliomas (control, 0/19; 500 mg/L, 15/20, $p < 0.001$) and thyroid follicular adenomas and adenocarcinomas (control, 0/16; 500 mg/L, 7/19, $p < 0.05$) were also observed. Also reported was a dose-related increase in nephropathy in aging treated rats; however, no information on doses or incidences was provided. (Kurokawa et al. 1986a). Male F344 rats (50 rats per group) were administered potassium bromate doses of 0, 0.02, 0.1, 0.2 or 0.4 g/L (corresponding to 0, 1.1, 6.1, 12.9 and 28.7 mg/kg-bw per day as bromate) for 100 weeks. The authors reported statistically significant dose-dependent increases in mesotheliomas (tunica vaginalis testis), renal cell tumours (adenomas and carcinomas) and thyroid follicular tumours (adenomas and carcinomas). For mesotheliomas (control, 0/47; 0.02 g/L, 4/49, $p = 0.06$; 0.1 g/L, 5/49, $p < 0.05$; 0.2 g/L, 10/47, $p < 0.002$; 0.4 g/L, 27/43, $p < 0.002$), significance was attained at doses greater than or equal to 0.1 g/L. For renal cell tumours (control, 1/45, not significant; 0.1 g/L, 4/47, not significant; 0.2 g/L, 3/39, not significant; 0.4 g/L, 12/45, $p < 0.002$) and thyroid follicular tumours (control, 0/36, not significant; 0.2 g/L, 4/35, $p < 0.05$; 0.4 g/L, 14/30, $p< 0.002$), significance was attained only at higher dose levels. For all three tumours, the incidences were statistically significant and dose related. Significant decreases in survival were observed in the 0.2 and 0.4 g/L dose groups. The high-dose group had significantly depressed body weight gain and average body weight and significantly increased kidney and thyroid weights and relative liver, kidney, thyroid and spleen weights. High-dose groups were euthanized and necropsied at week 94 because of a high rate of mortality and morbidity. A trend of increasing water consumption as potassium bromate concentration increased was observed (DeAngelo et al. 1998). In the above study, a portion of study rats (dose groups: 0, 1.1, 6.1, 12.9 and 28.7 mg/kg-bw per day as bromate) were euthanized at 12, 26, 52 and 78 weeks of treatment. Significant increases in incidences of testicular mesotheliomas, renal cell tumours and thyroid follicular tumours were observed at week 78 in the 0.4 g/L group. Additionally, non-neoplastic increases in the incidence of urothelial hyperplasia in the renal pelvis were observed at week 78 in both 0.2 and 0.4 g/L dose groups. Decreased total serum concentrations of bound and unbound triiodothyronine (but not thyroxine) were observed in all treatment groups (Wolf et al. 1998). [additional study: Kurokawa et al. 1987] **Oral (drinking water) carcinogenicity bioassay in mice** Male and female B6C3F1 mice (50 per group) were administered doses of 0, 500 or 1000 mg/L (corresponding to 0, 43.5 and 92.2 mg/kg-bw per day as bromate) for 78 weeks, then 26 weeks of water administration before analysis. The male study was discontinued because of fighting. Body weight gain was inhibited in

Endpoint	Lowest effect levels[1]/results
	females from the high-dose group, but survival was not affected. No significant increases in incidences in tumours were observed. Although the total number of tumour-bearing mice was greater in the high-dose group (22/47), it was not significant (15/46, controls). Renal cell tumour incidence was similar across treated and untreated groups (Kurokawa et al. 1986b). Male B6C3F1 mice (50 per group) were administered potassium bromate doses of 0, 0.08, 0.4 or 0.8 g/L in drinking water (corresponding to 0, 7, 32.6 or 59.9 mg/kg-bw per day as bromate) for 100 weeks. The authors reported statistically significant treatment-related, but not dose-related, increases in incidence of renal tumours (adenomas plus carcinomas) after 100 weeks of exposure. Specifically, an increased renal cell tumour incidence was reported in 5/38 ($p < 0.05$) mice in the 0.08 g/L group. The 0.4 and 0.8 g/L dose groups also showed increased incidences of renal cell tumours (3/41 and 1/44, respectively); when compared with controls (0/40), however, these groups did not achieve significance. The authors stated that since the background incidence of renal tumours in B6C3F1 mice is <0.5%, this result is biologically significant. No significant alterations were observed in final body weight or absolute and relative organ weights between treated groups and controls (DeAngelo et al. 1998) [additional study: Kurokawa et al. 1990] **Drinking water carcinogenicity bioassay in hamsters** Male Syrian hamsters (20 per group) were administered doses of 0, 125, 250, 500 or 2000 mg/L (corresponding to 0, 20.1, 40.2, 80.4 and 321.6 mg/kg-bw per day as bromate; Health Canada 1994) for 89 weeks. Incidences of renal cell tumours (did not distinguish between adenocarcinomas and adenomas) were 2/19, 4/20, 1/17, 0/19 and 0/20 in the 2000, 500, 250, 125 and 0 mg/L groups, respectively, and this result did not achieve significance. Dysplastic foci were found in eight animals given potassium bromate. All other tumours