Proposed Re-evaluation Decision PRVD2017-10

Sodium Bromide

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Table of Contents

Executive Summary

Health Canada's Pest Management Regulatory Agency (PMRA)

Health Canada's primary objective in regulating pesticides is to protect Canadians' health and their environment. Pesticides must be registered by Health Canada's Pest Management Regulatory Agency (PMRA) before they can be imported, sold, or used in Canada. Before being approved for registration, pesticides must go through rigorous science-based human health, environmental and value assessments.

Under the *Pest Control Products Act*, all registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure they continue to meet modern health and environment safety standards and continue to have value. The PMRA can however decide to initiate a re-evaluation sooner, when necessary. Re-evaluations may result in:

- changes to how products are used;
- changes to product labels to meet current health and environmental standards; or,
- removing products from the market to prevent future harm to health or the environment.

The re-evaluation considers all available information, including data from pesticide manufacturers, published scientific reports, information from other regulatory agencies and other available, relevant information. To reach its decisions, the PMRA applies internationally accepted hazard and risk assessment methods and modern risk management approaches and policies. For more information on how the PMRA regulates pesticides, as well as the assessment process, please visit the Pesticides and Pest Management portion of Canada.ca website.

Re-evaluation of Sodium Bromide

Sodium bromide is a slimicide used in industrial settings. It is also used to keep pool and spa water clean from algae and bacteria.

For the re-evaluation of sodium bromide, risks to human health and the environment were assessed. The human health assessment considered the exposure to workers and bystanders from industrial uses as well as the exposure to Canadians from swimming pool and spa water treated with sodium bromide. The environmental risk assessment focused on the exposure to aquatic organisms when industrial fluids are discharged into natural waters.

Key Findings

In most cases, the risks to human health or the environment can be mitigated through label directions. However, the risk to human health cannot be mitigated for some pool and spa products, for example, uses related to electrolysis devices. It is therefore proposed that pool and spa uses for which the risk cannot be mitigated be removed from the market.

Next Steps

The proposed re-evaluation decision is now open for public consultation for 90 days from the date of the publication of Proposed Re-evaluation Decision PRVD2017-10, *Sodium Bromide*. Once the PMRA considers the comments and any information received during the public consultation period, it will publish a final decision.

Overview

What Is the Proposed Re-evaluation Decision?

An evaluation of available scientific information found that most uses of sodium bromide products do not pose unacceptable risks to human health or the environment when used according to the proposed revised label directions as described in this document. However, the PMRA is proposing to remove the following pool and spa uses as the potential risks of concern to human health cannot be mitigated:

- Bromine generators and related sodium bromide products
- Sodium bromide products used in chlorine generators
- Scheduled spa sanitizers

Before making a final re-evaluation decision on sodium bromide, the PMRA will accept and consider written comments on this proposal received up to 90 days from the date of this publication. Please forward all comments to Publications (see contact information on the cover page of this document). The PMRA will consider any additional data/information submitted during the public comment period in the final decision.

What Is Sodium Bromide?

Sodium bromide is registered in Canada to control slime-forming bacteria and other microorganisms that form problematic biofilms on the surfaces of equipment in contact with process waters in pulp and paper mills, cooling towers, and air washers.

Sodium bromide is also used as a sanitizer in pool and spa waters. Many products containing sodium bromide are registered for use in pools and spas. In addition, certain spa products currently on the market were exempt from registration since they meet the criteria outlined in Schedule II of the Pest Control Product Regulations. This re-evaluation included both currently registered and scheduled pool and spa products.

In all cases, sodium bromide must be activated to be effective, for example using an electrolysis device or another compound such as chlorine. Once activated, sodium bromide is transformed into hypobromous acid (generally referred to as bromine), which is the actual biocide.

Can Approved Uses of Sodium Bromide Affect Human Health?

Sodium bromide products which are proposed for continued registration are unlikely to affect human health when used according to the proposed revised label directions.

Potential exposure to sodium bromide may occur when handling and applying the product in industrial settings. There may also be exposure to sodium bromide when swimming in water treated with sodium bromide products. In assessing human health risks of sodium bromide via pool/spa uses, bromate was also assessed as one of its disinfection by-products.

Toxicological studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The human health hazard identification for sodium bromide was based on toxicological data for sodium bromide and the related chemicals, potassium bromide and ammonium bromide, all of which dissociate to bromide in the body. The human health hazard identification for bromate was based on the studies conducted with potassium or sodium bromate.

The available data in laboratory animals indicate that technical grade sodium bromide is of low acute toxicity via the oral and dermal routes, and of moderate acute toxicity via the inhalation route. Sodium bromide is determined to be a minimal to mild eye irritant, but not to be an irritant to the skin nor to cause an allergic skin reaction. The findings of the acute inhalation toxicity testing trigger the requirement for the hazard signal words “WARNING POISON” to appear on the label for technical grade sodium bromide.

Data provided by the pesticide manufacturers, as well as information from the published literature, were assessed for the potential of sodium bromide and bromate to cause various toxicity effects including neurotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity. Although limited, the available information did not provide evidence that sodium bromide causes cancer while an increased incidence in several tumor types was observed following long-term dosing with bromate. Effects on the thyroid gland represented the most sensitive endpoint for the sodium bromide risk assessment, however, inconsistencies were noted with the dose level that caused these effects. The most sensitive endpoints used for the bromate risk assessment included effects on the kidney and the male reproductive system.

While the sensitivity to young age groups compared to the adults for either sodium bromide or bromate could not be fully determined due to limited available information, the risk assessment is conducted to be protective of all age groups from the potential toxicity effects with the proposed risk-mitigation measures. As such, sex and gender are taken into account in the risk assessment.

Risk from Handling and Applying Products Containing Sodium Bromide

Occupational risks to handlers are unlikely to affect human health when used according to the proposed revised label directions.

Workers can be exposed to sodium bromide through mixing, loading, or applying the pesticide in industrial settings. Exposure estimates for industrial processes were considered against the most sensitive indicator of toxicity, namely effects on the thyroid gland.

Health risks of concern were identified when mixing and loading industrial products containing sodium bromide with an open system. However, exposure is expected to be very low when using modern enclosed systems. The use of a closed transfer and loading via metered pump systems is therefore proposed for all industrial uses of sodium bromide. Increased personal protective equipment (PPE) is also proposed (protective eyewear, chemical-resistant coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves).

Postapplication risks are expected to be low and are not of concern.

Postapplication exposure to bromide may occur from handling treated process fluids or materials. No data are currently available to characterize potential for postapplication worker exposure to sodium bromide from its use in industrial settings. However, exposure is expected to be minimal when proposed revised label directions are followed.

Risk in Residential and Other Non-Occupational Environments

Non-occupational risks from bystander exposure in industrial settings are not of concern.

The potential for bystander exposure to sodium bromide is considered to be low during use in industrial process fluids (for example, pulp and paper mills or cooling towers) as these uses are limited to industrial settings. Similarly, no postapplication exposure to bystanders is expected.

Residential health risks from postapplication exposures related to the use of swimming pool or spa electrolysis devices and the scheduled spa sanitizers are of concern, therefore phase-out of these uses is proposed.

Residential postapplication exposure to bromide and bromate occurs while swimming in the treated pool or spa water. For exposures related to swimming pool or spa electrolysis devices, cancer risks associated with bromate and non-cancer risks associated with bromide are of concern for all subpopulations. Therefore, the phase-out of these uses is proposed.

For the scheduled spa sanitizers, health risks of concern were identified since the bromide exposure estimates were close to the levels associated with thyroid effects. Furthermore, the contribution of bromide exposure from the scheduled spa uses is significant when taking into consideration background exposure levels due to bromide naturally present in foods. Therefore, the phased-out of scheduled spa sanitizers is proposed.

Residential health risks from postapplication exposures related to the use of other pool and spa products are not of concern when used according to the proposed revised label directions.

Residential postapplication exposure to bromide and bromate occurs while swimming in pool or spa water treated with sodium bromide. For swimming pool and spa uses which do not include the use of electrolysis devices, label statements are proposed to prohibit the use of these products in combination with electrolysis devices, ozonation, or ultraviolet (UV) disinfection in order to mitigate the potential cancer risk as a result of bromate formation.

Aggregate risks are not of concern when the proposed mitigation is considered.

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). With the proposed mitigation, the contribution of sodium bromide to the aggregate risk from bromine or bromate is low and not of concern.

Can Sodium Bromide Affect the Environment?

Sodium bromide is not expected to pose risks of concern to the environment when used according to the proposed revised label directions.

Environmental exposure and risk is expected to be limited for sodium bromide used in pools and spas. Sodium bromide that is used in industrial processing waters is mixed with sodium hypochlorite or chlorine, to produce hypobromous acid, which works to control bacteria, fungi and slimes. Although levels of hypobromous acid are expected to be very low, it may cause toxic effects in aquatic organisms if it is allowed to enter natural waters. Label statements requiring that industrial water containing hypobromous acid be cleaned before being released to natural waters are therefore proposed for all industrial products.

What Value Does Sodium Bromide Provide to Canadians?

Sodium bromide has been registered and widely used in Canada as a slimicide and as a pool and spa sanitizer for over 40 years. As one of a handful of registered slimicide active ingredients, sodium bromide provides an important alternative for paper mills and cooling towers where the slime control program often involves rotating different biocide treatments to address biofilm resistance issues.

As a pool and spa sanitizer, sodium bromide reacts with an oxidizer to provide a source of bromine. The only alternative to bromine for spa and pool sanitization is chlorine. Even though they can both be formed from a number of different registered active ingredients, bromine and chlorine are the only two spa and sanitizer chemicals registered in Canada. Bromine has some practical advantages over chlorine by being less susceptible to degradation by the sun and a more effective sanitizer over a broader pH range.

Are Additional Measures Required to Further Minimize Risks?

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law.

As a result of the re-evaluation of sodium bromide, the PMRA is proposing further risk-reduction measures in addition to those already identified on the sodium bromide and related device product labels. Additional risk reduction measures are discussed below.

Human Health

To mitigate residential exposures, the following requirements are proposed:

- All bromine swimming pool or spa electrolysis devices and sodium bromide products intended to be used with swimming pool or spa electrolysis devices are proposed to be phased-out.
- All chlorine swimming pool or spa electrolysis device products are to indicate that they are not to be used to produce bromide.

- Scheduled spa products are proposed to be phased-out.
- All other sodium bromide pool and spa products are to indicate that they are not to be used in combination with electrolysis, ozonation or UV disinfection.

To mitigate occupational (industrial) exposures, the following requirements are proposed:

- Commercial industrial sodium bromide product labels are to require the use of protective eyewear, chemical-resistant coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves and footwear when handling the concentrate and contacting treated process fluids.
- Commercial industrial sodium bromide product labels are to indicate that they are for use with closed loading and transfer systems only.

Environment

- For industrial products, label statements requiring the detoxification of effluent prior to discharge are required due to the toxicity of hypobromous acid to aquatic organisms.

What Additional Scientific Information is Being Requested?

- No additional scientific information is requested.

Next Steps

The PMRA is inviting the public to submit comments on the proposed re-evaluation of sodium bromide, including proposals that may refine the risk assessment and risk management. Before making a final re-evaluation decision on sodium bromide, the PMRA will consider the comments and information received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision document, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments. Based on the final outcome of the re-evaluation, manufacturers will be expected to revise product labels to include new risk-reduction measures and/or phase-out uses according to the implementation schedule to be established by the PMRA.

Science Evaluation

1.0 Introduction

Sodium bromide must be oxidized in order to form hypobromous acid (referred to generally as bromine). Depending on the end-use product, this oxidation step may result from the addition of a form of chlorine (such as sodium hypochlorite), from another oxidizer (such as potassium monopersulphate) or from electrolysis within a bromine-generating device.

The hypobromous acid formed is a broad-spectrum, oxidizing antimicrobial active ingredient used as a slimicide in pulp and paper mills, cooling towers and air washers. It is also used as a swimming pool and spa sanitizer.

The purpose of this re-evaluation is to review available information on the active ingredient, sodium bromide, and on the currently registered sodium bromide technical, commercial and domestic class end-use products, to ensure that risks are acceptable and meet current standards.

Currently registered products containing sodium bromide are listed in Appendix I. It is noted that additional spa sanitizers not included in Appendix I are currently on the market. These were exempt from registration as per Schedule II of the Pest Control Product Regulations. These uses were also included in the re-evaluation.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Sodium bromide
Function	Swimming pool algicide/bactericide; slimicide
Chemical Family	Inorganic bromide
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	Sodium bromide
2 Chemical Abstracts Service (CAS)	Sodium bromide
CAS Registry Number	7647-15-6
Molecular Formula	NaBr
Structural Formula	NaBr
Molecular Weight	102.9

Purity of the Technical Grade Active Ingredient	97% (Reg. No. 21923) 98% (Reg. No. 22737) 40% (Reg. No. 25331) 45% (Reg. No. 26578) 99.2% (Reg. No. 28480) 98% (Reg. No. 28825)

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 20°C (45% dilution)	2333 Pa
Vapour pressure at 806°C (pure active)	133.32 Pa
Ultraviolet (UV) / visible spectrum	Not applicable
Solubility in water at 24°C	94.32 g/100mL
n-Octanol/water partition coefficient	Not applicable
Dissociation constant	Not applicable

2.3 Description of Registered Sodium Bromide Uses

Appendix I lists all sodium bromide products that are registered under the authority of the *Pest Control Products Act.*

In addition to products listed in Appendix I, it is noted that some sodium bromide spa sanitizers are exempt from registration since they meet the criteria outlined in Schedule II of the Pest Control Product Regulations. These were also included in the re-evaluation.

All uses of sodium bromide belong to the following use-site categories: industrial process waters and swimming pools. Uses of sodium bromide are:

- Control of biofilm and slime-forming microorganisms within pulp and paper mills, cooling towers and air washers up to a maximum residual rate of 9.0 ppm of total bromine.
- Sanitizing spa water at a range of 3.0-5.0 ppm total bromine and swimming pool water at a range of 1.0-3.0 ppm total bromine.

3.0 Impact on Human and Human Health

3.1 Toxicology Summary

A detailed review of the toxicological database for sodium bromide was conducted. The database consisted largely of information from the published literature, and was supplemented by reviews from other regulatory agencies, as well as toxicology studies conducted with ammonium bromide. The literature studies were conducted with sodium bromide or potassium bromide, both

of which dissociate in biological systems to bromide, which is responsible for the observed toxicity. Extensive information was available in the published literature. However, many of the studies were limited by a paucity of details in reporting, and/or by the fact that they were not designed to establish, or did not achieve, a no-observed-adverse-effect level (NOAEL). Further, several core toxicology studies were not available. These limitations with the toxicology database presented challenges with respect to fully characterizing the hazard of sodium bromide.

There is potential for formation of disinfection by-products (DBPs) under the conditions of pool/spa use. In view of this, additional information was requested from registrants regarding the toxicological effects of the DBPs. Based on this information, the approach to the health risk assessment for the DBPs took into consideration the potential for exposure, the identified toxicology concerns, as well as the extent of the available information for the DBPs. Having applied this strategy, it was determined that it would be appropriate to include the DBP bromate in the health assessment for sodium bromide pool/spa uses.

Sodium Bromide

Bromides have a long history of medicinal uses, including anticonvulsant and sedative uses. These uses were largely discontinued due to issues with chronic toxicity, involving the central nervous system, endocrine system, and gastrointestinal tract, as well as dermal reactions, which collectively is referred to as “bromism”. Limited uses as anticonvulsants in humans and dogs remain. The therapeutic, as well as toxic, effects of bromide are thought to occur via displacement of other halide ions (for example, chloride and iodide) in biological systems. For this reason, dietary and drinking water levels of these halides can significantly impact the toxicity of bromide. As documented in the published literature, environmental exposures to bromide commonly occur through various means, including the diet and exposure to sea water, due to its ubiquitous nature.

Information from the published literature reveals that the toxicokinetic profile of bromide is similar across different species, including rodents, rabbits, dogs and humans. Following oral ingestion, bromide is rapidly and highly absorbed in the gastrointestinal tract, and competes with chloride for tubular absorption in the kidneys. There is no evidence to suggest that bromide accumulates to a significant extent in any particular organ or tissue. The distribution of bromide is analogous to that of chloride in that bromide is found almost exclusively in the extracellular fluid. Bromide levels are generally highest in the blood, except in rats, in which the stomach has a higher intake of radiolabeled bromide compared to the blood. In humans, bromide levels in the brain and cerebral spinal fluid are 30% of that in the blood. The skin also shows relatively high levels of bromide in rats following oral administration or subcutaneous injection. Results from published studies in rats reveal that bromide crosses the placenta as well as the blood-brain barrier, and that fetal brain levels of bromide are greater than those in adults. Bromide is also transferred into breast milk. In lactating rats, 42% of the administered dose of bromide was transmitted through the mother’s milk into the young rats. In human case studies, newborns of mothers who were exposed to bromides had plasma levels of bromide which, in some cases, exceeded those of their mothers, providing evidence that in utero and/or lactational exposure to bromides occurs in humans as well.

Bromide can displace chloride in mammalian tissues; the converse also occurs. An exception to this is the thyroid gland, where bromide replaces iodide rather than chloride. In the rat, up to 40% of iodide in the thyroid is replaced in this manner. Bromide toxicity is dependent upon the state of iodine supply. In the rat, when there is a sufficient supply of iodine, a stable iodide to bromide concentration ratio ($[I^-]/[Br^-]$) in the thyroid is rapidly established. Under conditions of high bromide intake and sufficient iodine supply, there is increased iodide elimination from both the thyroid and skin in rats; the rate of elimination accelerates as iodine supply declines. The result is a marked decrease in iodide accumulation in the thyroid. In rats with moderate iodine deficiency, increased bromide intake results in decreased production of iodinated thyronines, as well as the $[I^-]/[Br^-]$ in the thyroid. Under these conditions, thyrotropic stimulation occurs as a compensatory response to restore iodide levels in the thyroid. Additional studies demonstrated that bromide displaces inorganic iodide ions in the thyroid more readily than those that are covalently bound; even a high bromide intake did not displace covalently bound iodine in these studies. In lactating rats, a high bromide intake caused a decrease in iodide accumulation in the mammary glands, and increased iodide elimination through the kidneys.

Bromide is excreted primarily in the urine. The elimination half-life of bromide is generally 3-8 days in rats and 12 days in humans; however, bromide's half-life decreases when sodium chloride intake is increased. Conversely, the half-life of bromide may be increased by a decreased sodium chloride intake.

Sodium bromide was of low acute toxicity via the oral route in rats and the dermal route in rabbits. No information was available regarding the acute toxicity of sodium bromide via the inhalation route. In rabbits, sodium bromide was a minimal to mild eye irritant and was not a dermal irritant. Testing in guinea pigs did not suggest that sodium bromide is a dermal sensitizer. Ammonium bromide had a similar acute toxicity profile to sodium bromide, and is considered to be of low acute toxicity via the oral and dermal routes in rats. An acute inhalation study with ammonium bromide in the rat revealed moderate acute toxicity via this route. In rabbits, ammonium bromide was a mild eye irritant, but was not irritating to the skin. It was not considered to be a dermal sensitizer based on a study conducted with guinea pigs.

Several short-term rat studies, ranging from two to 19 weeks in duration, were available in the published literature. These studies were conducted with either sodium bromide in the diet or potassium bromide in drinking water. Due to limited reporting details in most of the published studies, there were challenges with estimating administered doses. The focus of the investigations in many of these studies was the thyroid gland, and the results generally demonstrated that bromide exposure is associated with activation of the thyroid gland and hypothyroidism. This was evidenced by increases in thyroid weight and decreases in serum thyroxine (T_4), immunocytochemical staining for T_4, and colloid in treated rats. Histopathological examination revealed decreases in the size of thyroid follicular cells, accompanied by increases in the number of these cells. An increase in the height of the follicular epithelium was also observed. These histopathological findings have been described in the literature as resembling parenchymatous goitre in humans. Published 28- and 90-day dietary studies with sodium bromide also revealed histopathology indicative of thyroid activation at the higher dose levels. Effects on thyroid hormones and thyroid weight often occurred at lower dose levels in these studies. The LOAEL for thyroid findings in these rat dietary studies was estimated to be in the range of 48 to 93 mg Br^-/kg bw/day. More recent literature studies conducted with

potassium bromide administered in drinking water to rats for two to 19 weeks included more detailed histopathological examination of the thyroid. In these studies, morphological changes were observed in the thyroid gland that were similar to those reported in the older studies, but at significantly lower dose levels (estimated in the range of 0.7-1 mg Br^-/kg bw/day). These histopathological findings in the more recent studies were accompanied by decreases in serum T_4 levels and colloid content in the thyroid. Additional thyroid investigations were included in these studies, such as electron microscopy examinations, proliferating cell nuclear antigen assays, and measurements of iodide and bromide levels. The findings from these additional investigations included hypertrophy and hyperplasia of the endoplasmic reticulum, microfollicular rearrangements, increased mitotic activity of the follicular epithelium, and decreases in the $[I^-]$ /$[Br^-]$ ratio in the thyroid. These results correlate with the thyroid histopathology findings observed at the lower dose levels in the more recent sodium bromide studies. In an additional rat study using similar low dose levels of potassium bromide in drinking water, electron microscopy examinations revealed microvascular changes of the thyroid gland. Overall, while the available evidence demonstrates that bromide exposure is associated with activation of the thyroid gland and hypothyroidism, there were inconsistencies with respect to effect levels for thyroid histopathology when comparing the results among the studies. The reasons for these inconsistencies could not be determined and thus, there is uncertainty with respect to establishing a specific point of departure for thyroid effects in the rat.

There were other findings in the rat short-term dietary studies with sodium bromide. These included decreased relative prostate weight and secretory activity at the same dose level at which the thyroid findings were observed in a 28-day study. Clinical signs, hindleg motor incoordination, altered clinical chemistry findings, as well as decreases in body weight gain, organ weights (including testes), spermatogenesis, tubule diameter and number of corpora lutea were observed at the highest dose level tested in a 90-day study. In a 4- to 12-week study with male rats, increased TSH, FSH, and insulin, and decreases in testosterone, growth hormone and corticosterone were also observed at the highest dose level.

Rat short-term dietary studies with ammonium bromide were available. In a 28-day study, decreased testes weights were noted at all dose levels tested, whereas clinical signs of toxicity and decreases in other organ weights (epididymides, heart, kidneys and lungs) were observed at and above the mid-dose level. Additional findings at the high-dose level included decreases in body weight and food consumption. No histopathological examination was conducted in the 28-day study. A 90-day study included a neurotoxicity assessment, as well as a 4-week recovery period. Effects were observed at all dose levels in this study. These included clinical signs, some of which could be indicative of neurotoxicity (for example, decreased limb grip strength and gait abnormalities), as well as decreases in the weights of several organs (including brain, thyroid, kidney, liver, testes and epididymides) and cholesterol. At the mid-dose level, increases in several white blood cell parameters, as well as the incidence of histopathological findings in nervous tissue were observed, along with decreased body weight, bodyweight gain and food consumption. No thyroid histopathological findings were observed in this study; thyroid hormone levels were not examined.

Short-term dietary studies with sodium bromide administered to rats on chloride- or iodide-reduced diets were also conducted to investigate the impact of these ions on the toxicity of bromide. Reduction of these ions in the diet significantly enhanced bromide's toxicity. This was

most evident from the fact that mortality was observed with ion-reduced diets, whereas all animals receiving regular diet survived bromide treatment. Furthermore, in 4- and 12-week studies with chloride-reduced diets, mortality occurred at bromide dose levels at or below those producing thyroid effects in animals receiving regular diets. In the 12-week bromide study with chloride-reduced diets, thyroid activation occurred at lower dose levels than those at which thyroid findings were observed in bromide studies with regular diets. Other findings in the 12-week study were similar in nature (for example, clinical signs, hindlimb motor incoordination, and decreases in spermatogenesis and number of corpora lutea), but occurred at an approximately 10-fold lower dose level than in studies with regular diets. In a 4-week dietary study that focussed on the thyroid, sodium bromide was administered to rats fed an iodine-deficient diet. In this study, relatively high doses of sodium bromide were used, and so it was not possible to assess whether thyroid effects occurred at a lower dose compared to the studies using a regular diet. However, mortality, an endpoint not observed in any of the studies using regular diets, was observed at a dose generally associated with thyroid effects in the studies using regular diets. In each of the studies with reduced chloride or iodide diets, plasma levels of bromide were elevated compared to those in studies with regular diets, suggesting that these ions may impact the toxicity of bromide through a toxicokinetic mechanism, such as enhancing the clearance of bromide, or competing for absorption. In the available studies, dietary chloride was generally available as sodium chloride. Since sodium is actively reabsorbed in the kidneys, whereas the reabsorption of chloride is passive, it has been hypothesized in the more recent literature that the presence of the sodium ion, rather than the chloride ion, influences the toxicokinetics of bromide. One study demonstrated that the excretion rate of radiolabeled bromide was proportional to sodium intake, regardless of the anion with which it was accompanied (for example, Br^-, Cl^-, HCO_3^-, ClO_4^-), leading the authors to conclude that the elimination half-life of bromide depends on intake of sodium ion rather than chloride ion.

Several short-term dog studies with sodium bromide were available in the published literature; however they were of limited utility for hazard characterization purposes as they were either limited in scope or by reporting detail due to the age of the study. One study examined the concentration of bromide and chloride levels in prostatic secretions of dogs following five days of sodium bromide administration via capsule at a single dose level. Clinical signs and lethargy were noted in the treated dogs. Decreased levels of chloride were observed in the serum, as well as in prostatic secretions, whereas increased levels of bromide were observed in these matrices. In another study, potassium bromide was administered in the diet for 121 days at a single dose level; the dose was increased over the last six days. Neurological effects were noted following the dose increase, and included caudal paresis and ataxia, as well as agitated and hyperexcitable behaviour. Alterations in brain stem auditory evoked responses (BAERs) were also noted in treated animals throughout the study. The altered BAER findings suggest that bromide may cause delays in conduction along peripheral and central sensory pathways. In an older capsule study that incorporated dosing schedules from two to 20 weeks and included progressive dosing schedules in some of the experiments, clinical signs, skin lesions and mortality were observed at higher dose levels.

In a published two-year rat study in which a single potassium bromide dose level was administered in the diet, treatment-related findings included increases in body weight, food and water consumption, as well as an increase in the incidence of prostatitis. There was a statistically significant increase in the incidence of mononuclear cell leukemia in females treated with

potassium bromide that slightly exceeded the historical control range for the conducting laboratory. However, concern for these tumours was low given the fact that this is a common spontaneous tumour type in the strain of rats tested (F344), and other laboratories reported background incidences well in excess of those noted in this study. This study was considered supplemental in view of the single dose level tested. Guideline carcinogenicity studies in rats and mice were not available.

A full complement of genotoxicity studies were available, conducted with either sodium bromide or ammonium bromide. The results of these studies were negative, and the weight of evidence suggests that sodium bromide is unlikely to have genotoxic potential.

Bromide's association with neurological effects has been well-established through its long-standing use as a sedative and anticonvulsant. Guideline acute and short-term neurotoxicity tests were not available for sodium bromide. There are many studies in the published literature that investigate the neurological effects of sodium bromide in rodents; however, the majority of these are limited by a paucity of reporting details and/or by the fact that they were not designed to establish, or did not achieve a NOAEL. Notwithstanding these limitations, the available information in adult animals indicates that sodium bromide produces clinical signs of neurotoxicity at relatively high doses. At lower doses, it affects neurotransmission and cholinesterase levels, and exhibits GABA-like activity in peripheral nervous tissue (for example, in the rodent superior cervical ganglion). There is also evidence that bromide may exert neurological action via displacement of chloride ions at chloride channels. In a short-term dietary neurotoxicity study in the mouse, sodium bromide was associated with decreased evasion time (that is, time to escape a small isolated area), increased motor activity, and alterations in the temporal pattern of activity. The study authors suggested that these effects were indicative of behavioural 'disinhibition.' In a 90-day dietary study in which adult rats received ammonium bromide, clinical signs and neurohistopathology were observed at relatively low dose levels.

There is evidence in the published literature that sodium bromide impacts the developing nervous system following in utero and/or post-natal exposure. In a modified developmental neurotoxicity (DNT) study in rats, sodium bromide administration to dams via drinking water from gestation day 5 to 15 resulted in treatment-related effects in offspring at the single dose level tested. These effects included decreases in brain and body weight, as well as protein content in the brain, all of which persisted into adulthood. Additional brain examinations revealed effects on the olfactory glomeruli, which included an initial delay (approximately 2-3 days) in the appearance of acid phosphatase activity, as well as an increase in the size of the glomerular profiles. An enucleation study investigating neurological effects of sodium bromide administered in drinking water on developing rat offspring was available. Although the dosing regime was unclear, it appeared that pups received the test substance via lactational exposure until weaning, after which point it was assumed that they received it directly through drinking water. In this study, pup eyes were enucleated on post-natal day (PND) 1, 15 or 30. When pups were 3-4 months of age, evoked potentials in response to electrical stimulation were mapped to investigate whether sodium bromide affected the period of neuroplasticity during which somatosensory projections can by modified by visual deafferentation. It had been demonstrated in previous studies that the normal period of neuroplasticity was within the first postnatal week. In offspring that had undergone enucleation on PND 15, sodium bromide treatment caused an expansion of cortical areas responsive to electrical stimulation, similar to that observed in rats

enucleated on PND 1. This provided evidence that sodium bromide treatment may extend or shift the critical period of neuroplasticity in offspring by 15 days or more after birth. A guideline DNT study was not available.

A rat three-generation reproductive toxicity study with sodium bromide administered in the diet was available in the published literature. Decreased fertility was observed in the F_0 generation at the second highest dose level, and at the highest dose level, no females became pregnant. Cross-mating experiments demonstrated that the observed effects were due to infertility in both sexes. It is noteworthy that decreases in spermatogenesis and in the number of corpora lutea were observed in the 90-day dietary study with sodium bromide. Additional findings in adult animals in the reproductive toxicity study included decreases in serum T_4 levels in males at all dose levels, and decreased body weight, adrenal weights and relative uterine weights in females at the higher dose levels. No results were reported for thyroid histopathology, and it was unclear whether this parameter was examined in the study. In offspring, decreased viability occurred at the same dose level at which decreased fertility was observed in the parental animals. Investigations of transplacental transport of bromide revealed that bromide levels in the kidneys of fetuses and dams were similar, demonstrating in utero exposure to bromide. A rat one-generation reproductive toxicity range-finding study with ammonium bromide administered in the diet revealed similar effects on fertility and offspring viability. A guideline multi-generation reproductive toxicity study with sodium bromide was not available.

Two lactational transfer studies in rats conducted with sodium bromide in the drinking water were available in the published literature. In the first study, sodium bromide was administered to dams during the lactation period in one experiment, and during pre-mating, gestation and lactation period in a second experiment. Treatment in both experiments resulted in decreased retention of radiolabeled iodine (^{131}I) in dams, as well as decreased lactational transfer of ^{131}I to nursing pups and pup body weights at both dose levels tested. Additional findings included decreases in plasma T_3 and T_4 levels in pups and dams, as well as in milk production. It was unclear whether these latter findings were from the first or second experiment (that is, following lactational exposure or in utero/lactational exposure). In the second lactational transfer study, sodium bromide was administered to dams during the lactation period only. Decreases in food and water consumption, as well as in body weight were observed in dams at the highest dose level. Milk production and chloride levels in the milk were also decreased at this dose level. At the same dose level, mortality and deceased body weight were observed in pups. Following subcutaneous injection with radiolabelled bromide ($^{82}Br^-$; in the form of potassium bromide) to lactating dams, $^{82}Br^-$ appeared in the bodies of the pups beginning three hours after administration to dams, and levels continued to increase over the following 22 hours. In this study, it was estimated that pups received a dose through the milk that was approximately 3-fold lower than that received by the dams. The effects observed in the pups, however, were more severe, as evidenced by pup mortality, as well as greater decreases in body weight compared to dams. This suggests a greater sensitivity of the young animal compared to the adult animal to the effects of sodium bromide. Collectively, these lactational exposure studies demonstrate that bromide is transferred to offspring via lactation, where it can impact thyroid function and cause other toxicity in the young animal. However, as there is evidence in the published literature that bromide affects the production and composition of breast milk, it is difficult to determine whether the mortality and decrease in body weights in pups observed in the lactational studies were directly related to bromide toxicity or were secondary to the effects on breast milk.

Guideline rat developmental toxicity studies conducted with sodium bromide and ammonium bromide were available. In the study with sodium bromide, maternal toxicity was observed at the highest dose level. This was characterized by mortality, increased food consumption during gestation, decreased body weight gain, and clinical signs of toxicity. At the highest dose level, fetal toxicity was characterized by an increased incidence of variations and malformations. Variations included irregular ossification of one or more cranial centres and unossified or reduced ossification of sternebrae. Treatment-related malformations were observed in the urogenital tract (absent/small kidney and/or ureter), gonads (absent/narrow uterine horn, small indeterminate gonad) and ribs (distorted/abnormal). At a lower dose level, reduced ossification was observed. Although there was no evidence of maternal toxicity at this dose level based on the parameters examined, other effects, including thyroid findings in adult animals, were observed at lower dose levels in other studies. It should be cautioned that many of these other studies were conducted with males only, and with a different test substance (potassium bromide) and route of administration (drinking water). In the developmental toxicity study conducted with ammonium bromide, a similar spectrum of developmental toxicity was observed. However, the effects in the fetus were observed at a lower dose level compared to the sodium bromide study, and some additional variations (for example, undescended/displaced testes, dilated renal pelvis or ureter, haemorrhages in various locations) and malformations (for example, reduced/absent thyroid) were observed. A guideline developmental toxicity study in a non-rodent species was not available.

Several studies designed to assess the effects of sodium or potassium bromide in humans were available in the published literature. A clinical trial investigating the use of potassium bromide in adults suffering from an autoimmune disease of the thyroid gland known as Graves' disease was available. This disease is characterized by excessive production of thyroid hormones, goitre, and symptoms of hyperthyroidism such as rapid heartbeat and weight loss. Treatment with potassium bromide in combination with the standard treatment for this disease, methimazole, resulted in improved clinical hyperthyroidism symptoms; these symptoms also improved significantly faster with the combined treatment. Compared to treatment with methimazole alone, the combined treatment also further decreased T_3 and T_4 levels, while further increasing TSH levels. In another study, 22% of adults with thyroid disorders had plasma bromine levels that were considered to exceed the normal range. Further, the percentage of patients with high TSH levels, but normal T_4 levels, was increased in the group with higher-than-normal bromine levels. Published literature studies assessing the systemic toxic effects of bromide in humans are not included in this assessment due to the PMRA's policy on the use of human data (SPN2016-01, *Restricted Use of Human Studies with Pesticides for Regulatory Purposes*).

Many human case studies for sodium and potassium bromide were available in the published literature. The majority of these related to historical medicinal uses of bromides, and when available, the dose and/or plasma levels of bromides in many cases were relatively high. Collectively, the case studies indicated that oral exposure to bromides during pregnancy was associated with effects in newborns including clinical signs of toxicity such as hypotonia and diminished reflexes. These signs were most often seen in the presence of overt symptoms in the mothers as well, and plasma levels in the newborns and mothers, when available, were greater than 25 mmol/L. Case studies in adults with a history of medicinal use of bromides indicated that such uses were associated with clinical signs that included tremors, diminished reflexes, drowsiness, hallucinations, delusions, mental confusion, ataxia, fatigue, speech abnormalities,

memory deficits, and aggressive behaviour. Plasma levels in these patients, when available, ranged from approximately 4 to 150 mmol/L (mean value of 34 mmol/L). A few case studies also reported dermal symptoms associated with oral bromide use. In one case, an infant who had been treated with sodium bromide for approximately one month had several large vegetative plaques with an erythematous base, described as bromoderma. In addition, there were two adult cases describing ulcerated, necrotic and/or granulomatous lesions diagnosed as bromoderma. Plasma levels were reported for the adult cases of bromoderma, and were much lower (approximately 0.9 to 1.5 mmol/L) than those documented for the other clinical symptoms described above.