seemed to conform to background incidence. Spontaneous incidence of renal tumours in Syrian golden hamsters is reportedly very low (less than 1 in 1000), and the authors speculated that this finding may be biologically significant. No difference in mean survival times between treated groups and controls was observed. The high-dose group had significantly lower mean body weights and significantly higher mean absolute and relative kidney weights. Relative kidney weights were also increased in the 125 mg/L group (Takamura et al. 1985). **Dietary carcinogenicity bioassay in mice and rats** Male and female Theiller's Original strain mice (number of mice per group was not specified in the study) were administered potassium bromate at doses of 0, 50 or 75 mg/kg (corresponding to 0, 2.8 and 4.2 and 0, 3.2 and 4.8 mg/kg-bw per day as bromate for males and females, respectively) for 80 weeks. No significant changes in mortality or mean body weights were observed between the groups. Dose-related increases in brain, thyroid and kidney relative weights were observed. A dose-related decrease in pituitary weight was also observed. However, these effects were minimal. Additionally, dose-related increases in blood glucose levels were observed in females; however, this effect was not observed in males. No pathological changes were observed in any of the treated animals. However, small amounts of bromine were detected in adipose tissue, indicating that some bromate may bioaccumulate in tissues (Ginocchio et al. 1979).

Endpoint	Lowest effect levels[1]/results
	Male and female Wistar rats (number of rats per group was not specified in the study) were administered potassium bromate at doses of 0, 50 or 75 mg/kg (corresponding to 0, 0.8 and 1.2 and 0, 1.1 and 1.6 mg/kg-bw per day as bromate in males and females, respectively). No significant evidence of carcinogenicity was observed in this study. Additionally, no bioaccumulation was observed in adipose tissue (Fisher et al. 1979). Dermal (topical application) carcinogenicity bioassay in mice Female Sencar mice (20 per group) were administered potassium bromate at a concentration of 40 mg/mL on the dorsal skin and observed for 51 weeks. No skin tumours, squamous cell carcinomas or epidermal hyperplasias were observed (Kurokawa et al. 1984). **Other carcinogenicity bioassays** *Tumour initiation assay* Male F344/NCr rats (29 or 39 rats per group) were administered potassium bromate at 229.8 mg/kg-bw as bromate in a single intragastric dose. Two weeks after treatment with potassium bromate, a basal diet or a diet with the renal tumour promoter sodium barbital (4000 mg/kg) was administered. Rats were examined at 30, 52 and 104 weeks for occurrence of renal tumours and nephrotoxicity. Inhibition of growth and increased mortalities were observed in the co-administered and sodium barbital alone groups. At 31–52 weeks, incidences of dysplastic tubular foci in the sodium barbital alone group were greater than those in the co-administered group. Furthermore, at 53–104 weeks, incidences of dysplastic tubular foci were similar in both the co-administered and sodium barbital alone groups, with the sodium barbital alone group showing actual progression to renal tumours. A single intragastric dose of potassium bromate was not sufficient to initiate renal tumorigenesis (Kurata et al. 1992). F344 rats (10–15 per group) were administered potassium bromate at 0, 60, 125, 250 or 500 mg/kg for 13 weeks. After 2 weeks, rats received the renal carcinogenesis promoter nitrilotriacetic acid (NTA) at a concentration of 1% in the diet for 37 weeks. Body weights were significantly decreased in the 500 mg/kg potassium bromate/NTA treatment group and in the NTA treatment alone group. Increased incidences of preneoplastic lesions were observed in the study. The numbers of atypical tubules and hyperplasias per rat were significantly increased in the 500 mg/kg potassium bromate/NTA group. It is important to note that the 500 mg/kg potassium bromate/basal diet group showed no significant increases in incidences of preneoplastic lesions. No neoplastic lesions were observed in this study (Umemura et al. 2006). *Tumour-promoting assay* Male F344 rats (total 128 rats) were treated with potassium bromate (500 mg/L) after EHEN administration (1000 or 500 mg/L) in a 26-week oral drinking water study. Co-administration of potassium bromate with EHEN induced significantly greater average numbers of both dysplastic foci per square centimetre of kidney and renal cell tumours per square centimetre of kidney. The promoting effects of potassium bromate in the kidney were not observed in the liver (Kurokawa et al. 1983b). Female Sencar mice (15 or 20 per group) were tested for the promoting ability of potassium bromate (40 mg/mL) after topical administration of DMBA (20 nmol) for a study duration of 51 weeks. No skin tumours, squamous cell carcinomas or epidermal hyperplasias were observed (Kurokawa et al. 1984).