Overall, the available toxicity data indicate that sodium bromide causes effects on the thyroid and nervous system. There is clear evidence in the published literature that bromide causes thyroid effects in the young animal through in utero and lactational exposure, as well as the adult animal. However, thyroid histopathology, which was the critical endpoint in adult animals, was not assessed in the young animal. Effects of bromide on the nervous system in adults, as well as in the young animal following in utero and/or lactational exposure, have also been well-documented in the literature. However, NOAELs have not been established for most of these findings, and guideline neurotoxicity testing, including the DNT study, is not available. Consequently, there is insufficient information to fully characterize the neurological effects of sodium bromide on the adult and the developing animal, as well as thyroid toxicity in the young. In addition, a guideline multi-generation reproductive toxicity study and developmental toxicity testing in a non-rodent species were not available. For the above reasons, sensitivity of the young cannot be adequately assessed. There are also limitations with respect to the assessment of chronic toxicity and carcinogenicity in adult animals.

The effects noted on the thyroid in the special studies assessing thyroid effects in rats following two and nine weeks exposure to potassium bromide in the drinking water were considered to represent the most sensitive indicator of toxicity in the available toxicology information. Thyroid effects were observed at a concentration of 10 mg Br^-/L, which was the lowest tested concentration. This was estimated to correspond to a dose of approximately 1 mg Br^-/kg bw/day. The thyroid effects included morphological changes, accompanied by decreased plasma T_4 levels, colloid content, and I^-/Br^- thyroid molar concentration ratio. Electron microscopy examination revealed changes in the thyroid at this dose level. Although the 1 mg Br^-/kg bw/day value serves as a reference point for health risk assessment, there were some inconsistencies in the thyroid literature findings as previously noted, since this was a lower value than had been reported for similar endpoints in earlier publications. These inconsistencies, along with the limitations in the toxicology database noted above, precluded the establishment of a robust point of departure. For this reason, target margins of exposure for risk assessment were not set.

Due to its ubiquitous nature, background levels of bromide in both food and seawater were also taken into consideration when characterizing hazards of sodium bromide. Dietary intakes of bromide are reported to be in the range of 2-8 mg/day, which results in approximate daily doses in the range of 0.025-0.1 mg/kg bw/day for an 80 kg adult, and bromide levels in sea water are reported to be in the range of 65-80 mg/L. As described in Section 3.5.3.2, use of some sodium bromide spa products results in bromide levels that are similar to those reported in sea water. However, sea water, unlike spa water, contains relatively high levels of other ions (for example, chloride, sodium and iodide) which have been shown to decrease the toxicity of bromide based

on evidence from rat toxicity and toxicokinetic studies. For this reason, use of sea water bromide levels as a reference point for assessing human health risks for spa scenarios is likely to underestimate risk.

Results of the toxicology studies conducted on laboratory animals with sodium bromide are summarized in Appendix II, Tables 1 and 2.

Bromate

Bromate is a DBP of human health concern that appears in drinking water as a result of some water disinfection methods. There is evidence that bromate may also be formed in pool and/or spa water with the use of bromide-based sanitizers. Bromate health assessments were conducted recently by other regulatory bodies, including Health Canada's Federal-Provincial-Territorial (FPT) Committee on Drinking Water (2015), the California Environmental Protection Agency (2009), and the World Health Organization (2005). A summary of the toxicological profile for bromate based on information from these recent health assessments is included below, with emphasis on the recent Health Canada assessment. The studies included in these assessments were conducted with potassium or sodium bromate, which, like sodium and potassium bromide, dissociate to the ionic forms in biological systems.

Potassium bromate administered via gavage to rats was rapidly absorbed, with maximum plasma bromate concentration reached after 15 minutes and peak urine concentrations reached after two hours. Oral and intravenous studies in rats with potassium bromate suggested that bromate degradation was saturated at high doses, and that gastric and plasma degradation may reduce the systemic bioavailability of orally administered bromate at low dose levels.

Orally administered potassium bromate was rapidly degraded in rats, with no bromate detected in tissues 24 hours after dosing; however, significant increases in bromide concentrations were observed in kidney, pancreas, stomach, liver, spleen, red blood cells and plasma. In vitro studies suggested that bromate was reduced to bromide in body tissues, probably by glutathione or another sulfhydryl-containing compound; however, other studies suggested that bromate was stable in the body and that only small amounts were reduced to bromide. An in vivo radioisotope (^{18}O) study in rats administered single doses of varying concentrations of potassium bromate suggested that in the low-dose range there was a dose-dependent distribution of bromate to target organs. Concentrations were highest in liver and kidney; the thyroid concentration was approximately 3-fold lower than that in the kidney. Bromate was excreted primarily in the urine as both unchanged bromate and as bromide.

Potassium bromate was highly acutely toxic via the oral route in rats, mice, hamsters, and rabbits. Effects in rats following acute oral administration included hemochromatosis in kidney, liver and spleen, diarrhea, sedation, reversible oxidative damage to the kidney, and indication of oxidative stress in the blood. Based on evidence from human case studies, effects following acute oral exposure to bromate include vomiting, diarrhea and abdominal pain. Other effects include oliguria, anuria, deafness, vertigo, hypotension, depression of the central nervous system, thrombocytopenia and renal failure. Serious poisonings in children were reported at doses of 46-92 mg bromate/kg bw/day, and lethal doses are estimated to be 150-385 mg bromate/kg bw/day.

Administration of potassium bromate in drinking water to mice and rats for periods of two to 13 weeks resulted in decreases in body weight and increases in various blood clinical chemistry parameters. In male rats, increased kidney weights and the appearance of hyaline droplets in renal tubules were observed following two and 13 weeks of exposure. The lowest reported no-observed-effect level (NOEL) was 8.1 mg/kg bw/day (100 mg/L) based on the absence of any microscopic alterations in the kidneys in rats.

A number of studies investigated the chronic toxicity of potassium bromate in rats, mice and hamsters that were dosed either via drinking water or via potassium bromate-treated bread-based diets. The key studies were conducted in rats exposed via drinking water. Most studies were conducted in males only; chronic toxicity testing in females was limited to a single study in rats which included only two dose levels. The kidney was the major target organ and non-neoplastic lesions included renal tubular degeneration and necrosis, hyaline droplets in proximal tubules, and increased hyperplasia of the renal papilla and pelvis (termed urothelial hyperplasia). Body weight was also significantly reduced. The NOAEL of 1.1 mg bromate/kg bw/day for renal pelvis urothelial hyperplasia was the lowest reported NOAEL for non-carcinogenic effects. Similar effects were not observed in rats or mice administered bread-based diets; it was noted that some bromate would be converted to bromide in baking, and that the diets were not assayed for bromate content.

Three 35-day National Toxicology Program (NTP) screening-level reproductive toxicity studies in rats administered sodium bromate via drinking water were available. The first study investigated effects on conception and early gestation, the second study assessed effects during late gestation and birth, and the third study examined effects on male reproductive parameters. These studies did not reveal any effects on litter data or reproductive parameters in females; however, decreased epididymal sperm density was observed in males at the highest dose level tested (22 mg bromate/kg bw/day). Sodium bromate was considered a selective male reproductive toxicant based on these findings. An additional multi-generation reproductive toxicity study was conducted with sodium bromate administered in drinking water to rats. There was evidence of renal toxicity in parental animals, as well as decreased sperm density in males; there were no effects on reproductive litter data. No developmental toxicity studies were available.

Animal toxicity studies and human case studies indicated that high oral dose levels of bromate produces ototoxicity, which appears to be mediated by peripheral auditory nerve dysfunction as opposed to central brainstem intoxication. Guideline neurotoxicity studies were not available for bromate. Potassium bromate administered subcutaneously to guinea pigs in combination with thioglycolate (used in permanent hair curling solutions) resulted in prolonged auditory wave I latency, suggesting a delayed auditory nerve conduction velocity. Human case studies demonstrated that high-dose ingestion of bromate could produce rapid-onset (within 4-16 hours) hearing loss described as severe to profound in nature. There is uncertainty regarding whether the hearing loss is reversible, as well as the effects on this parameter following long-term exposures to lower doses. The absence of DNT testing is of concern given the effects that have been observed on ototoxicity.

A 4-week immunotoxicity study in mice exposed to sodium bromate in drinking water was available. Treatment-related effects included increased spleen weights and a dose-related increase in reticulocytes. Although not dose-related, there was a slight decrease in the ability of macrophages to suppress melanoma cell proliferation, which may indicate potential for bromate to suppress immunological defenses against tumour cells.

Potassium bromate caused genetic damage in in vitro and in vivo assays. In vitro findings included chromosomal aberrations, micronuclei formation, and DNA strand breaks, as well as increases in gene mutations in bacteria, rats, mice, and humans. In vivo assays revealed micronuclei induction in rats and mice. Oxidative stress and loss of heterozygosity have been suggested as possible mechanisms of mutagenicity.

Carcinogenicity studies were available in several species. Potassium bromate administered via drinking water caused various tumours, including renal cell adenomas and adenocarcinomas in male mice and rats of both sexes. Thyroid adenomas and adenocarcinomas, as well as mesotheliomas in the tunica vaginalis of the testes, were also observed in male rats. The rat appeared to be more sensitive to the carcinogenic effects of bromate than other species tested. There were limitations with regards to carcinogenicity testing in that testing in females was limited to a single study in rats in which only two dose levels were tested. Studies investigating the relationship between dose and time-to-tumour formation were conducted in male rats receiving potassium bromate in drinking water. These investigations demonstrated treatment-related renal cell tumours and mesotheliomas of the tunica vaginalis following 52 weeks of treatment, and thyroid follicular tumours as early as 26 weeks into treatment. A series of NTP studies were conducted investigating the effects of bromate on genetically modified mice (Tg.AC hemizygous or p53 haplosufficient). In these studies, potassium bromate was administered dermally or in drinking water for 27-48 weeks. Neoplastic lesions were not observed, and it was concluded that these mice were not sensitive models for detecting carcinogenic effects of bromate.

Additional studies were conducted with SENCAR mice, selectively bred for sensitivity to skin tumor induction. In these studies, potassium bromate administered dermally or in drinking water was not carcinogenic following 51 weeks of treatment in the presence or absence of dimethylbenzanthracene (DMBA) initiation.

Many mechanistic studies were generated to investigate modes of action (MOAs) for bromate-induced tumour formation in rats. In the recent review by Health Canada's FPT Committee on Drinking Water, several MOAs were explored using the ILSI/IPSC human relevance framework.[1] These included oxidative stress, α_{2u}-globulin nephropathy, direct-acting mutagenesis, thyroid hormone imbalance, sex hormone imbalance, immunosuppression, and alterations in apoptosis. Although oxidative stress was considered to be a plausible MOA for the induction of kidney tumours, insufficient data were available to support this MOA. It was considered that the MOA involving α_{2u}-globulin nephropathy may play a contributing role in inducing kidney tumours observed in male rats; however, it did not appear to be the main cause of these tumours. The possibility that bromate causes tumours via a MOA involving direct-acting

[1] A full description of the various MOAs that were explored appears in the 2015 bromate assessment by Health Canada's FPT Committee on Drinking Water

mutagenesis was considered to be questionable as less evidence existed for bromate mutagenicity at tumour-relevant doses in rats. The other MOAs noted above were found to have insufficient data for analysis. Overall, MOAs were not adequately supported for any of the various tumour types. The PMRA is in agreement with this assessment. Therefore, low-dose linear extrapolation was used to quantitatively assess bromate cancer risks.

Overall, the available toxicity data demonstrated that the kidney and testes are targets of bromate toxicity. Effects on the kidney provided the lowest point of departure following short- and long-term dosing, with effects on sperm parameters also occurring in reproductive toxicity studies at similar doses. There was evidence suggesting that bromate is associated with neurotoxicity in the form of ototoxicity. Guideline neurotoxicity testing, including the DNT study, and developmental toxicity studies are not available. Therefore, sensitivity of the young could not be adequately assessed. There were also limitations with respect to the assessment of chronic toxicity and carcinogenicity in female animals. Consistent with the recent Health Canada drinking water assessment, an additional 10-fold uncertainty factor was applied in the risk assessment to account for these data gaps.

The toxicology endpoints for bromate for use in the human health risk assessment are summarized in Appendix II, Table 2.

3.1.1 *Pest Control Products Act* Hazard Considerations

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

Sodium Bromide

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database included a guideline developmental toxicity study in the rat conducted with sodium bromide, as well as a guideline developmental toxicity study and a range-finding reproductive toxicity study conducted with ammonium bromide in rats. There were also several studies in the published literature that examined effects on the developing young; these studies were either limited by factors such as not examining all parameters required in the respective guidelines or by not identifying a NOAEL. The literature studies in rats included a 3-generation reproductive toxicity study, two studies examining the effects of lactational and/or in utero exposure to bromide, and a study that examined neurological endpoints following in utero bromide exposure. The available toxicity data indicate that sodium bromide causes effects on the thyroid and nervous system. There is evidence in the published literature that bromide causes thyroid effects in the young animal through in utero and lactational exposure, as well as in the adult animal. However, thyroid histopathology, which was the critical endpoint in adult animals, has not been assessed in the young animal. Effects of bromide on the nervous system in adults, as well as in the young animal following in utero and/or lactational exposure, have also been well-documented in the literature. However, NOAELs have not been established for most of these findings, and guideline neurotoxicity testing, including the DNT study, was not available.

Consequently, the neurological effects on the adult or the young animal and potential thyroid toxicity in the young have not been fully characterized. In addition, a guideline multi-generation reproductive toxicity study and developmental toxicity testing in a non-rodent species were not available. For the above reasons, sensitivity of the young cannot be adequately assessed.

With respect to potential prenatal and postnatal toxicity, in the rat developmental toxicity study with sodium bromide, malformations were observed at the high dose level in the presence of maternal toxicity. Decreased ossification was observed at a lower dose level in the absence of maternal toxicity. However, evidence from other studies suggests that maternal effects in the form of thyroid toxicity would likely be occurring at these same doses. A similar spectrum of developmental effects was observed in the rat study conducted with ammonium bromide, but at lower doses. Decreased offspring viability was noted in the 3-generation reproductive toxicity study, as well as in the lactational transfer studies, all of which were conducted with sodium bromide. These effects on offspring viability occurred at doses associated with maternal toxicity such as decreased body weight and/or food consumption. In the published study that examined neurological endpoints in the developing rat, decreases in brain weight and protein content, as well as structural changes in the brain following in utero exposure to sodium bromide were observed. In an enucleation study, alterations to the critical period of neuroplasticity were observed following exposure of young animals to sodium bromide. Although there were limited data available to assess the effects of bromide exposure on thyroid function in the young animal, the available information demonstrated that thyroid hormones were decreased following in utero and lactational exposure. Collectively, the lactational exposure studies demonstrated that bromide is transferred to offspring via lactation, where it can impact thyroid function and cause other toxicity in the young animal. The effects observed in the pups in these studies were more severe, as evidenced by greater decreases in body weight as well as mortality in the pups. This suggests a greater sensitivity of the young animal compared to the adult animal to the effects of sodium bromide. However, as there is evidence in the published literature that bromide affects the production and composition of breast milk, it was difficult to determine whether the mortality and decrease in pup body weights observed in the lactational studies were secondary to the effects on breast milk, or rather reflected an increase in sensitivity.

As previously mentioned, there were limitations in the toxicology database, including the fact that many studies did not provide NOAELs, and that there were inconsistencies in the effect levels for thyroid findings. These limitations precluded the establishment of a robust point of departure. For this reason, target margins of exposure for risk assessment were not set. Given that a qualitative approach was selected for risk assessment, quantitative determination of a *Pest Control Products Act* factor was not undertaken.

Bromate

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, several studies investigating reproductive toxicity were available. Developmental toxicity studies were not available. There is evidence in the published literature suggesting that bromate causes effects in the nervous system. Findings from animal toxicity studies and human case reports suggest that bromate produces neurotoxicity in the form of ototoxicity. Findings from a subcutaneous study in guinea pigs suggested that potassium bromate produced a delay in auditory nerve conduction velocity.

Human case studies demonstrated that high-dose ingestion of bromate could produce rapid-onset hearing loss described as severe to profound in nature. However, a DNT study, in addition to guideline neurotoxicity testing, is not available for bromate.

With respect to potential prenatal and postnatal toxicity, the available reproductive toxicity studies did not provide evidence of effects on litter parameters or effects indicative of sensitivity of the young.

Overall, residual uncertainty remains concerning characterizing potential sensitivity of the young due to the lack of developmental toxicity and DNT testing. As this concern was addressed through the use of a database uncertainty factor of 10-fold in the risk assessment, as previously described, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose (ARfD)

Bromide and Bromate

An ARfD was not required as there are no associated food uses.

3.3 Determination of Acceptable Daily Intake (ADI)

Bromide and Bromate

An ADI was not required as there are no associated food uses.

3.4 Cancer Risk Assessment

Bromide

The weight of evidence did not suggest that bromide was genotoxic. Although limited, the available information did not suggest carcinogenic potential, and consequently a cancer assessment was not conducted.

Bromate

Treatment-related increases in several tumours were observed following administration of potassium bromate, including renal cell adenomas and adenocarcinomas in male mice and rats of both sexes. Thyroid adenomas and adenocarcinomas, as well as mesotheliomas in the tunica vaginalis of the testes, were also observed in male rats. It was concluded that the weight of evidence was not sufficient to support any of the proposed MOAs. Therefore, low-dose linear extrapolation was used to quantitatively assess bromate cancer risks. The most conservative q_1^* value was 0.115 $(mg/kg\ bw/day)^{-1}$ for the testicular tumours, and this value was used for the cancer risk assessment for bromate.

3.5 Occupational and Non-Occupational Risk Assessment

Bromide

Occupational and non-occupational risk is typically estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). As a robust point of departure and target MOE for bromide were not established, a qualitative approach to the exposure assessment was used for assessing potential non-cancer health risks of concern. Exposure estimates were calculated using a weight-of-evidence approach that is based on the best available data and scenario-specific models. The exposure outputs were then considered qualitatively within the context of the most sensitive indicator of toxicity, namely effects on the thyroid, in addition to considering non-pesticidal sources of exposures (sea water, dietary).

As health risks of concern were identified for bromide, risk mitigation is proposed by reducing pesticidal exposure, to the extent possible, with emphasis on the highest exposure products.

Bromate

For bromate (swimming assessment only), the best available data for the cancer exposure estimates were surrogate data from the related active BCDMH (1-bromo-3-chloro-5,5-dimethylhydantoin). Due to this, a qualitative approach to the exposure assessment was also used to assess cancer health risks of concern. Both cancer and non-cancer risks were assessed; however, cancer was the risk driver from bromate exposure.

As health risks of concern were identified for bromate, risk mitigation is proposed by reducing pesticidal exposure, to the extent possible, with emphasis on the highest exposure products.

3.5.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

Bromide

Short- and Long-term Oral and Dermal

The effects noted on the thyroid gland in the special studies assessing thyroid effects in rats following two and nine weeks of exposure to potassium bromide in the drinking water were considered to represent the most sensitive indicator of toxicity in the available toxicology information. Thyroid effects were observed at a concentration of 10 mg Br^-/L in the drinking water, which was the lowest tested concentration and was estimated to correspond to a dose of approximately 1 mg Br^-/kg bw/day. These effects included morphological changes in the thyroid gland, accompanied by decreases in plasma T_4 levels, colloid content in the thyroid gland, and in the $[I^-]/[Br^-]$ thyroid ratio, as well as changes in the thyroid gland as viewed by electron microscopy examination. Although the 1 mg Br^-/kg bw/day value serves as a reference point for health risk assessment, the limitations in the toxicology database outlined previously precluded the establishment of a robust point of departure. For this reason, target margins of exposure for risk assessment were not set. A qualitative approach to the risk assessment was undertaken instead, which also included consideration of environmental exposures to bromide.

Bromate

Short-term Oral and Dermal

For short-term oral and dermal risk assessments, a NOAEL of 8 mg/kg bw/day from short-term toxicity and reproductive toxicity drinking water studies, which were considered co-critical, was selected. In short-term drinking-water studies with potassium bromate in rats there was evidence of renal toxicity beginning after two weeks of exposure. The lowest reported NOEL was 8.1 mg/kg bw/day (100 mg/L) based on microscopic alterations in the kidneys at higher dose levels. In reproductive toxicity studies, a NOAEL of 7.7 mg bromate/kg bw/day was established overall based on changes in sperm density at 22 mg bromate/kg bw/day. Short-term toxicity studies via the dermal route assessing the endpoints of concern were not available.

The target MOE for occupational and residential scenarios is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. Consistent with the recent Health Canada drinking water assessment for bromate, an additional 10-fold factor was applied to account for database deficiencies as outlined previously. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization Section.

Bromate

Long-term Oral and Dermal

For long-term risk assessments via the oral and dermal routes, the NOAEL of 1.1 mg/kg bw/day was selected, which was the lowest reported point of departure (POD) for renal toxicity from chronic toxicity testing of potassium bromate administered in drinking water to rodents. Renal pelvis urothelial hyperplasia was observed at dose levels of 6.1 mg/kg bw/day and above. Some repeat-dose dermal studies (up to 51-weeks in duration) were available; however, they were conducted with genetically modified mice and designed to primarily assess carcinogenic potential.

The target MOE for occupational and residential scenarios is 1000. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. Consistent with the recent Health Canada drinking water assessment for bromate, an additional 10-fold factor was applied to account for database deficiencies as outlined previously. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Dermal Absorption

A dermal absorption value was not required for bromate, as bromate exposure is not expected from the industrial uses of sodium bromide, and dermal exposure from residential uses is addressed by the oral exposure assessment. A dermal assessment was however required for the occupational risk assessment of bromide, given that the skin is the primary route of exposure for the occupational uses. No dermal absorption studies were submitted by the registrant or identified in the literature for sodium bromide. As such, a value of 100% was used in the occupational risk assessment for bromide.

3.5.2 Occupational Exposure and Risk Assessment

Workers can be exposed to sodium bromide through mixing, loading, or applying the pesticide in industrial settings. Postapplication exposure may occur from handling treated process fluids or materials.

3.5.2.1 Handler Exposure and Risk Assessment

There are potential exposures to mixers, loaders, and applicators of sodium bromide in industrial settings. The following scenarios were assessed, as they are supported by the use pattern:

- Mixing/transfer of liquids, open pour
- Mixing/transfer of liquids, pump method (closed system)
- Mixing/transfer of solids, pour method
- Mixing/transfer of solids, place method (closed system)

Exposure to sodium bromide from its use in industrial settings is expected to be intermittent (a few minutes daily or once a week) over an intermediate to long-term duration, predominantly via the dermal route.

As bromate exposure is not expected to result from the industrial uses of sodium bromide, the occupational risk assessment focuses solely on exposure to bromide.

Exposure estimates were based on the American Chemical Manufacturer's Association (CMA), Antimicrobial Exposure Assessment Study. Even though there are a number of limitations associated with the study, it is currently the only occupational study available to assess potential exposure from antimicrobial uses. The study monitored 46 replicates for 6 active ingredients used in 4 different settings for 4 different application methods. Each replicate was representative of the time spent performing the antimicrobial-related task in one day; therefore the data was not normalized. Since application of biocides in industrial processes is similar regardless of the use site (for example, cooling towers, pulp and paper, etc.), it was considered appropriate to combine replicates based on the application method. Due to limitations in the exposure study (low and variable laboratory and field recoveries), the 90th percentiles generated from the input CMA data were used to estimate potential exposure to operators handling industrial products containing sodium bromide.

Exposure estimates for the industrial processes were considered qualitatively within the context of the most sensitive indicator of toxicity, namely effects on the thyroid. Health risks of concern were identified since the exposure estimates were close to the levels associated with thyroid toxicity. Additional mitigation measures such as the use of a closed transfer and loading system and increased PPE (protective eyewear, chemical-resistant coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves, and footwear) is being proposed for all industrial end-use products.

3.5.2.2 Postapplication Worker Exposure and Risk Assessment

There are no data currently available to characterize potential for postapplication worker exposure to sodium bromide from its use in industrial settings; however, exposure is expected to be low. Furthermore, postapplication workers will be wearing PPE in commercial and industrial sites, which would further limit any potential exposure.

3.5.3 Non-Occupational and Residential Exposure and Risk Assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

3.5.3.1 Bystander Exposure and Risk Assessment

The potential for bystander exposure is considered to be low during use in industrial process fluids (for example, pulp and paper mills, cooling towers, etc.) as these uses are limited to industrial settings. Similarly, no postapplication exposure to bystander/consumers is expected.

3.5.3.2 Residential Postapplication Exposure and Non-Cancer Risk Assessment

Swimmers are expected to have short- to long-term exposure to bromide and bromate while using swimming pools and spas.

Exposure estimates were based on the United States Environmental Protection Agency's (USEPA) Swimmer Exposure Model (SWIMODEL). The exposure equations used in SWIMODEL were originally conceived by the USEPA Office of Pesticide Programs Antimicrobials Division. These equations are used to develop screening exposure estimates tailored to swimmers exposed to pool chemicals and breakdown products in indoor pools and spas. The model uses well-accepted screening exposure assessment equations to calculate swimmers' total exposure expressed as a mass-based intake value (mg/day), or lifetime average daily dose (mg/kg/day). SWIMODEL focuses on potential chemical intakes only; it does not take into account metabolism or excretion of the chemical of concern.

Quantitative exposure estimates were based on the oral route of exposure. While short- and long-term dermal endpoints were established in Section 3.5.1, dermal, as well as inhalation, exposure is expected to be low for bromide and bromate due to their chemical and physical properties. In addition, a determination was made that overall exposure will be appropriately addressed by SWIMODEL's screening-level oral exposure estimate.

Bromide

For electrolysis devices used in swimming pools or spas, bromide exposure estimates are close to levels of bromide associated with thyroid effects considered to represent the most sensitive indicator of toxicity, as noted in Section 3.5.1. Therefore, these use scenarios pose a risk of concern.

For the scheduled spa sanitizers, bromide exposure estimates are approaching levels associated with effects of toxicological concern for bromide; therefore there is a risk of concern for these products. Because the application rate for these products results in bromide concentrations in the spa water that are similar to background levels (i.e. bromide concentrations in sea water), additional information was examined to confirm that the risk from these products differs from the risk from environmental levels of bromide.

Unlike spa water, sea water includes relatively high levels of other ions that decrease the toxicity of bromide based on evidence from animal studies. For this reason, use of sea water bromide levels as a reference point for assessing human health risks for spa scenarios is likely to underestimate risk. Additionally, since bromide is naturally present in foods, a comparison to the estimated adult daily dietary intake was considered. When aggregated (with dietary), the contribution of bromide exposure from the scheduled spa uses is not negligible.

For the non-scheduled pool and spa products, exposure estimates are below the levels associated with toxicological effects of concern, and the exposure from these products will not contribute significantly compared to the environmental levels of bromide. Therefore, there are no health risks of concern for these products when used according to the proposed revised label directions.

Bromate

For bromate, separate short-term and long-term exposures were assessed. The best available data were surrogate data from in-use pools treated with the active ingredient BCDMH. Exposure estimates are below the levels associated with toxicological effects of concern for both short- and long-term scenarios. Therefore, there are no health risks of concern for these products when used according to the proposed revised label directions.

3.5.3.3 Residential Postapplication Cancer Risk Assessment

Bromide

The weight of evidence did not suggest that bromide was genotoxic. Although limited, the available information did not suggest carcinogenic potential, and consequently a cancer assessment was not conducted.

Bromate

A qualitative approach to the exposure assessment was used to assess the cancer risks of concern. The best available data were surrogate data from in-use pools treated with the active ingredient BCDMH. A laboratory study using sodium bromide at lower rates was also used to inform the risk assessment.

The highest bromate concentration in the cancer risk assessment was for typical outdoor commercial swimming pools and showed lifetime risks of concern for competitive and non-competitive swimmers. The bromate concentration data for outdoor residential pools and indoor commercial pools and showed lifetime risks of concern for competitive swimmers, but did not show lifetime risks of concern for non-competitive swimmers. The bromate concentration data

from the laboratory study did not show lifetime risks of concern for competitive or non-competitive swimmers.

Given that the pool and spa electrolysis devices used to produce bromide have a higher potential for bromate formation than typical pool uses (high sodium bromide application rates and the use of electrolysis), the cancer risks for the pool and spa electrolysis devices are of concern.

For the scheduled spa sanitizers, the available bromate concentration values are not directly representative of these products, but could indicate a potential risk of concern. Further considerations suggest that the bromate concentration may be lower for the scheduled spa sanitizers than the available bromate concentration values which are based on typical pool use. The assessment for competitive swimmers is not relevant for spa use. Oral exposure is less likely in spas than in pools. Electrolysis is not used with these products, removing one potential pathway for bromate formation, which may lead to lower levels of bromate. In addition, spas are typically covered when not in use, which would also limit the formation of bromate due to UV exposure. Label statements could reduce bromate formation; however, they are not proposed for these products as risks of concern were identified in the non-cancer risk assessment.

The non-scheduled pool and spa santizers have lower application rates that are more similar to the laboratory data, which did not show lifetime risks of concern for competitive or non-competitive swimmers. Since this data is not representative of in-use pools or spas, label statements are proposed to reduce bromate formation.

3.5.3.4 Residential Handler Exposure and Risk Assessment

Only the products which were not of concern for the swimmer exposure assessment are considered for applicator exposure. The remaining products are domestic class only. Applicator exposure is to adults only. Residential applicators have the potential for exposure to sodium bromide when handling dry formulations.

The signal words “CAUTION POISON” appear on product labels. Precautionary statements to mitigate exposure, including “Harmful if swallowed” and “Avoid contact with skin and eyes”, also appear on the labels. As a result of the re-evaluation, the labels of end-use products that are repackaged technical grade sodium bromide will be required to include the signal words “WARNING POISON” and the precautionary statements “May be fatal if inhaled. DO NOT inhale dusts.”

The swimmer risk assessment is expected to address any potential applicator exposure.

3.6 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.6.1 Non-Occupational and Dietary Aggregate Exposure and Risk Assessment

The aggregate assessment was based on exposures for uses that did not have any risk concerns. Therefore, only the non-scheduled pool and spa products are considered.

Bromide

Canadians are exposed to bromide through diet (food and drinking water). Bromide concentrations in seawater are generally in the range of 65 mg/L to well over 80 mg/L in some confined sea areas. Concentrations of bromide in fresh water typically range from trace amounts to about 0.5 mg/L. Concentrations of bromide in desalinated waters may approach 1 mg/L. The typical daily dietary intake of bromide in the United States of America is 2-8 mg from grains, nuts and fish. Assuming an 80 kg adult, this would be 0.025-0.1 mg/kg bw/day.

There were limited data available to qualify aggregate risk. For bromide in swimming pools/spas, SWIMODEL was used to develop screening exposure estimates and therefore the risk assessment was considered to be high-end and likely addresses exposure from other sources. The non-scheduled spa sanitizers and pool algaecide use are not expected to contribute significantly to aggregate risk in comparison to typical daily dietary intake.

With the proposed mitigation, the contribution of sodium bromide to the aggregate risk from bromine is low and not of concern.

Bromate

Canadians are exposed to bromate through its presence in drinking water (including ozonated bottled water), and in some consumer products such as cosmetics. Little bromate is expected to be found in air or soil. Bromate is difficult to remove from drinking water once formed; therefore, limiting formation is recommended by Health Canada. The maximum acceptable concentration of bromate in drinking water is 0.01 mg/L (Health Canada, 2015).

There were limited data available to attempt to qualify aggregate risk. Bromate is a byproduct in drinking water treatment as well as swimming pool / spa uses. Drinking water regulation treats the presence of bromate as part of a risk-benefit analysis that concludes that the health concerns from the technically feasible amounts of bromate are acceptable when considered against the risks of untreated drinking water. It is recommended that steps be taken to minimize bromate formation, and this was considered in the swimming pool and spa assessment. All bromine swimming pool or spa electrolysis devices and related sodium bromide products are proposed for phase-out to remove the electrolysis formation pathway. For the non-device products, label wording is recommended to limit the ozonation and UV formation pathways by disallowing the use of ozonation or UV disinfection as secondary disinfection methods. For those products that are proposed for continued registration, risks from bromate exposure are considered to be low due to their low application rates. They are expected to have concentrations of bromate lower than the drinking water maximum acceptable concentration of 0.1 ppm recommended by Health Canada.

With the proposed mitigation, the contribution of sodium bromide to the aggregate risk from bromate is low and not of concern.

3.7 Cumulative Risk Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pesticides sharing a common mechanism of toxicity. Upon completion of the re-evaluation of the individual chemicals (sodium bromide and BCDMH), it will be determined whether a cumulative effects assessment is necessary and if so, this will be performed with all relevant chemicals of the common mechanism group.

4.0 Impact on the Environment

For the purpose of this re-evaluation, the environmental assessment relied on the USEPA Reregistration Eligibility Decision (RED) as the primary source of information (PMRA 1460777).

4.1 Fate and Behaviour in the Environment

Sodium bromide is used as a microbicide/slimicide in pulp and paper industries, recirculating cooling water systems, and wastewater treatment facilities, as well as in pools and spas. Industrial process water applications would have the greatest environmental exposure, as exposure could occur through effluent discharge to rivers, marine waters, or other aquatic systems. Pool and spa uses are expected to result in minimal environmental exposure; therefore, these uses were not considered further for the environmental assessment. As the environmental exposure through industrial uses is expected to occur primarily through effluent discharge into waterbodies, the environmental behaviour and fate of sodium bromide in the aquatic environment, rather than terrestrial, is most relevant and was the focus of the current assessment.

Sodium bromide dissociates in water to sodium and bromide ions, which do not undergo any further dissociation. When combined with an activating agent, such as chlorine or sodium hypochlorite, hypobromous acid is formed. Hypobromous acid (HOBr) is a strong oxidant, and is the intended reaction product that provides the actual biocidal activity during use in industrial process water. Therefore, hypobromous acid was the focus of the environmental fate characterisation.

Hypobromous acid oxidizes organic and inorganic material, including bacteria and fungi, present in industrial process water. The USEPA reported a half-life of approximately 125 hours in process water, and depending on the amount of material present with which the acid can react, a shorter half-life (<125 hours) is expected. Since hypobromous acid reacts quickly with other compounds, its presence is variable under environmental conditions; therefore, hypobromous acid is typically measured as “residual bromine”.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media. In the context of this assessment, water was the medium of

interest, and the EECs are estimated using a model which takes into consideration the application rate(s), and dilution factors. For this assessment, ecotoxicology information includes acute toxicity data for various organisms or groups of organisms from aquatic habitats including invertebrates, and vertebrates. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Using data from the USEPA review, a quantitative risk assessment was carried out to estimate the potential adverse effects to aquatic organisms.

4.2.1 Risks to Terrestrial Organisms

Based on the current use pattern in industrial process waters, the use of sodium bromide is not expected to result in terrestrial exposure; therefore, risk to non-target terrestrial species is expected to be limited and is not considered further for this assessment.