Endpoint	Lowest effect levels[1]/results
	Male F344 rats (15 rats per group) were treated with distilled water or the tumour initiator EHEN (500 mg/L) for 2 weeks, then with potassium bromate (15, 30, 60, 125, 250 or 500 mg/L) or distilled water for the following 24 weeks in a drinking water study. Mean final body weights were decreased in rats given potassium bromate (after EHEN treatment) at doses higher than 125 mg/L. Meanwhile, relative and absolute kidney weights were observed to be lower in these rats. Dose-dependent increases in dysplastic foci per square centimetre of kidney were observed when potassium bromate was co-administered at doses of 30 mg/L or higher. The mean number of renal cell tumours per square centimetre of kidney was also significantly increased in the high co-administered dose group. The dose-dependent increases in preneoplastic lesions per area of kidney indicate that potassium bromate is an enhancer of renal tumorigenesis (Kurokawa et al. 1985) Male F344 rats (19–23 rats per group) were given EHEN (500 or 1000 mg/L) for 2 weeks followed by potassium bromate at 500 mg/L for the following 24 weeks in a drinking water study. The average number of dysplastic foci per square centimetre of kidney and the average number of renal cell tumours per square centimetre of kidney were significantly increased in the co-administration groups. Incidences of renal cell tumours were not increased in any of the treatment groups. As with the study mentioned above, no significant liver tumour–promoting activities were observed. The authors therefore stated that potassium bromate has promoting activity in the kidney, but not the liver (Kurokawa et al. 1990). [additional study: Umemura et al. 1995] **Non-neoplastic endpoints** Male F344 rats (50 per group) were administered potassium bromate at doses of 0, 0.02, 0.1, 0.2 or 0.4 g/L (corresponding to 0, 1.1, 6.1, 12.9 and 28.7 mg/kg-bw per day as bromate) for 100 weeks. The authors reported no significant increases in severity of progressive nephropathy; however, they did report that foci of mineralization of the renal papilla and eosinophilic droplets in the proximal tubule epithelium were observed in treated rats. No information as to the doses at which these effects occurred was provided. Significant non-neoplastic observations were reported in the renal pelvis, where a dose-dependent increase in urothelial hyperplasia was observed (control, 7/44; 0.1 g/L, 25/47, $p < 0.002$; 0.2 g/L, 32/39, $p < 0.002$; 0.4 g/L, 30/32, $p < 0.002$). Based on these effects, a NOAEL of 1.1 mg/kg-bw per day as bromate and a LOAEL of 6.1 mg/kg-bw per day as bromate were deduced (DeAngelo et al. 1998). Male Wistar rats were given 0% and 0.04% (at intake of 0.1 L/kg-bw per day = 30 mg/kg-bw per day as bromate; US EPA 2001a) potassium bromate in drinking water for up to 15 months. Histological examination of kidneys at 7–11 weeks revealed karyopyknotic foci in tubules of the inner medulla. Also at 15 months, increased blood urea nitrogen and marked structural abnormalities of the cortical tubules were observed. This was a limited study, in that only one dose was tested; therefore, a LOAEL could not be identified (Nakano et al. 1989). Male and female F344 rats (53 per sex per group) were administered potassium bromate at 0, 250 or 500 mg/L in drinking water (equivalent to approximately 0, 9.6 and 21.2 mg/kg-bw per day as bromate for males and 0, 9.6 and 19.5 mg/kg-bw per day as bromate for females) for up to 110 weeks. In addition to the cancerous effects reported above, the authors also reported non-cancer effects, such as degenerative, necrotic and regenerative changes in renal tubules,

Endpoint	Lowest effect levels[1]/results
	formation of hyaline casts in the tubular lumen, formation of hyaline droplets, papillary hyperplasia and growth and thickening of transitional epithelium of the renal pelvis. The authors also reported an increase in calcium deposits in rats showing hyperplastic changes and alteration in biochemical parameters. Information as to the doses at which these effects were observed was not provided; therefore, a LOAEL or NOAEL could not be identified (Kurokawa et al. 1983a).
Developmental/ reproductive toxicity	Sodium bromate was administered to male and female Sprague-Dawley rats at doses of 0, 25, 80 or 250 mg/L in drinking water (corresponding to 0, 1.7, 5.5 and 16.1 mg/kg-bw per day as bromate and 0, 2.5/2.7, 8.4/9.4 and 24.1/26.6 mg/kg-bw per day as bromate for males and females, respectively [Group A/Group B female groups]) in a short-term reproductive (35 day) and developmental toxicity assay. Sodium bromate did not induce any female reproductive toxicity, although there was an increase in number of early resorptions and post-implantation losses in the high-dose females (did not attain significance). Males showed a significant decrease (18%) in epididymal sperm density at the 250 mg/L level. Therefore, based on these effects, sodium bromate is a selective male reproductive toxicant with a LOAEL of 16.1 mg/kg-bw per day as bromate and a NOAEL of 5.5 mg/kg-bw per day as bromate (NTP 1996).
Genotoxicity and related endpoints: *in vivo*	**Micronuclei induction** *Positive results:* **Positive:** Micronuclei induction in male MS/Ae and CD1 mouse erythrocytes. Route: oral and intraperitoneal (Nakajima et al. 1989). **Positive:** Micronuclei induction in male and female MS and male ddY mouse bone marrow erythrocytes. Route: intravenous (Hayashi et al. 1982). **Positive:** Micronuclei induction in male B6C3F1 mouse peripheral erythrocytes. Route: drinking water (Allen et al. 2000). **Positive:** Micronuclei induction in male CD1 mouse peripheral erythrocytes. Route: intraperitoneal (Awogi et al. 1992). **Positive:** Micronuclei induction in male and female CD1(S) mice bone marrow erythrocytes. Route: intraperitoneal (CSGMT 1986). **Positive:** Micronuclei induction in male F344 rat peripheral reticulocytes. Route: intraperitoneal (Sai et al. 1992a). **Positive:** Micronuclei induction in male Sprague-Dawley rat kidney cells. Route: oral gavage (Robbiano et al. 1999). **Positive:** Micronuclei induction in male and female Tg.AC hemizygous mouse peripheral blood erythrocytes. Route: dermal (sodium bromate) (NTP 2007). **Positive:** Micronuclei induction in male and female Tg.AC hemizygous mouse peripheral blood erythrocytes. Route: drinking water (sodium bromate) (NTP 2007). **Positive:** Micronuclei induction in male and female p53 haplosufficient mouse peripheral blood erythrocytes. Route: drinking water (NTP 2007). **Positive:** Micronuclei induction in male Sprague-Dawley rat peripheral blood and bone marrow erythrocytes. Route: oral gavage and drinking water (Hamada et al. 2001). *Negative results:* **Negative:** Micronuclei induction in male B6C3F1 mouse spermatids. Route: drinking water (Allen et al. 2000). **DNA comet assay** *Positive results:* **Positive:** DNA damage induction in male Sprague-Dawley rat kidney cells.