4.2.2 Risks to Aquatic Organisms

Non-target aquatic organisms may be exposed to hypobromous acid residues through effluent discharge to water. Facilities may be located in proximity of either freshwater or marine water bodies, and both environments were considered in the risk assessment. Through chemical reactions within the treatment system, and through biological degradation during secondary treatment where applicable, the amount of hypobromous acid discharged into the aquatic environment is expected to be considerably less than the starting material at treament initaition. Notwithstanding, the use of technical sodium bromide could result in environmental exposure to residual amounts of the biocide (hypobromous acid) through discharge of effluent to receiving water bodies (for example, rivers). Thus, concentrations in water were estimated to conduct a quantitative aquatic risk assessment.

As part of the USEPA reevaluation of sodium bromide and hypobromous acid, a fate model was used to conduct a “Tier Ic EEC modelling assessment”. The Tier Ic EEC modelling determined the maximum concentration of hypobromous acid immediately downstream from a point source discharge under conditions of low (or worst case) flow and “typical” flow in a receiving waterbody. The concentration of residual bromine in the waste stream, prior to discharge, was based on US federal permit regulations for total residual oxidants.

The model applies dilution factors to the concentration in effluent at the point of discharge to estimate “reasonable worst case” and “typical” EECs; the concentrations (measured as bromine) were determined to be 0.45 mg/L and 0.0012 mg/L (highest concentration under the “typical” exposure scenario) , respectively (Appendix III, Table 1).

In addition to carrying out the modelling, the USEPA received two aquatic residue monitoring studies conducted at a once-through cooling system (discharge into estuarine section of the Potomic River), and at wastewater treatment facility (discharge into a freshwater stream). According to the USEPA RED, the studies were conducted at application rates that exceeded permitted levels. Results indicated that the modelled reasonable worst case Tier Ic EECs were comparable to the levels detected in the aquatic residue studies. However, the EECs from the Tier Ic modelling for the “typical” exposure scenario were considerably less than levels found in monitoring studies. It should be noted that the Tier Ic modelling was based on parameters that are expected to represent most industrial use scenarios while the monitoring results were based on higher application rates than what is permitted on the labels. The higher application rates were likely used to enhance measurements of patterns of dissipation within treatment and after discharge. In the case of the freshwater monitoring study, no residues were detected beyond 80 metres downstream.

In Canada, limited monitoring data are available. In one report conducted in 1995 (PMRA 1167887), a sodium bromide product (Busan 1167, 40% NaBr) was added with an activator agent into pulp and paper process water with overall residual amounts maintained at 0.1 to 0.2 mg/L. The effluent was sampled for total halgens twice over the trial (between October and December); each sample resulted in a total halogen concentration of <0.1 mg/L, of which bromine from the sodium bromide addition would have been a component.

In another study conducted in 1992 (PMRA 1158304), a sodium bromide product (Actibrom 1338, 42.8% NaBr) was combined with sodium hypchlorite in a paper industry application. Occasional monthly sampling of process water a few minutes after the addition of the product showed a maximum of 0.1 mg/L residual bromine. Effluent samples were taken periodically over a 3 month period at a point just prior to discharge. All samples recorded a residual bromine level of 0 ppm, which is interepreted to be at a level below the level of detection.

The results of the available Canadian monitoring studies agree with the results of the USEPA Tier Ic modelling for “typical” exposures.

The reasonable worst case scenario EEC of 0.45 mg/L was used for the PMRA screening level risk assessment, and the “typical” exposure scenario EEC of 0.0012 mg/L was used for refinement. Although there are no prescribed limits for residual oxidants under Canadian federal regulations for industrial discharges (permitting related to discharges can occur through

provincial and municipal jurisdictions), the USEPA Tier Ic EEC modelling results were considered to be conservative and relevant for the Canadian assessment based on the following assumptions:

- In general, it is assumed that industrial processes, where sodium bromide is used, are similar in Canada and the United States, and would result in similar amounts of total residual oxidants in effluent discharges.
- The Canadian use patterns and rates for sodium bromide as a microbicide in industrial process fluids are very similar to those of the United States.
- It is assumed that the dilution factors used in the USEPA Tier Ic EEC model are representative of waterbodies receiving discharge from Canadian industries.

In addition, although monitoring data are limited for Canadian uses, the values that are available (<0.1 ppm total halides, and non-detect residual bromine) fall within the range of values generated by the USEPA model, implying the modeling results are representative.

As hypobromous acid is the biocide of concern in aquatic environments, studies assessing the effects on aquatic organisms are required to be conducted with hypobromous acid. As part of the 1993 USEPA RED, the USEPA reviewed several aquatic toxicity studies where hypobromous acid was formed as the test compound. The PMRA database also contains these original studies, and the EPA review of these studies was considered acceptable for the current re-evaluation. In addition, summary information was available in the PMRA database for other aquatic toxicity studies using hypobromous acid, based on a published journal document (PMRA 2707724). A summary of the studies for all applicable freshwater and marine endpoints is provided in Appendix III, Table 2. These endpoints were used in the risk assessment. Results indicated that hypobromous acid, measured as residual bromine, can be highly to very highly toxic to all freshwater and marine species.

The endpoints used in the risk assessment for the active as well as uncertainty factors applied for hypobromous acid are presented in Appendix III, Table 3.

Using the EEC values of 0.45 mg/L and 0.0012 mg/L to represent reasonable worst case exposure (high exposure, screening level) and typical exposure scenarios (refined), respectively, and the toxicity endpoints as outlined in Appendix III, Table 3, RQ values were determined. The data and results are summarised in Appendix III, Table 4.

The potential EEC of hypobromous acid residuals, as determined in the high exposure scenario, poses a risk to all aquatic organisms except for *Daphnia* and molluscs. Using the “typical” exposure scenario EECs, the RQs for all aquatic organisms were well below the LOC.

Typical use is not expected to result in risks of concern for aquatic organisms. In the rare event that levels reach those modelled in the higher exposure scenario, various other federal, provincial, and municipal regulations and permitting requirements that restrict effluent discharge rates in relation to waterbody flow, as well as regulating potential toxic components and effects of effluent in general, would be applicable and are expected to limit the amount of hypobromous acid entering natural waters.

In addition, the monitoring data provided by the EPA indicated hypobromous acid was not detected further than 80 m downstream of the point of discharge, under study conditions where higher than normal application rates were used.

Therefore, under a worst case scenario for effluent discharge, residual levels of hypobromous acid would be expected to dilute within a relatively short distance from the point of discharge. However, because of high toxicity of the hypobromous acid to aquatic organisms, a hazard label statement warning of the toxicity to aquatic organisms as well as a label statement for the detoxification of effluent prior to discharge are required (Appendix IV).

5.0 Value

Sodium bromide is an important source of bromine – a broad-spectrum, oxidizing antimicrobial biocide. As the only registered alternative to chlorine for spa and pool sanitization, bromine is particularly important. In addition, bromine has a number of important advantages over chlorine as a spa and pool sanitizer. It is an effective sanitizer, essentially independent of pH, while chlorine's sanitizing ability is highly susceptible to pH. Furthermore, bromamines, formed as by-product of bromine oxidizing organic matter continue to be good sanitizers and do not irritate swimmers eyes or lungs, unlike the chloramines formed with chlorine sanitization.

As a slimicide for paper mills, cooling towers and air washers, bromine formed from sodium bromide is an important biocide. The nature of biofilms and microbial slime is that they tend to be resistant to biocides. It is often necessary for operations using process fluids susceptible to biofilms to change the biocide regime from time to time in order to maintain effective control and prevent the build-up of biofilm resistance to any one biocide chemistry. As a powerful oxidizing biocide, bromine is an important alternative for effective control of microbial slime.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, sodium bromide and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[2] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Sodium bromide does not meet the Track 1 criteria and will not form any transformation products which meet the Track 1 criteria. See Appendix III, Table 5 for comparison with

[2] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

Track 1 criteria. Sodium bromide is a naturally occurring substance and is not expected to be persistent or bioaccumulative in the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[3] The list is used as described in the PMRA Notice of Intent NOI2005-01[4] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[5] as well as taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade sodium bromide does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. The database was searched for incident reports involving sodium bromide.

As of 3 October 2016, five human incident reports involving sodium bromide have been submitted to the PMRA. Four incidents were determined to have some degree of association with the stated exposure scenario. The symptoms were all minor. Each exposure scenario was different than the other, and there were no commonalities in symptoms reported. The incident report data were incorporated into the evaluation of sodium bromide, and did not affect the risk assessment. There were no environmental incident reports involving sodium bromide submitted to the PMRA.

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3 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

4 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

5 DIR2006-02, *PMRA Formulants Policy and Implementation Guidance Document.*

8.0 Organisation for Economic Co-operation and Development Status of Sodium Bromide

Canada is a member of the Organisation for Economic Co-operation and Development (OECD), which groups 35 member countries and provides a forum in which governments can work together to share experiences and seek solutions to common problems.

As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of an active ingredient in other jurisdictions, including OECD member countries. In particular, decisions by an OECD member to prohibit all uses of an active ingredient for health or environmental reasons are considered for relevance to the Canadian situation.

Sodium bromide is currently acceptable for use in other OECD member countries, including Australia and the United States. As of 10 January 2017, no decision by an OECD member country to prohibit all uses of sodium bromide for health or environmental reasons has been identified.

9.0 Proposed Re-evaluation Decision

The PMRA is proposing that most uses of sodium bromide are acceptable for continued registration with implementation of additional risk-reduction measures. The proposed mitigation measures are listed in Appendix IV. However, sodium bromide uses that are related to swimming pool or spa electrolysis devices as well as the scheduled spa sanitizers are proposed for phase-out due to human health concerns that cannot be mitigated with additional risk-reduction measures.

9.1 Proposed Regulatory Actions Related to Human Health

9.1.1 Proposed Mitigation Related to Toxicology

Updated hazard labeling will be required for some products to reflect the acute toxicity hazard via the inhalation route.

9.1.2 Proposed Mitigation Related to Occupational and Residential Exposure

To mitigate residential exposures, the following requirements are proposed:

- All bromine swimming pool or spa electrolysis devices and sodium bromide products intended to be used with electrolysis devices are proposed for phase-out.
- All chlorine swimming pool or spa electrolysis device products are to indicate that they are not to be used to produce bromide.
- The scheduled spa products are proposed for phase-out.
- All other sodium bromide pool and spa products are to indicate that they are not to be used in combination with electrolysis, ozonation, or UV disinfection.

To mitigate occupational exposures, the following requirements are proposed:

- Commercial industrial sodium bromide product labels require the use of protective eyewear, chemical-resistant coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves and footwear when handling the concentrate and contacting treated process fluids.
- All products containing sodium bromide with industrial uses are to indicate that they are for use with closed loading and transfer systems only.

For specific label amendments, see Appendix IV.

9.2 Proposed Regulatory Actions Related to the Environment

For pool and spa uses, environmental exposure of sodium bromide is expected to be low and is not expected to pose a risk of concern. For products containing sodium bromide with industrial uses, a hazard label statement is required to inform users of the toxicity of hypobromous acid to aquatic organisms and users will be required to detoxify effluent prior to discharge.

9.3 Additional Data Requirements

No additional data are required.

List of Abbreviations

abs	absolute
ACC	American Chemistry Council
AChE	acetylcholinesterase
ACTH	adrenocorticotrophic hormone
AD	administered dose
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
A/G	albumin/globulin
a.i.	active ingredient
ALP	alkaline phosphastase
AP	action potential
ARfD	acute reference dose
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
bwg	body-weight gain
Ca^{2+}	calcium ion
CAP	compound action potential
CAS	chemical abstracts service
Cl^-	chloride ion
$ClO4^-$	perchlorate ion
CMA	Chemical Manufacturer's Association
CSF	cerebral spinal fluid
DBP	disinfection by-product
dL	decilitre
DNT	developmental neurotoxicity
EC_{50}	effective concentration on 50% of test population
EEC	estimated environmental concentration
F_0	parental generation
F_1	first generation
F_2	second generation
fc	food consumption
FSH	follicle stimulating hormone
FT_3	free triiodothyronine
FT_4	free thyroxine
g	gram
GABA	gamma-aminobutyric acid
GD	gestation day
GH	growth hormone
GI	gastrointestinal
h	hour
$HCO3^-$	bicarbonate ion
Hgb	hemoglobin
I^-	iodide ion
i.p.	Intraperitoneal

IUPAC	International Union of Pure and Applied Chemistry
K^+	potassium ion
Kg	kilogram
L	litre
LC_{50}	lethal concentration to 50% of test population
LD_{50}	lethal dose to 50% of test population
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
LOC	level of concern
MOA	mode of action
MOE	margin of exposure
MCL	mononuclear cell leukemia
mEq	milliequivalents
mg	milligram
Mg^{2+}	magnesium ion
mL	millilitre(s)
mM	millimole
mmol	millimole
MOE	margin of exposure
NaBr	sodium bromide
NaCl	sodium chloride
NADH	nicotinamide adenine dinucleotide
NADH-cyt. c red	nicotinamide adenine dinucleotide cytochrome c reductase
NOAEL	no observed adverse effect level
PCNA	proliferating cell nuclear antigen
PCPA	*Pest Control Product Act*
PCV	packed cell volume
PMRA	Pest Management Regulatory Agency
PND	postnatal day
POD	point of departure
PPE	personal protective equipment
ppm	parts per million
PTP	post-tetanic potentiation
q_1*	cancer potency factor
RBC	red blood cell
rel	relative
RQ	risk quotient
SCG	superior cervical ganglion
SSEP	somatosensory evoked potential
SWIMODEL	United States Environmental Protection Agency's Swimmer Exposure Model
T_3	triiodothyronine
T_4	thyroxine
TGAI	technical grade active ingredient
TPO	thyroid peroxidase
TRH	thyrotropin-releasing hormone
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy

USEPA	United States Environmental Protection Agency
UV	ultraviolet
WBC	white blood cells
wc	water consumption
WHO	World Health Organization
wk(s)	weeks(s)
wt(s)	weight(s)
♂	males
♀	females
↑	increased
↓	decreased