Endpoint	Lowest effect levels[1]/results
	Route: oral gavage (Robbiano et al. 1999). **Positive:** DNA damage induction in male CD1 mouse kidney and liver cells. Route: intraperitoneal (Sasaki et al. 1997). **Positive:** DNA damage induction in male ddY mice stomach, colon, liver, kidney, bladder, lung, brain and bone marrow cells. Route: intraperitoneal and oral gavage (Sekihashi et al. 2001). **Positive:** DNA damage induction in male Sprague-Dawley rat thyroid, kidney and liver cells. Route: gastric intubation (Mattioli et al. 2006). **Positive:** DNA damage induction in male Wistar rat kidneys. Route: intraperitoneal (McLaren et al. 1994). *Inconclusive results:* **Inconclusive:** Inconclusive DNA damage in male OFA Sprague-Dawley rat kidneys. Route: oral gavage. Although induction of DNA damage was positive when data were pooled for all animals, heterogeneity of results was observed (some animals actually showed decreased DNA damage induction) (Nesslany et al. 2007). *Negative results:* **Negative:** No observed DNA damage induction in male CD1 mouse lung, spleen or bone marrow cells. Route: intraperitoneal (Sasaki et al. 1997). **Chromosomal aberrations** *Positive results:* **Positive:** Chromosomal aberration induction in male Long-Evans rat bone marrow cells. Route: oral and intraperitoneal (Fujie et al. 1988). **Positive:** Chromosomal aberrations induced *in vivo*. Route: not stated (Kawachi et al. 1980). **DNA modifications** *Positive results:* **Positive:** Increased 8-hydroxyguanine levels in male and female Ogg1 −/− mouse kidneys. Route: drinking water (Arai et al. 2002). **Positive:** Increased 8-hydroxyguanine levels in male and female Ogg1 −/− mouse livers. Route: drinking water (Arai et al. 2003). **Positive:** Increased 8-hydroxyguanine levels in male and female Ogg1 −/− mouse kidneys. Route: drinking water (Arai et al. 2006). **Positive:** Increased 8-hydroxydeoxyguanine levels (highest dose tested) in male Big Blue® rat kidneys. Route: drinking water (Yamaguchi et al. 2008). **Positive:** Increased 8-hydroxydeoxyguanosine levels in female F344 rat kidneys. Route: oral intragastric (Umemura et al. 1995). **Positive:** Increased 8-hydroxydeoxyguanosine levels in male and female F344 rat kidneys. Route: drinking water (Umemura et al. 1998). **Positive:** Increased 8-oxodeoxyguanosine levels in female F344 rat kidneys. Route: intraperitoneal and oral intragastric (Umemura et al. 2004). **Positive:** Increased 8-oxodeoxyguanosine levels in male and female F344 rat kidneys. Route: drinking water (Umemura et al. 2004). **Positive:** Increased 8-hydroxy-2′-deoxyguanine levels in male gpt delta rat kidneys. Route: drinking water (Umemura et al. 2006). **Positive:** Increased 8-hydroxydeoxyguanosine levels in male and female gpt delta rat kidneys. Route: drinking water (Umemura et al. 2009). **Positive:** Increased 8-hydroxy-2′-deoxyguanine levels in male Wistar rat kidneys. Route: intraperitoneal (Cadenas and Barja 1999).

Endpoint	Lowest effect levels[1]/results
	Positive: Increased 8-oxodeoxyguanosine levels in male Sprague-Dawley rat kidneys. Route: intraperitoneal (Chipman et al. 1998). **Positive:** Increased 8-hydroxydeoxyguanine levels in male and female Sprague Dawley rat kidneys and livers. Route: intraperitoneal (Cho et al. 1993). **Positive:** Increased 8-hydroxydeoxyguanosine levels in male F344 rat kidneys. Route: oral intragastric (Kasai et al. 1987). **Positive:** Increased 8-oxoguanine levels in male Long-Evans and Eker mutation rat kidneys. Route: drinking water (McDorman et al. 2005). **Positive:** Increased 8-hydroxydeoxyguanosine levels in male F344 rat kidneys Route: intraperitoneal (Sai et al. 1991). **Positive:** Increased 8-hydroxydeoxyguanosine levels in male F344 rat kidneys Route: intraperitoneal (Sai et al. 1992b). *Negative results:* **Negative:** No increase in 8-hydroxydeoxyguanosine levels in female F344 rat liver. Route: oral intragastric (Umemura et al. 1995). **Negative:** No increase in 8-hydroxydeoxyguanosine levels in male F344 rat liver. Route: oral intragastric (Kasai et al. 1987). **Negative:** No increase in apurinic/apyrimidinic sites in male Long-Evans and Eker mutation rat kidneys. Route: drinking water (McDorman et al. 2005). ***In vivo* mutagenicity assay** *Positive results:* **Positive:** Increased *gpt* mutation frequency in male gpt/Ogg1 +/+ and gpt/Ogg1 −/− mouse kidneys. Route: drinking water. Observed increases in GC–TA, GC–AT and deletion mutations (Arai et al. 2002). **Positive:** Increased *lacI* mutation frequency (highest dose tested) in male Big Blue® rat kidneys. Route: drinking water. Mutation analysis showed that GC to TA transversions were induced (Yamaguchi et al. 2008). **Positive:** Increased *Spi*⁻ mutation frequency (highest dose tested) in male gpt delta rat kidneys. Route: drinking water (Umemura et al. 2006). *Inconclusive Results* **Inconclusive:** Inconclusive results in *gpt* and *red/gam* mutation frequencies in male and female *gpt* delta kidneys. Route: drinking water. An increase in *gpt* mutation frequency was observed in males and females (statistical analysis was not performed on males). *Red/gam* mutation frequencies were increased, but not significantly, in male and female kidneys. Addition of antioxidants was confounding, in that males and females responded differently to treatment (Umemura et al. 2009). *Negative results:* **Negative:** No increase in *gpt* mutation frequency in male gpt/Ogg1 +/- and gpt/Ogg1 −/− mouse livers. Route: drinking water (Arai et al. 2003). **Negative:** No increase in *gpt* mutation frequency in male gpt delta rat kidneys. Route: drinking water (Umemura et al. 2006).
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity assays** *Positive results:* **Positive:** Ames tests in *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 with and without metabolic activation and modified Ames test on *Escherichia coli* [O157:H7 (1 and 7) with metabolic activation (Kawachi et al. 1980; Ishidate et al. 1981, 1984; Zeiger et al 1992; Akintonwa et al. 2007). **Positive:** Increase in *TK* gene mutation frequency in TK6 cells. Induced

Endpoint	Lowest effect levels[1]/results
	significant cell cytotoxicity (Luan et al. 2007). **Positive:** Increase in mutation frequency at the *HPRT* locus in V79 Chinese hamster cells. Induced significant cell cytotoxicity (Speit et al. 1999). **Positive:** Increase in mutation frequency at the *TK* locus in the $Tk^{+/-}$-3.7.2C heterozygote of the L5178Y mouse lymphoma cell line (Harrington-Brock et al. 2003). *Weakly positive results:* **Weakly positive:** Ames test was weakly positive in *Salmonella* TA97 (Zeiger et al. 1992). *Equivocal results:* **Equivocal:** Ames test was equivocal in TA100 and TA1535 (Zeiger et al. 1992). *Negative results:* **Negative:** Ames test in *Salmonella typhimurium* TA98 and rec assay in *Bacillus subtilis* with and without metabolic activation (Kawachi et al. 1980). Ames test was negative in TA98 and TA1537 (Zeiger et al. 1992). **Negative:** Negative response in silk worm mutagenicity assay (Kawachi et al. 1980). **Comet assay** *Positive results:* **Positive:** DNA damage induction in mouse lymphoma L5178Y cells (+ lesion-specific endonucleases) (Smith et al. 2006). **Positive:** DNA damage induction in TK6 cells. Also induced dose-dependent increases in cytotoxicity, although positive response in neutral DNA comet assay was observed at equal to or above 50% cell cytotoxicity (Luan et al. 2007). **Positive:** DNA damage induction in primary cultured human thyroid cells. No cell cytotoxicity observed (Mattiolli et al. 2006). **Positive:** DNA damage induction (single cell gel electrophoresis assay) in Chinese hamster ovary cells. Significant cell cytotoxicity observed (Plewa et al. 2002). **Positive:** DNA damage induction in CHO K1 cells (Poul et al. 2004). **Positive:** DNA damage induction in primary cultured rat and human kidney cells (Robbiano et al. 1999). **Positive:** DNA damage induction in V79 Chinese hamster cells (Speit et al. 1999). **Positive:** DNA damage induction in human white blood cells (Parsons and Chipman 2000). **Positive:** DNA damage induction in cultured rat kidney epithelial cells (NRK-52E) (Parsons and Chipman 2000). **Micronucleus assay** *Positive results:* **Positive:** Micronuclei induction in mouse lymphoma L5178Y cells (Fellows et al. 2008) **Positive:** Micronuclei induction in human lymphoblastoid cell line TK6 (without S9 metabolic activation) (Platel et al. 2009). **Positive:** Micronuclei induction in cultured human peripheral lymphocytes (Kaya and Topaktaş 2007). **Positive:** Micronuclei induction in TK6 cells. Induced significant cell cytotoxicity (Luan et al. 2007). **Positive:** Micronuclei induction in CHO K1 cells (Poul et al. 2004).