Appendix I Sodium Bromide Products Registered in Canada as of 13 January 2017

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
Technical Grade Active Ingredients and Manufacturing Concentrates					
21923	Technical Grade Active Ingredient	BWA Water Additives US LLC	Liquibrom 100	Soluble Powder	Sodium Bromide 97%
22737	Technical Grade Active Ingredient	Bromine Compounds Ltd	Sodium Bromide Technical Microbicide	Solid	Sodium Bromide 98%
24216	Manufacturing Concentrate	Bromine Compounds Ltd	Sodium Bromide MP Microbicide	Pellets	Sodium Bromide 98%
24703	Manufacturing Concentrate	BWA Water Additives US LLC	Liquibrom 4600	Solution	Sodium Bromide 46%
25331	Technical Grade Active Ingredient	Albemarle Corporation	Sanibrom 40 Biocide Technical	Solution	Sodium Bromide 40%
25701	Manufacturing Concentrate	BWA Water Additives US LLC	Liquibrom 4000T Manufacturing Concentrate	Solution	Sodium Bromide 40%
26578	Technical Grade Active Ingredient	Albemarle Corporation	Sanibrom 45 Biocide Technical	Solution	Sodium Bromide 45.0%
28480	Technical Grade Active Ingredient	Sani-Marc Inc	Cambrex NaBr	Soluble Granules	Sodium Bromide 99.2%
28824	Manufacturing Concentrate	Bromine Compounds Ltd	Sodium Bromide MP-SP	Soluble Powder	Sodium Bromide 98%
28825	Technical Grade Active Ingredient	Bromine Compounds Ltd	Sodium Bromide Technical Microbicide-SP	Soluble Powder	Sodium Bromide 98%
Commercial Slimicide Products					
21318	Commercial	GE Water And Process Technologies Canada	Spectrus OX1201	Solution	Sodium Bromide 40%
21678	Commercial	Nalco Canada ULC	Acti-Brom 1338 Chlorine Enhancer Biodispersant	Solution	Sodium Bromide 42.8%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
21922	Commercial	BWA Water Additives US LLC	Liquibrom 4000	Solution	Sodium Bromide 40.0%
22577	Commercial	Buckman Laboratories of Canada Ltd	Busan 1167 Liquid Microbicide	Solution	Sodium Bromide 40.0%
22578	Commercial	Buckman Laboratories of Canada Ltd	Bulab 6040 Liquid Microbicide	Solution	Sodium Bromide 40%
23624	Commercial	Solenis Canada ULC	Biosperse XD9400	Solution	Sodium Bromide 40%
24770	Commercial	ICL – IP America Inc	Bromide Plus Microbiocide	Solution	Sodium Bromide 38%
24911	Commercial	Klenzoid Canada Inc.	Klenzoid Sodium Bromide	Solution	Sodium Bromide 40.0%
25178	Commercial	Constant America Inc	Bromocon 40	Solution	Sodium Bromide 40%
25202	Commercial	Solenis Canada ULC	Spectrum XD9400 Microbiocide Agent	Solution	Sodium Bromide 40%
25320	Commercial	Buckman Laboratories of Canada Ltd	Eclipse 632 Microbicide	Solution	Sodium Bromide 40%
25478	Commercial	Nalco Canada ULC	Stabrex ST70	Solution	Sodium Hypochlorite 6.36% Sodium Bromide 9.23%
25535	Commercial	Nalco Canada ULC	Stabrex ST95	Solution	Sodium Hypochlorite 6.36% Sodium Bromide 9.23%
25930	Commercial	Occidental Chemical Corporation	Oxychem Towerbrom 90M Tablets	Tablet	Trichloro-s-Triazinetrione 83% Sodium Bromide 7%
26145	Commercial	Nalco Canada ULC	Stabrex ST100	Solution	Sodium Hypochlorite 6.36% Sodium Bromide 9.23%
26539	Commercial	Chemtreat Inc	Chemtreat CL-40	Solution	Sodium Bromide 40.0%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
26557	Commercial	Baker Hughes Canada Company	Cl2out 1000 Slimicide	Solution	Sodium Bromide 40.0%
26856	Commercial	BASF Canada Inc	Basabrom 40	Solution	Sodium Bromide 40%
26945	Commercial	Kemira Chemicals Canada Inc	Fennosan 111-C	Solution	Sodium Bromide 40%
27275	Commercial	Occidental Chemical Corporation	Towerbrom 60M Granules	Granular	Sodium Dichloro-s-Triazinetrione 57% Sodium Bromide 6.86%
27275.01	Commercial	State Industrial Products	Bio-Bully	Granular	Sodium Dichloro-s-Triazinetrione 57% Sodium Bromide 6.86%
27663	Commercial	Nalco Canada ULC	Towerbrom 960	Soluble Granules	Sodium Dichloro-s-Triazinetrione 57% Sodium Bromide 6.86%
27674	Commercial	Nalco Canada ULC	Towerbrom 991	Tablet	Trichloro-s-Triazinetrione 83% Sodium Bromide 6.86%
27759	Commercial	Nalco Canada ULC	Acti-Brom 1318 Chlorine Enhancer	Solution	Sodium Bromide 42.8%
27788	Commercial	Guardian Chemicals Inc	Aquaguard 609	Solution	Sodium Bromide 40%
27796	Commercial	Produits Chimiques Magnus Ltée	Magnatrol 47A	Solution	Sodium Bromide 40%
28357	Commercial	Dubois Chemicals Canada Inc	X-Cell 430	Solution	Sodium Bromide 40%
28729	Commercial	Aquarian Chemicals Inc	Aquabrom 4000	Solution	Sodium Bromide 40%
29141	Commercial	Nalco Canada ULC	Stabrex ST70 For Kits	Solution	Sodium Hypochlorite 6.36% Sodium Bromide 9.23%
29408	Commercial	Enviro Tech Chemical Services Inc	Brommax 7.1 Microorganism Control Chemical	Solution	Trichloro-s-Triazinetrione 7.45% Sodium Bromide 10.09%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
29501	Commercial	IPAC Chemicals Ltd	Ipacide LWT 629	Solution	Sodium Bromide 40%
29880	Commercial	Chemtreat Inc	Cl-4907 Microorganism Control Chemical	Solution	Trichloro-s-Triazinetrione 7.45% Sodium Bromide 10.09%
29971	Commercial	Nalco Canada ULC	Controlbrom CB70	Solution	Sodium Bromide 30%
30035	Commercial	Produits Chimiques Magnus Ltée	Magnatrol 477a	Solution	Trichloro-s-Triazinetrione 7.45% Sodium Bromide 10.09%
30146	Commercial	Chemtreat Inc	Chemtreat Cl-41	Solution	Sodium Bromide 40%
30291	Commercial	NCH Canada Inc	Chem-Aqua 42171	Solution	Trichloro-s-Triazinetrione 7.45% Sodium Bromide 10.09%
30659	Commercial	IPAC Chemicals Ltd	Ipacide LWT 639A	Solution	Trichloro-s-Triazinetrione 7.45% Sodium Bromide 10.09%
31031	Commercial	Water Sciences Technologies LLC	K-Brom 40	Solution	Sodium Bromide 38%
31106	Commercial	Québec-O-Chimie Inc	Unica 310	Solution	Trichloro-s-triazinetrione 7.45% Sodium Bromide 10.09%
31359	Commercial	Centrale Thermique BC-Plus	A-210	Solution	Trichloro-s-triazinetrione 7.45% Sodium Bromide 10.09%
32155	Commercial	U.S. Water Services, Inc	Biotrol 407	Solution	Trichloro-s-triazinetrione 7.45% Sodium Bromide 10.09%
32521	Commercial	U.S. Water Services, Inc	Biotrol C140	Solution	Sodium Bromide 40%
Domestic Pool/Spa Sanitizers					
25299	Domestic	KIK Holdco Company Inc	Spaguard Brominating Concentrate	Granular	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
26561	Domestic	KIK Holdco Company Inc	Aqua Chem Clear And Simple Spa Brominating Concentrate	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
26562	Domestic	KIK Holdco Company Inc	Omni Brominating Concentrate For Spas & Hot Tubs	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
26563	Domestic	KIK Holdco Company Inc	Spa Essentials Sanitizer Brominating Concentrate	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
26579	Domestic	Sani-Marc Inc	Easy Brome Sanitizer For Spas	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27197	Domestic	Sani-Marc Inc	Calypso Spa Power Brome # 15	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27308	Domestic	Beachcomber Hot Tubs Plus Inc	Bromo Blast	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27329	Domestic	I.P.G/G.P.I Independent Pool Group Inc	Aquapro Spa Easy Brome	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27589	Domestic	Capo Industries Ltd	Spaboss Brominating Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27589.02	Domestic	Aqua Coastal Imports Inc	Aqua Coastal Brominating Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27589.03	Domestic	Alliance Trading Inc	E-Z Clor Bromine Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27589.04	Domestic	Capo Industries Ltd	Jacuzzi Brominating Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
27888	Domestic	Sani-Marc Inc	Spa Sani Brom	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
28099	Domestic	Capo Industries Ltd	Spachem Brominating Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
28100	Domestic	Catalina Spas	Catalina Spas Bromine Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
28101	Domestic	Arctic Spas	Arctic Pure Peak Boost Brominating Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
28230	Domestic	Canadian Tire Corp. Ltd	Aquarius Spa Gran-Brom	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
29102	Domestic	Backyard Brands Inc	Dazzle Bromine Granules For Hot Tub	Granular	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
29396	Domestic	Lawrason's Inc	Spa Life EZ Brom	Soluble Granules	Sodium Dichloro-s-Triazinetrione 47.5% Sodium Bromide 14.88%
29782	Domestic	ICL - IP America Inc	Bromicharge	Solid	Sodium Bromide 98%
29878	Domestic	Le Club Piscine Plus Québec	Bromine Gran	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
30023	Domestic	Lawrason's Inc	Clear Spa EZ Brom	Soluble Granules	Sodium Dichloro-s-Triazinetrione 47.5% Sodium Bromide 14.88%
30289	Domestic	Hydropool Inc	EZ Brome +	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
30290	Domestic	Mursatt Chemicals Ltd	Brome +	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
30776	Domestic	Arch Chemicals Inc	GLB Green Free Algaecide	Soluble Powder	Sodium Bromide 98%
30804	Domestic	KIK Holdco Company Inc	Soft Soak Clearly Clean For Bromine Spas	Granular	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
30986	Domestic	Alliance Trading Inc	Brom Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
31109	Domestic	KIK Holdco Company Inc	Soft Soak Brominating Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
31691	Domestic	Backyard Brands Inc	Mineraluxe Bromine Granules For Hot Tub	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
31880	Domestic	Easy 123 Pool Care LLC	Clorox Spa Brominating Concentrate	Granular	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.7%
31956	Domestic	Sani-Marc Inc	Halogen	Soluble Granules	Sodium Bromide 99.2%
32027	Domestic	Trevi	Brom-Gen	Soluble Granules	Sodium Bromide 99.2%
32075	Domestic	Central Spa & Pool Supply	Bromine Generator Salt	Soluble Granules	Sodium Bromide 99.2%
32085	Domestic	Le Club Piscine Plus Québec	Eclipse	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.79% Sodium Bromide 14.6%
32182	Domestic	Sani-Marc Inc	Bromide Salt	Soluble Granules	Sodium Bromide 99.2%
32214	Domestic	Capo Industries Ltd	Marquis 1 Step Bromine Granules	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%
32519	Domestic	Sani-Marc Inc	EZ San	Soluble Granules	Sodium Dichloro-s-Triazinetrione 52.7% Sodium Bromide 14.6%

This table excludes discontinued products or products with a submission for discontinuation as well as scheduled spa sanitizers.

Appendix II Toxicology Profile and Endpoints for Health Risk Assessments

Table 1 Toxicity Profile of Technical Sodium Bromide

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.

Study Type/Animal/PMRA#	Study Results
Toxicokinetics (PMRA# 1463203, 1460752, 1460766, 2588942, 2588952, 2588957, 2637306, 2637309, 2642095)	
The toxicokinetic profile of bromide is generally the same across different species. The ADME information presented below is known or assumed to apply to rodents, rabbits, dogs, and humans unless otherwise stated. **Absorption:** After oral ingestion, bromide is rapidly and completely absorbed in the GI tract and competes with chloride for tubular reabsorption. **Distribution/Metabolism:** Bromide does not accumulate to any marked degree in any particular organ or tissue, and species differences in tissue bromide concentration are small. The distribution of bromide is analogous to that of chloride, being found almost exclusively in the extracellular fluid. In humans, the bromide levels in the brain and CSF are 30% of that in the blood; these levels are more elevated in fetal brains. The administration of bromide results in some displacement of chloride and vice versa. The exception to this is in the thyroid gland, where bromide replaces iodide rather than chloride. In rat thyroid, up to 40% of the amount of iodide in the thyroid was replaced by bromide. In rats, radioactive ^{82}Br in various tissues reached its largest uptake within a few hours, and the concentration ratio of ^{82}Br in the tissues to blood remained practically constant between 8 h and 396 h after subcutaneous injection or administration via drinking water. The stomach was the only organ in the rat that had a larger uptake of ^{82}Br than blood. The highest concentration of radioactive bromide was found in the skin, due to the skin's large mass. At 8 hours following the subcutaneous injection of $Na^{82}Br$ in rats, approximately 32% of the applied dose of ^{82}Br was deposited in the skin. Approximately 20% of the radioactivity was in the inner organs, 12% in the digestive tract, and the remaining part (39%) in the carcass. Pregnant rats exposed to bromide between the 5th and 15th gestational days transferred this ion to embryos via the placenta. In lactating dams, 42% of the AD of bromide was transmitted through the mother's milk into the young rats. Bromide toxicity is dependent upon the state of iodine supply; under moderate iodine deficiency, bromide can interfere with the production of thyroid hormones. As the concentration of bromide increases, the production of iodinated thyronines decreases. Under conditions of increasing bromide intake, the $[I^-]/[Br^-]$ concentration ratio in the thyroid was up to 5-fold lower in rats with marginal iodine deficiency than in animals with a sufficient or an excessive iodine intake. When there is a sufficient supply of iodine, a stable $[I^-]/[Br^-]$ concentration ratio in the thyroid is rapidly established. In fractionated thyroids, the high-molecular weight soluble fraction, containing covalently bound halogenated residues of tyrosine and thyronines in thyroglobulin, did not have a significant change in the $[I^-]/[Br^-]$ ratio, indicating that even a high bromide intake did not displace organically bound iodine. High bromide intake (>150 mg Br^-/day) under sufficient iodine supply (>25 µg I^-/day) led to increased iodide elimination both from the thyroid and skin in rats, and resulted in a marked decrease in iodide accumulation in the thyroid. Under deficient iodine supply (<1 µg I^-/day), there was increased iodide accumulation in the rat thyroid due to thyrotropic stimulation. When iodine deficiency was combined with a high bromide intake, this resulted in accelerated rates of iodide elimination from both the thyroid and skin. In lactating dams, a high bromide intake caused a decrease in iodide accumulation in the mammary glands, and increased iodide elimination through the kidneys. **Elimination:** Bromide is mostly excreted in the urine at a rate of approximately 5% of the AD/24 h. Generally, the half-life of bromide is 3-8 days in rats and 12 days in humans; however, bromide's biological half-life decreases when chloride is administered. Likewise, the half-life of bromide may be increased by a salt-deficient diet (up to 25 days in rats on a salt-free diet). In rat tissues, bromide half-life values ranged from 94 h in the thyroid to 235 h in the liver, with most of the studied tissues having shorter half-lives than the whole body (198 h). Most of the rat tissues	

also showed a significant correlation between the values of the steady-state concentration of bromide and the corresponding half-life in the respective tissue. The half-life of bromide in the rat thyroid is shorter than in the whole body, and is also very similar to the half-life of iodine (108 h) in the thyroid. In male rats exposed to bromide, it was found that bromide had a single half-life while iodine was excreted in two different pools. The first pool had a half-life of 12 h, characterizing the clearance from the whole body; the second pool had a half-life of 108 h, accounting for the iodine release from the thyroid.	
Acute Toxicity Studies	
Acute oral toxicity Sodium bromide Sprague Dawley Rats PMRA# 1460777	LD_{50} = 4500/3900 mg/kg bw (♂/♀) LD_{50} = 4200 mg/kg bw (combined) Low toxicity
Acute oral toxicity Sodium bromide Sprague Dawley Rats PMRA# 1460756	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Dermal Toxicity Sodium bromide New Zealand White Rabbits PMRA# 1163634	LD_{50} >2000 mg/kg bw Low toxicity
Acute Dermal Toxicity Sodium bromide New Zealand White Rabbits PMRA# 1460754	LD_{50} >2000 mg/kg bw Low toxicity
Dermal irritation Sodium bromide New Zealand White Rabbits PMRA# 1163636, 1460757	Non-irritating
Eye irritation Sodium bromide New Zealand White Rabbits PMRA# 1163635	Mild eye irritant
Eye irritation Sodium bromide New Zealand White Rabbits PMRA# 1460758	Minimal eye irritant

Dermal Sensitization Magnusson-Kligman Maximization Test Sodium bromide Hartley/Dunkin Guinea-Pigs PMRA# 1163637	Not a dermal sensitizer
Acute oral toxicity Ammonium bromide Sprague Dawley Rats PMRA# 665852	LD_{50} = 2868/2566 mg/kg bw (♂/♀) LD_{50} = 2714 mg/kg bw (combined) Low Toxicity
Acute dermal toxicity Ammonium bromide Sprague Dawley Rats PMRA# 665853	LD_{50} > 2000 mg/kg bw Low Toxicity
Acute inhalation toxicity Ammonium bromide Sprague Dawley Rats PMRA# 665854	LC_{50} > 0.10 mg/L Moderate Toxicity
Dermal Irritation Ammonium bromide New Zealand White Rabbits PMRA# 665856	Non-irritating
Eye Irritation Ammonium bromide New Zealand White Rabbits PMRA# 665855	Mildly Irritating
Dermal Sensitization Magnusson-Kligman Maximization Test Ammonium bromide Guinea Pig PMRA# 665857	Not a dermal sensitizer

Short-term Toxicity Studies	
4-wk oral toxicity (diet) Sodium bromide Wistar rats (♀ only) PMRA# 1460784	**Supplemental** **≥4800 ppm NaBr (305 mg Br^-/kg bw/day):** ↑ rel liver wt **19200 ppm NaBr (1473 mg Br^-/kg bw/day):** dirty/unkempt appearance, signs of hindleg motor incoordination, ↓bwg, ↑ rel kidney wt, ↑ rel liver wt Note: thyroid hormones were not assessed **Limitations:**♀ only, and small group sizes (4/group); bw data, absolute organ wts not reported; lack of many guideline parameters/organs assessed; thyroid not examined
4-wk oral toxicity (diet) – Range-finding with a ↓ chloride diet Sodium bromide Wistar rats As referenced in WHO 2009 review (PMRA# 2637706)	**Supplemental** **≥75 ppm NaBr (5.8 mg Br^-/kg bw/day):** ↑ kidney wt (♂) **≥4800 ppm NaBr (373 mg Br^-/kg bw/day):** mortality (3♂, 2♀), ↓ fc and growth (♂/♀) **19200 ppm NaBr (1491 mg Br^-/kg bw/day):** all animals died Note: thyroid hormones did not appear to be assessed **Limitations:** insufficient details available regarding study methods; unclear whether thyroid was examined
28-day oral toxicity (diet) Ammonium bromide Sprague-Dawley rat PMRA# 665858	**Supplemental** **≥100 mg/kg bw/day:** ↓ abs testes wt **≥500 mg/kg bw/day:** clinical signs of toxicity, including rolling gait, hunched posture, eyes partially closed and piloerection (♂/♀); subdued behaviour, ↓ bw and bwg ↓ abs epididymides, heart, kidneys, testes, lung and liver wts (likely secondary to ↓ bw) (♂); nervous/ hyperactive /agitated behaviour (♀) **1000 mg/kg bw/day:** ↓ fc (♂/♀); subdued behaviour, ↓ bw and bwg, ↑ liver and ovary wt (abs and rel) (♀) **Limitations:** No histopathology performed
4-wk oral toxicity (gavage) Ethanolammonium perbromide Charles River Rats As referenced in USEPA (2005) review (PMRA# 2671576)	**Supplemental** **≥20 mg/kg bw/day:** pale urine, proteinurea (♂) **200 mg/kg bw/day:** salivation and noisy respiration after dosing, ↓ fc, ↓ bwg, ↑ PCV, ↑ Hgb, ↑ RBC, ↑ glucose, histopathology in stomach (hyperkeratosis and acanthosis accompanied by edema, inflammation and ulceration of keratinized region); ↑ platelet count, ↑ AST, ↑ creatinine, ↑ albumin, ↑ total protein, ↓ cholesterol (♂); underactive, brown staining on the muzzle, occasional salivation prior to dosing, ↓ abs brain wt (♀) **2-wk recovery phase (control and high dose only)** **200 mg/kg bw/day:** ↑ platelet count (♂/♀); ↑ bwg (♂); ↓ bwg, ↓ abs brain wt, stomach histopathology in one animal (hyperkeratosis, inflammation, erosion of keratinized region) (♀)

90-day oral toxicity (diet) Sodium bromide Wistar rats PMRA# 1460785	**Supplemental** **≥75 ppm NaBr (5.8 mg Br^-/kg bw/day):** adrenal histopathology (↓ vacuolization of zona fasciculata); this finding was reported at all dose levels in this study, but only at high dose when the results were reported in a subsequent publication **≥4800 ppm NaBr (373 mg Br^-/kg bw/day):** ↓ rel prostate wt, ↓secretory activity of the prostate (♂); ↑ thyroid activation (evidenced by ↓ in follicle size) (♀) **19200 ppm NaBr (1491 mg Br^-/kg bw/day):** Dirty/unkempt appearance/↓grooming behaviour, signs of hindleg motor incoordination, ↓ bwg, ↑ neutrophils, ↑ ALP, ↓ aminopyrine demethylase, ↑ rel thyroid wt, thymus involution (♂/♀); ↓ RBC, ↓ aniline hydroxylase, ↑ rel adrenal and spleen wts, ↑ pituitary cysts, ↑ thyroid activation (↓ follicle size), ↓ spermatogenesis (♂); ↑fc, ↓ rel thymus and uterus wts, ↓ # corpora lutea (♀) Note: thyroid hormones were not assessed **Limitations:** bw/bwg data only presented graphically; absolute organ wts data not shown; (bwg data presented in subsequent publication; see PMRA #1460783); no incidence data for histopathology (description only); limited details regarding methods; results from this study are also reported in PMRA # 1460783, and there were several discrepancies in effect levels or findings reported in the two publications, particularly with regards to adrenal, prostate and thymus histopathology findings.
90-day oral toxicity (diet) with a reduced chloride diet Sodium bromide Wistar rats PMRA# 1460783	**Supplemental** **≥500 ppm NaBr (39 mg Br^-/kg bw/day):** ↑ thyroid activation, adrenal histopathology (↓ vacuolization of zona fasciculata), ↓ zymogen granulae in pancreas (♂/♀) **2000 ppm NaBr (155 mg Br^-/kg bw/day):** mortality (3♀/3♂), ↓ grooming behaviour, hindlimb motor incoordination, ↓bwg, ↑ neutrophils, ↑ total leukocytes, brain hyperaemia, degeneration of myocardium, granulocytes along blood vessels in lungs, ↓ secretory activity of salivary glands (♂/♀);↑ rel adrenal wt, ↑ rel thyroid wt, ↓ rel testes wt, inhibited spermatogenesis (♂); ↓ rel pituitary wt, ↓ rel ovary wt, ↓ # corpora lutea, delayed uterine maturation (♀) Note: thyroid hormones were not assessed **Limitations:** bw and absolute organ wt data not shown; no incidence data for histopathology (description only); effects not reported by sex (presented in table above for both sexes; but cannot be confirmed); relative organ wt data (relative to heart wt) only shown for control and high dose groups, despite the fact that the study authors noted effects on thyroid wts at lower doses; this study also reported the findings from PMRA #1460785 (animals treated with NaBr on a regular Cl^- diet), and there were several discrepancies in effect levels or findings reported in the two publications, particularly with regards to adrenal, prostate and thymus histopathology findings.

90-day oral toxicity (diet) with Neurotoxicity assessment Ammonium bromide Sprague-Dawley Rat PMRA #665859, 930894, 930896, 1067317	**Systemic toxicity** NOAEL not established; LOAEL = 100 mg/kg bw/day **Neurotoxicity** **Supplemental** (Note: Effects indicative of neurotoxicity observed at all dose levels) **Main Study** **≥100 mg/kg bw/day (82 mg Br^-/kg bw/day):** ↓ hind limb grip strength (♂/♀); posture/gait abnormalities and limp, ↓ abs brain , thyroid, kidney, liver testes and epididymides wts, ↑ landing foot splay (♂); clinical signs (long claws), ↓ cholesterol and ↑ phosphate (♀) **≥225 mg/kg bw/day (184 mg Br^-/kg bw/day):** clinical signs (long claws, rolling gait, staggering, subdued behaviour, splayed hind limbs, piloerection [♂]; limpness, posture/gait abnormalities [♀]),↓ cholesterol, ↑ phosphate,8WBC, neutrophils, lymphocytes, monocytes and leukocytes, slight ↑ in total animals with axon ballooning and/or digestion chamber formation in nerve slices (♂/♀); ↓ bw (94-8%, 5-17%), bwg and fc, ↑ eosinophils, delayed tail flick response, ↓ abs adrenal, heart, lung, salivary gland and prostate wt (♂); ↓ uterus wt (♀) **500/750 mg/kg bw/day (408/612 mg Br^-/kg bw/day; ♂/♀):** Clinical signs (↓ activity and hunched posture, nasal bleeding [♂/♀]; rolling gait, staggering, subdued behaviour and splayed hind limbs [♀]), ↓ bw and bwg, ↓ urine pH, delayed tail flick response, increased landing foot splay (♂/♀); ↓ abs pituitary wt (♂);↓ rel adrenal, kidney, liver and salivary gland wt (♂); lung inflammation, isolated histopathological findings in adrenal, testes, epididymides and prostate (♂); ↓ bilirubin, ↓ absolute brain, heart, salivary glands, thymus, spleen wts, ↓ rel thymus wt, poor lung inflation, isolated findings in harderian gland (♀) **4-Wk Recovery phase (control and high dose only)** **500/750 mg/kg bw/day (408/612 mg Br^-/kg bw/day; ♂/♀):** Clinical signs (subdued behaviour, rolling gait, staggering, reduced activity, splayed hind limbs, hunched posture, nasal bleeding, long claws, body staining, eyes partially closed, piloerection, irregular/slow respiration, body held low), ↓ bw and bwg, ↓ WBC, lymphocytes, leukocytes, ↓ abs thymus wt, ↑abs adrenal wt, ↑ rel adrenal and thyroid wts (♂/♀); ↓ monocytes, eosinophils, ↓ abs heart, liver, salivary glands, prostate, and testes wts, ↓ rel epididymides, prostate, and thymus wts (♂); ↓ cholesterol, albumin, A/G ratio, calcium and ↑ globulin, ↑ abs thyroid wt , and ↑ ovary wt (♀) **Limitations for neurotoxicity assessments**: Missing required tissues for neurohistopathology; inadequate data provided for motor activity assessments

Short-Term Toxicity Studies (non-guideline) – Thyroid investigations	
Special thyroid 2-wk oral toxicity (diet) Sodium bromide or sodium chloride Wistar rats (♂ only) PMRA# 2637313	**Supplemental** **Chloride:** **667 mg Cl^-/kg bw/day:** ↑ abs and rel thyroid wt, ↑ NADH-cytochrome c reductase activity **Bromide:** **1476 mg Br^-/kg bw/day:** ↓ bw, ↑ thyroid wt, ↓ T_4, ↑ TSH, ↓^{125}-I thyroid uptake, ↓ I-TPO, ↓ guaiacol-TPO, ↑ NADH-cytochrome c reductase The above results indicate that bromide inhibits iodide uptake by the thyroid, oxidation of iodide to iodine, and thus incorporation of iodine in tyrosine residues, and the coupling of tyrosine residues to thyronine. They also suggest that bromide causes an increase in NADH-cytochrome c reductase activity (likely as a result of increased TSH stimulation). **Limitations:** Purity not specified; only one dose tested
Special thyroid 4-wk oral toxicity (diet) Sodium bromide Sprague-Dawley rats (♂ only) PMRA# 2637303	**Supplemental** **≥200 ppm (16 mg Br^-/kg bw/day):** ↓ abs thyroid wt **2000 ppm (155 mg Br^-/kg bw/day):** ↓ bwg, ↑ T_4 levels **Limitations:** Purity not specified; only two doses tested and effects noted at both; no histopathological examination of thyroid
Special thyroid 4-wk oral toxicity study (diet) with an iodine-deficient diet Sodium bromide Sprague-Dawley rat PMRA# 2588925	**Supplemental** **≥4000 ppm (155/310 mg Br^-/kg bw/day):** ↓ fc, ↑ plasma TSH, ↓ plasma T_4 (free and total), ↓ thyroid T_3 and T_4 **≥8000 ppm (310/621 mg Br^-/kg bw/day):** hypoactivity, mortality **16000 ppm (621/1243 mg Br^-/kg bw/day):** ruffled fur and emaciation, ↓ bw (Note: group had to be terminated after 3 wks of NaBr treatment) **Limitations:** Purity not specified; doses used were high and effects noted at all levels tested; no histopathological examination of thyroid

Special endocrine 4- and 12-wk oral toxicity study (diet) Sodium bromide Wistar rat (♂ only) PMRA# 1460747	**Non-guideline** NOAEL for thyroid effects = 300 ppm (23 mg Br^-/kg bw/day) **4-wk study:** **≥1200 ppm NaBr (93 mg Br^-/kg bw/day):** ↑ rel thyroid wt, ↓ plasma T_4 **19200 ppm NaBr (1491 mg Br^-/kg bw/day):** ↓ bw, ↓T_4 immunostaining in thyroid, ↑ plasma TSH, ↑ FSH, ↓ LH, ↑ insulin, ↓ corticosterone, thyroid histopathology (↑ number of follicles and ↓ size; ↑ height of follicular epithelium, ↓ colloid) **12-wk study:** **≥1200 ppm NaBr (93 mg Br^-/kg bw/day):** ↑ rel thyroid wt, ↑FSH **19200 ppm NaBr (1491 mg Br^-/kg bw/day):** ↓ bw, ↓ testis wt , ↓ spermatogenesis and ↓ tubule diameter, ↑ TSH and ACTH immunostaining in pituitary, thyroid histopathology (↑# follicles and ↓ size; ↑ height of follicular epithelium, ↓ colloid), ↓ T_4 immunostaining in thyroid, ↓ plasma T_4 (with and without TRH) and ↑ plasma TSH (with and without TRH), ↑ FSH (with and without TRH), ↓ testosterone (with and without TRH), ↓ GH (with and without TRH), ↑ insulin (with without TRH), ↓ corticosterone (with and without TRH) **Limitations:** Only examined the thyroid, pituitary and testes; tested ♂s only
Special thyroid 2- and 9-wk oral toxicity study (drinking water) Potassium bromide Wistar rat (♂ only) PMRA# 1463160	**Non-guideline** NOAEL not established; treatment-related effects noted at all dose levels tested. **16-day experiment:** **≥10 mg Br^-/l (1 mg Br^-/kg bw/day):** morphological changes in the thyroid (activation of the follicular epithelium, ↑ mitoses in follicular cells, ↑ microfollicular reorganization of parenchyma, formation of minute follicles, ↑height of follicular cells relative diminished lumina), ↓ thyroid colloid content, ↓ plasma T_4 , ↓ iodine/bromine thyroid molar concentration ratio **66-day experiment:** **≥10 mg Br^-/l (1 mg Br^-/kg bw/day):** morphological changes in the thyroid (as above), ↓ thyroid colloid content, ↓ plasma T_4 and T_3, ↓ iodine/bromine thyroid molar concentration ratio **Limitations:** Purity not specified
Special thyroid 19-wk study in the rat (drinking water) Potassium bromide Wistar rat (♂ only) PMRA# 2588954	**Non-guideline** NOAEL not established; treatment-related effects noted at all dose levels tested. **≥100 mg Br^-/l (10 mg Br^-/kg bw/day):** histopathological and morphological changes in the thyroid (microfollicular rearrangements with large number of very small follicles with very small, 'slit-like' or no lumina, and ↑ thyrocyte height), changes in the localization and extent of the Golgi apparatus, rough endoplasmic reticulum, lysosomes and microvilli in thyrocytes, ↓ thyroglobulin immunoreactivity, ↓ thyroid colloid content, ↓ plasma T_4, ↓ iodine/bromine thyroid molar concentration ratio **Limitations:** Purity not specified; discrepancy between results and discussion sections with regards to effects on T_3 levels (data not shown)

Special thyroid investigations – Proliferating cell nuclear antigen (PCNA) in rat thyroid tissue from 2-, 9- and 19-wk oral toxicity studies (drinking water) Potassium bromide Wistar rat (♂ only) PMRA# 1463129	**Supplemental** **≥1 mg Br^-/kg bw/day:** ↑ mitotic activity of the follicular epithelium (PCNA analyses); PCNA indices were highest in the animals exposed to potassium bromide for the shortest duration (16 days). **Note:** Accompanies the 2-, 9- and 19-wk studies above (PMRA #1463160 and 2588954)
Special thyroid investigations – electron microscopy examination of rat thyrocytes from 2-, 9- and 19-wk oral toxicity studies (Drinking water) Potassium bromide Wistar rat (♂ only) PMRA# 2588956	**Supplemental** ≥ **1 mg Br^-/kg bw/day:** hypertrophy and hyperplasia of the endoplasmic reticulum, microfollicular rearrangement and lowered volume of colloid. **Note:** Accompanies the 2-, 9- and 19-week studies above (PMRA #1463160 and 2588954)
Special thyroid investigations – electron microscopy examination of rat thyroid micro-vascularization following 16 or 66 days oral exposure (drinking water) Potassium bromide Wistar rat (♀ only) PMRA# 2637283	**Supplemental** **≥0.7 mg Br^-/kg bw/day:** ↑ density and number of meshes in the capillary network of the follicle and flattening of the walls of peripheral vessels; follicles received less blood flow compared to controls in rats exposed for 66 days
Special thyroid investigations – iodine/bromine ratio in the rat thyroid following 15 or 57 days oral exposure (drinking water) Potassium bromide Wistar rat (♂ only) PMRA #2637316	**Supplemental** ≥**0.7 mg Br^-/kg bw/day:** ↓ iodine levels in thyroid tissue with increasing bromine consumption; ↓ iodine/bromine ratios in the thyroid gland following either 15 or 57 days; the change in the iodine/bromine ratio in the rat thyroid was noted to depend on the number of halogen binding positions, and on the bromide supply.

Short-term studies - Dog	
5-day oral toxicity (capsule) – Investigation of prostate Sodium bromide 'Mongrel' dogs (♂) PMRA #1463183	**Supplemental** **70 mg Br^-/kg bw/day**: Clinical signs and lethargy; ↓ serum Cl^- levels and ↑ Br^- levels; overall serum levels of Cl^- plus Br^- equivalent to pre-test levels of Cl^-, indicating that Br^- had replaced an equivalent amount of Cl^- in the serum; similar trend in basal prostatic secretions; following stimulation with pilocarpine, Br^- was concentrated in prostatic fluid to a greater extent than Cl^-, exceeding serum levels of Br^- **Limitations:** Single dose tested
2-20 wk oral toxicity (capsule) Sodium bromide 'Mongrel' dogs PMRA #1460769	**Supplemental** **Experiment 1 (140 days)** **100 mg/kg bw/day):** Slow/steady elevation of bromide blood levels (approximately ≤ 34 mEq/L); no mortality **Experiment 2 (134 days)** **100 to 400 mg/kg bw/day (progressive dosing):** Slow/steady elevation of bromide blood levels (approximately ≤ 51 mEq/L); mortality (days 82-134), clinical signs, skin lesions **Experiment 3 (185 days)** **200 - 600 mg/kg bw/day (progressive dosing):** Slow/steady elevation of bromide blood levels (approximately ≤ 60 mEq/L); mortality (days 29-185), clinical signs, skin lesions **Experiment 4 (42 days)** **400 mg/kg bw/day:** Rapid elevation of bromide blood levels (approximately ≤ 50 mEq/L); all dogs died within 44 days (mortality days 27-44), clinical signs, skin lesions **Limitations:** No control group; progressive dosing schedules render it difficult to identify effect levels; number of dogs used in Experiments 1-3 was unclear; incidence of clinical signs and skin lesions were not presented; limited confidence due to age of study
Chronic Toxicity/Oncogenicity Studies	
2-year oral toxicity (diet) Potassium bromide Fischer (F344) rats PMRA #2588938	**Supplemental** NOAEL not established; effects noted at single dose tested, 500 ppm (equivalent to 11.1/13.4 mg Br^-/kg bw/day). **500 ppm (11.1/13.4 mg Br^-/kg bw/day):** ↑ fc (beginning of study), ↑ bw (♂/♀); prostatitis (20/60 vs. 10/60 in controls) (♂); ↑ wc, ↑ incidence MCL tumours (equivocal) (♀) **Limitations:** Single dose tested

Developmental/Reproductive Toxicity Studies	
Developmental toxicity (gavage) Sodium bromide CDBR VAF/Plus Rats PMRA# 1167650	**Maternal** NOAEL = 234 mg Br^-/kg bw/day **≥234 mg Br^-/kg bw/day:** ↓ bwg (GD 16-20); considered non-adverse at this dose level **780 mg Br^-/kg bw/day:** one mortality, ↑ fc (gestation), ↓ bwg (GD6-12; GD16-20), unsteady gait, weakness, loss of coordination, reduced body tone, hair loss **Developmental** NOAEL = 78 mg Br^-/kg bw/day **≥234 mg Br^-/kg bw/day:** ↑ incidence (on fetal and litter basis): reduced ossification of one or more cranial centres, unossified/reduced ossification of sternebrae **780 mg Br^-/kg bw/day**: Variations (↑ fetal and litter basis): irregular ossification of vertebral centra, minimal distortion of rib, shortened/absent 13th ribs, Malformations: urogenital (absent/small kidney and/or ureter), absent/narrow uterine horn, small indeterminate gonad, distorted/abnormal ribs. **Developmental toxicity in the absence of maternal toxicity**
Developmental toxicity (gavage) Ammonium bromide Sprague-Dawley (CD) Rat PMRA# 665862	**Maternal** NOAEL = 245 mg Br^- /kg bw/day **820 mg Br^- /kg bw/day:** clinical signs starting day after first dose (rolling gait, limp when handled, hunched posture, subdued behaviour, dark eyes, slow respiration, piloerection, staining, thin appearance, white lower incisors), one dam sacrificed GD 10 due to severe clinical signs, one dam with uterus filled with red fluid at necropsy, ↓ bwg GD 6-12 and GD 6-20 . **Developmental** NOAEL not established **≥ 82 mg Br^- /kg bw/day:** Visceral variations: ↑ incidence of undescended/displaced testes, Skeletal variations: kinked ribs, incomplete ossification of ribs. **≥ 245 mg Br^- /kg bw/day:** Skeletal variation: reduced size of 13th rib. **820 mg Br^- /kg bw/day:** ↓ mean fetal wt, ↑ incidence of small fetus, Malformations: left kidney absent/small/displaced, flattened/small spleen, narrow left uterine horn with flattened ovarian end and displaced from ovary, reduced/absent thyroid Visceral variations: dilated renal pelvis, dilated ureter, haemorrhage affecting brain ventricles/surrounding tissues, subcutaneous haemorrhage affecting cranium/trunk/limbs, left umbilical artery, small intraventricular septal defect, Skeletal variations: curved scapula, cervical rib. **Variations in the absence of maternal toxicity**