Endpoint	Lowest effect levels[1]/results
	Positive: Micronuclei induction in primary cultured rat and human kidney cells (Robbiano et al. 1999). **Positive:** Micronuclei induction in V79 Chinese hamster cells (Speit et al. 1999). **Positive:** Micronuclei induction in AS52 Chinese hamster cells (Ballmaier and Epe 2006) **Positive:** Micronuclei induction in cultured Chinese hamster lung (CHL) cells (Matsuoka et al. 1992). **Chromosomal aberration assay** *Positive results:* **Positive:** Chromosomal aberration test in Chinese hamster fibroblast line and Chinese hamster cell line (Don-6) (Kawachi et al. 1980; Sasaki et al. 1980; Ishidate et al. 1981, 1984). **Positive:** Chromosomal aberration induction in cultured human peripheral lymphocytes (Kaya and Topaktaş 2007). **Positive:** Chromosomal aberration induction in cultured Chinese hamster cell lung (CHL) cells (Matsuoka et al. 1992). *Weakly positive results:* **Weakly positive:** Chromosomal aberration induction in V79 Chinese hamster cells. Weakly positive induction of chromosomal aberrations was observed at doses that did not induce significant amounts of cytotoxicity (greater induction of chromosomal aberrations was observed at a dose that induced almost 100% decreases in cell survival) (Speit et al. 1999). **DNA repair synthesis assay** *Positive results:* **Positive:** Increased induction of DNA repair in cultured human thyroid cells (Mattioli et al. 2006). **Sister Chromatid Exchange** **Positive**: increased Sister Chromatid Exchange in cultured human peripheral lymphocytes. Significant toxicity was observed. (Kaya and Topaktas 2007). **DNA modifications** *Positive results:* **Positive:** Increased 8-oxodeoxyguanosine levels in V79 Chinese hamster cells (Speit et al. 1999). **Positive:** Increased 8-oxodeoxyguanosine levels in cell-free system (administered to calf thymus DNA, only in the presence of GSH) (Chipman et al. 1998). **Positive:** Increased 8-oxodeoxyguanosine levels in cell-free system (administered to calf thymus DNA, only in the presence of GSH, *N*-acetylcysteine and iron sulphate) (Parsons and Chipman 2000). **Positive:** Increased 8-oxodeoxyguanosine levels in cultured rat kidney epithelial cells (NRK-52E) (Parsons and Chipman 2000). **Positive:** Increased DNA modifications (as measured in a PM2 DNA relaxation assay) in cell-free system and in LLC-PK1 and L1210 cells (as measured by alkaline elution assay). Effect observed only in the presence of GSH (Ballmaier and Epe 1995). **Positive:** Increased DNA modifications (as measured by alkaline elution assay) in AS52 cells (only in the presence of GSH) (Ballmaier and Epe 2006).

Endpoint	Lowest effect levels[1]/results
	Positive: Increased 8-oxo-7,8-dihydro-2′-deoxyguanosine levels in human cultured leukemia cells (HL-60 and HP-100) (Murata et al. 2001). **Positive:** Increased 8- dihydro-2′-deoxyguanosine levels in calf thymus DNA in a cell-free system (only in the presence of GSH and its constituent compounds) (Murata et al. 2001). **Positive:** Increased 8-hydroxydeoxyguanosine levels in renal nuclear fractions. Lipid peroxidation was also observed (Sai et al. 1994). *Negative results:* **Negative:** No increase in 8-oxodeoxyguanosine levels was observed in isolated perfused male Sprague-Dawley rat kidneys. No increase in 8-oxodeoxyguanosine levels was observed in either total or mitochondrial DNA (Chipman et al. 1998). **Negative:** No increase in 8-hydroxydeoxyguanosine levels was observed in calf thymus DNA in a cell-free system (Sai et al. 1994).
Immunotoxicity	Sodium bromate was administered in drinking water for 28 days to female B6C3F1 mice at doses of 0, 80, 200, 400, 600 or 800 mg/L (corresponding to 0, 10.6, 26.2, 52.1, 71 and 97.5 mg/kg-bw per day as bromate, calculated based on average intake of water of 3.63 g/day per mouse, reported in study, and average body weight of dose group on day 29). Exposure to sodium bromate did not induce any signs of overt toxicity or differences in body weights or body weight changes. Similarly, no gross pathological lesions were observed. Animals exposed to sodium bromate at 80, 600 and 800 mg/L had significantly increased absolute spleen weights (by 20%, 28% and 23%, respectively). Increased relative spleen weights were also observed. Mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were significantly increased (2%), but the authors stated that this effect was not biologically significant. A dose-related increase in reticulocytes was also observed, with significance being observed at the two highest dose levels (78% increase at the highest dose level). Increases in total spleen cells and B cells were observed, but again the authors stated that this finding was not biologically significant. Treatment of sodium bromate also decreased macrophage activities at the 200, 600 and 800 mg/L dose levels. Based on this study, a LOEL of 10.6 mg/kg-bw per day as bromate (80 mg/L group), based on increases in absolute spleen weights, is derived. A lack of clear dose–response for these effects reduces confidence in this LOEL determination (Guo et al. 2001).
Humans	
Acute toxicity	Bromate has been known to induce acute toxicity in humans. Specifically, numerous case reports exist of accidental or intentional ingestion of bromate contained in home permanent wave solutions by adults and children (Benson 1951; Parker and Barr 1951; Quick et al. 1975; Matsumoto et al. 1980; Gradus et al. 1984; Kuwahara et al. 1984; Warshaw et al. 1985; Lue et al. 1988; Mack 1988; Lichtenberg et al. 1989; Hamada et al. 1990; Kutom et al. 1990; Watanabe et al. 1992). Reversible effects of acute ingestion of bromate are abdominal pain, gastrointestinal effects (nausea, vomiting and diarrhea), anuria, central nervous system depression, hemolytic anemia and pulmonary edema. Irreversible effects include kidney failure and ototoxicity (Health Canada 1999; IARC 1999; US EPA 2001a; WHO 2005). Doses that induced acute toxicity were reported to be between 20 and 1000 mg/kg-bw as bromate for children (Lue et al. 1988; Watanabe et al. 1992) and between 100 and 150–500 mg/kg-bw as bromate for adults (Matsumoto et al. 1980; Kuwahara et al. 1984).
Case–control study	From May 1996 to April 2000, 6002 patients with inner ear symptoms were

Endpoint	Lowest effect levels[1]/results
	examined at the clinic of the Department of Otolaryngology, National Taiwan University Hospital. Of these patients, 10 (0.17%) were hairdressers (age: 35–62) with no systemic disease or previous ear infections. Among the 10 patients, 4 had worked for >30 years, 4 for >20 years and 2 for >10 years. All patients were exposed to permanent cold wave setting solutions containing 2–4% potassium bromate and thioglycolate. Twenty age-matched women were also selected for this study. All 10 patients reported vague dizziness, and half reported experiencing rotational vertigo attacks. Seventy percent and 50% of patients reported hearing loss and tinnitus, respectively. Thirty percent and 20% of patients had altered eye movement, depending on the test used. Caloric tests were performed, and significant altered slow-phase velocity was observed when compared with the age- and sex-matched normal control group (Young et al. 2001).
Chronic toxicity/ carcinogenicity	No studies have been reported for humans.
Genotoxicity and related endpoints	No studies have been reported for humans.
Reproductive/ developmental toxicity	No studies have been reported for humans.
Irritation	No studies have been reported for humans.

[1] LD_{50}, median lethal dose; LO(A)EL, lowest-observed-(adverse-)effect level; NO(A)EL, no-observed-(adverse-)effect level.