Range-finding reproduction (one-generation) (diet) Ammonium bromide Sprague-Dawley rat PMRA# 1093412	**Supplemental (range-finding)** Parental effects noted at ≥3200 ppm (226/283 mg Br^-/kg bw/day) Offspring effects noted at ≥1600 ppm (123/144 mg Br^-/kg bw/day) Effects on reproduction noted at ≥3200 ppm (226/283 mg Br^-/kg bw/day) **Parental Toxicity** **≥3200 ppm (226/283 mg Br^-/kg bw/day):** Staining of the body (♂/♀); ↓ overall bwg and ↓ group mean fc towards end of treatment period (♂); clinical signs of toxicity, including rolling gait (starting around 5th week of treatment), piloerection, hunched posture (♀) **6400 ppm (482/585 mg Br^-/kg bw/day):** Unkempt coat (♂/♀); ↓ bwg (♂); clinical signs of toxicity appearing during the first days of treatment and persisting throughout treatment period (rolling gait in all animals, piloerection, hunched posture, hyperactivity), ↓ bwg during gestation for the single pregnant animal (♀) **Offspring Toxicity** **≥1600 ppm (123/144 mg Br^-/kg bw/day):** one pup killed due to physical condition (cold to touch, subdued behaviour, abnormal breathing) on or before PND 12 **≥3200 ppm (226/283 mg Br^-/kg bw/day):** ↑ pup mortality (all pups died prior to PND 21 in 3/9 litters, ↓ mean litter and pup wts throughout lactation, 3 pups from 2 litters were killed due to their physical condition (cold, subdued behaviour, abnormal breathing) on or before PND 12 **6400 ppm (482/585 mg Br^-/kg bw/day):** The one litter produced died prior to PND 4 **Reproductive Toxicity** **≥3200 ppm (226/283 mg Br^-/kg bw/day):** One litter with all pups born dead (vs 0 in control and low dose groups) **6400 ppm (482/585 mg Br^-/kg bw/day):** ↓ fertility index (although 7/10 & showed a positive mating sign, only 1/10 became pregnant, vs 10/10 in controls), the one litter produced died prior to PND 4 **Limitations:** Microscopic examination was not performed

Special reproduction investigations (diet) (3-generations; 2 litters/generation) Sodium bromide Rat (strain not given) PMRA# 1460782 <u>Transplacental transport</u>: A 3rd litter was raised in the first generation in order to investigate transplacental transport of bromide. Following 7 months of dietary exposure to sodium bromide, plasma and kidney levels of bromide were then compared in dams and their 20-day old fetuses. <u>Reversibility of effects</u>: An additional litter was bred with parent animals of the highest dose group (19200 ppm) who were fed treated diet for 7 months followed by control diet for 3 months before mating, in order to investigate the reversibility of effects. <u>Fertility investigations</u>: Due to the lack of fertility at 19200 ppm a Acriss-cross@ experiment was carried out to investigate whether the infertility was due to the males or females (untreated males and females were mated with males and females from the 19200 ppm dose group).	**Supplemental** Thyroid hormone effects at ≥ 75 ppm (5.8 mg Br^-/kg bw/day) Parental systemic effects observed at ≥75 ppm (5.8 mg Br^-/kg bw/day) Reproductive/offspring effects observed at ≥4800 ppm (373 mg Br^-/kg bw/day) **Parental** **≥75 ppm (5.8 mg Br^-/kg bw/day):** ↓ T_4 serum (F_0 ♂), ↓ bw for F_2 ♂ **≥1200 ppm (93 mg Br^-/kg bw/day):** ↓ bw for F_2 ♀ adults, ↓ rel adrenal wt in F_0 ♀ adults (does not appear that histopathology was performed) **≥4800 ppm (373 mg Br^-/kg bw/day):** ↓ T_4 serum (F_0 ♀) **19200 ppm (1491 mg Br^-/kg bw/day):** ↓ lymphocytes and ↑ neutrophilic granulocytes **Reproductive** **≥4800 ppm (373 mg Br^-/kg bw/day):** ↓ rel uterine wt in F_1 ♀adults, ↓ fertility index in F_0 generation **19200 ppm (1491 mg Br^-/kg bw/day):** No dams became pregnant **Offspring** **≥4800 ppm (373 mg Br^-/kg bw/day):** ↓ viability in F_0 gen. offspring, ↓ lactation index in 1st litter of F_0 gen. offspring **Additional investigations conducted** <u>Transplacental transport of bromide</u>: Investigation of transplacental transport of bromide revealed that fetuses in utero are exposed to bromide since the concentration of bromide in kidneys of corresponding dams and fetuses were similar. <u>Reversibility of effects on reproduction</u>: Parental animals that were fed 19200 ppm in the diet for 7 months, and then control diet for 3 months before mating showed some reversibility of effects when compared to the main study results. Compared to the infertility noted in the main study, fertility index was 62%, viability index was 61%, and lactation index was 90%. <u>Infertility investigations</u>: Of the treated ♀ mated with untreated ♂, only 20% became pregnant, and none of the untreated♀ mated with treated ♂ became pregnant. Therefore, it was concluded that the observed effects were due to infertility in both sexes. **Serious effect in offspring at a dose that is toxic to parental animals** **Limitations:** Methodology and study details unclear, purity not specified, missing data (and no individual data); missing several required parameters for guideline reproduction study; no histopathology examination conducted

Special lactational transfer investigations (drinking water) Sodium bromide Wistar rat PMRA# 2637310	**Supplemental** **Experiment 1 (Dams treated during the lactation period only):** **≥1 g/L (100 mg Br^-/kg bw/day):** ↓^{131}I lactational transfer to pups, ↓ ^{131}I retention in dams, ↓ pup wt **Experiment 2 (Dams treated during pre-mating, mating, gestation and lactation periods):** **≥1 g/L (100 mg Br^-/kg bw/day):** ↓^{131}I lactational transfer to pups, ↓ ^{131}I retention in dams, ↓ pup wt **Note:** It is unclear whether the following results were from Experiment 1 or 2: **≥ 100 mg Br^-/kg bw/day:** ↓ plasma T_3 and T_4 in pups and dams, ↓ milk production **Limitations:** Purity not specified; some experimental details unclear (for example, not clear whether data shown for milk production and thyroid hormone levels are from Experiment 1 or 2)
Special lactational transfer investigations (drinking water) Sodium bromide Wistar rat PMRA# 1460786	**Supplemental** **Experiment 1 (Effects of bromide on nursing pups):** **1 g/L (277 mg Br^-/kg bw/day):** equivocal ↑ in pup mortality (5% vs. 0 in control; # of affected litters not identified) **5 g/L (858 mg Br^-/kg bw/day):** ↓ fc, wc and bw in dams, 44% pup mortality, ↓ pup bw (from PND 4) **Experiment 2 (Effects of bromide on milk production):** **5 g/L (858 mg Br^-/kg bw/day):** ↓ milk production and ↓Cl^- levels in milk **Experiment 3 (Lactational transfer of bromide):** ^{82}Br appeared in the bodies of the young beginning at 3 h after application to dams, and levels increased over the next 22 h. It was noted that the dose received by the nursing pups was lower compared to the dams (for example, on PND 11, high dose pup intake was estimated to be 26.3 mg/100g bw vs. 82.2 mg/100g bw in dams), and yet caused a much more severe bw effect in the pups, as well as mortality in pups. **Limitations:** Purity not specified; duration of dosing unclear; unclear whether doses reported in sodium bromide or Br^- (assumed to be Br^-)
Genotoxicity Studies – Sodium bromide	
Ames Test Sodium bromide *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 PMRA# 1163639	Negative

Ames Test Sodium bromide *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and *Escherichia coli* WP2*uvrA*$^-$ PMRA# 2588920	Negative
Chromosome aberrations in vitro Sodium bromide Human lymphocyte cells PMRA# 1163638	**Supplemental** Negative **Limitations:** Inadequate exposure period and number of cells scored
Unscheduled DNA repair synthesis Sodium bromide HeLa S3 epithelioid cells PMRA#1163640	Negative
Gene mutations in bacteria Ammonium bromide *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. Coli* WP2uvrA PMRA# 665849	Negative
Gene mutations in mammalian cells in vitro Ammonium bromide Mouse lymphoma L5178Y cells (TK locus) PMRA# 665850	Negative
Micronucleus assay in vivo Ammonium bromide CD-1 (ICR) mice PMRA# 665851	Negative

Neurotoxicity Studies	
Short-term neurotoxicity (diet) Sodium bromide NMRI albino mice PMRA# 1460740	**Supplemental** **≥400 ppm (47 mg Br^-/kg bw/day**): ↓ evasion time (equivocal) **≥1200 ppm (140 mg Br^-/kg bw/day):** ↓ evasion time **≥3600 ppm (419 mg Br^-/kg bw/day):** ↑ motor activity and altered temporal pattern of activity **10800 ppm (1258 mg Br^-/kg bw/day):** ↓bw, animals noted to move more continuously (without noticeable rest time), but total amount of movement is lower and ↓ treadmill activity **Limitations:** Data only presented graphically
Modified developmental neurotoxicity (drinking water) Sodium bromide Sprague Dawley rat PMRA# 1460728	**Supplemental** **2500 mg/L (equivalent to 97 mg Br^-/kg bw/day):** ↓ bw (↓≤15%; by PND 19; differences from controls became greater in adulthood); ↓ brain wt (↓10%; by PND 10 and persisting into adulthood); ↓ protein content in brain (by PND 19 and persisting throughout development); effects on olfactory glomeruli including an initial delay (approximately 2-3 days) in appearance of acid phosphatase activity and ↑ size of glomerular profiles (↑ 30%; measured by synaptophysin immunohistochemistry and quantitative microscopic assessment); increase first apparent by PND 8, and continued to increase in magnitude for more than a month after birth. There were three apparent phases of developmental delay (PND 1-10, PND 10-40 and PND 40-90), with what was described as apparent attempts at compensation in between, providing evidence that bromide may affect development indirectly through action on some mechanism involved in the regulation of postnatal development. **Limitations:** Purity not specified; single dose tested; limited parameters tested
Special Studies (non-guideline) – Neurotoxicity mode of action investigations	
In vitro study of frog sympathetic ganglion Sodium bromide Bull frog PMRA# 2588939	**Supplemental** **Synaptic transmission (extracellular recording):** NaBr caused an immediate slight increase in the amplitude of the postganglionic compound action potential (CAP) response **Ganglion cell membrane (intracellular recording):** Hyperpolarization of the ganglion cell membrane occurred in 30 of 31 cells within 1-2 min of treatment with NaBr; transient effects (lasted for ~30 min); prolongation of post-spike positivity and ↑ overshoot and spike rate of rise **Synaptic excitatory effects (extracellular recordings):** ↑ post-spike negativity; acted synergistically with ethanol to produce more intense stimulus-bound responses following a single preganglionic stimulus; these effects were not transient These results suggest that **s**ince bromide rapidly increased the rate of rise in evoked action potentials, it may interact with sodium channels, augmenting sodium entry in the active membrane. Hyperpolarization may reflect bromide inhibition of sodium entry in the resting membrane.

In vitro study with murine neuroblastoma cells Sodium bromide PMRA# 2588946	**Supplemental** **≥0.1 mM:** Changes in the number, length and shape of cell processes (as detected by light microscopy); ultrastructural changes, including the appearance of numerous coated vesicles and mitochondria within the varicosities of axon-like processes, ↑ number of dense-core vesicles, and the formation of symmetrical contact specializations between varicosities and potential postsynaptic elements (as detected by electron microscopy). These results demonstrated that sodium bromide induced changes in murine neuroblastoma cells similar to those induced by GABA (as noted in other studies). GABA and NaBr cause hyperpolarization by manipulating chloride channels and depress the synaptic effects of preganglionic axons on the ganglion cells. NaBr induces specific morphological changes that may be interpreted as steps in the maturation of presynaptic elements and primitive stages of synaptogenesis.
In vitro study with murine neuroblastoma cells Sodium bromide PMRA# 2588927	**Supplemental** **≥0.1 mM NaBr or GABA:** ↑ length and branching of the processes; ↑ number of neuroblastoma cells It was noted that the length of processes, the number of branchings and the cell number per area were significantly dependent on the concentration of NaBr or GABA and that the structural alterations represent a type of neuronal plasticity, which may be related to functional changes in the activity of the neuroblastoma cells.
In vivo investigation – effects of sodium bromide on ethanol withdrawal reactions (i.p. injection) Sodium bromide Swiss-Webster mice (♂ only) PMRA# 1463186	**Supplemental** **Ethanol-dependent mice** **≥ 0.2 g/kg bw (equivalent to 155 mg Br^-/kg bw):** Sodium bromide caused a dose-related decrease in seizure scores for mice undergoing ethanol withdrawal reactions; the effect at the lowest dose (155 mg Br^-/kg bw) was transient (lasted 7-30 hours at doses of 388 to 777 mg Br^-/kg bw); no convulsions were observed at the highest dose tested during the observation period (30 h); mortality was increased during the withdrawal period with NaBr treatment; 1-2 deaths occurred at each dose group (6/30 bromide-treated mice vs. 1/21 control mice) **Normal mice** **≥2.0 g Br^-/kg bw (≥ 1553 mg Br^-/kg bw):** Sedative effects; ataxia was noted for approximately 4 hrs **4.0 g/kg bw (3106 mg Br^-/kg bw):** loss of righting reflex These results suggest that NaBr may suppress ethanol withdrawal reactions through action at the chloride ionophore that is associated with the GABA receptor.
Microinfusion study - superior cervical ganglion (SCG) Sodium bromide Sprague Dawley rat PMRA# 2588935	**Supplemental** **500 mM NaBr:** Plastic changes in the rat SCG (as detected by electron microscopy), similar to those induced by GABA (as noted in other studies), including formation of non-innervated postsynaptic membrane thickenings, accumulation of microvesicles and changes in the shape of dendrites This study revealed that plastic changes were seen in dendrites after sodium bromide treatment, which were similar to those described in earlier studies with GABA. It was hypothesized that the changes may have occurred through a long-lasting hyperpolarization of ganglion cells as a result of displacing chloride.

Nerve implantation study - superior cervical ganglion (drinking water) Sodium bromide Adult rats (strain/sex not specified) PMRA# 2642882	**Supplemental** **Experiment 1 (Hyglossal nerve transplanted to the surface of the SCG):** Stimulation of the implanted hypoglossal nerve was able to evoke action potentials (APs) only in the animals treated with NaBr (2800 mg/L; equivalent to 217 mg Br^-/kg bw/day). **Experiment 2 (Vagus nerve transplanted to the surface of the SCG):** Ganglionic action potentials could only be evoked after stimulation of the vagal nerve in groups receiving NaBr prior to implantation. Those treated with NaBr received 217 mg Br^-/kg bw/day for 5 days before implantation and tap water afterwards or 217 mg Br^-/kg bw/day throughout, beginning 5 days prior to implantation and afterwards. These APs could be blocked by hexamethonium. These results indicate that the cells in the SCG are able to build up additional active synapses with foreign nerves following administration of NaBr, in a similar manner to GABA.
Perfusion and in vitro investigations of the SCG Sodium bromide Sprague Dawley rat PMRA# 2642097	**Supplemental** **In vitro experiments:** **1 mM NaBr:** ↓ [^{3}H]AChE release in the presence and absence of K^+ stimulation; inhibitory effects of NaBr on [^{3}H]AChE release persisted in the presence of a $GABA_A$ receptor antagonist or a Cl^--channel blocker; NaBr further ↓ [^{3}H]AChE release caused by a $GABA_B$ receptor agonist **Perfusion experiments** **1 mM NaBr:** ↓ amplitude of evoked APs; ↓ APs that had been further stimulated by a $GABA_A$ receptor antagonist; additive inhibitory effect on the evoked APs when co-treated with a $GABA_B$ receptor agonist The results demonstrate that NaBr reduces both the K^+-stimulated release of AChE in vitro and the amplitude of the potentials evoked following perfusion by preganglionic nerve stimulation in the rat SCG. The in vitro results indicate that NaBr has a general effect on the presynaptic cholinergic axon terminals since the decrease in AChE release could not be altered by either of the $GABA_A$ or $GABA_B$ receptor activators or inhibitors.
In vitro and in vivo investigations of ACh activity - SCG Sodium bromide Sprague Dawley rat PMRA# 2642100	**Supplemental** **In vitro experiments (0.1-50 mM NaBr):** No significant effect on AChE activity in SCG preparations. **In vivo experiments (108 mg Br^-/kg bw/day):** ↓AChE activity; enzyme activity began to fall within 2 days, reaching a minimum between 5-13 days, and then slowly returning to control levels by about 30 days of treatment; changes in the relative proportions of the three molecular forms of AChE that were detected in the rat SCG after 13 days of treatment, notably, a significant ↑ in the relative amount of the A_{12} AChE molecular form. The results suggested that based on the absence of effects in the in vitro experiments, NaBr does not influence the activity of AChE directly. In light of these findings, it was suggested that free postsynaptic membrane thickenings caused by NaBr, which are dense in AChE (as shown in previous studies), may promote the accumulation of A_{12} AChE.

In vivo effects on synaptic potentiation and calcium accumulation in superior cervical ganglion (drinking water) Sodium bromide Sprague Dawley rat PMRA# 2642099	**Supplemental** **NaBr treatment (109 mg Br^-/kg bw/day):** Prevented the enhancement of the ganglionic response that was observed in the control group following tetanizing stimulation (that is, prevented the development of post-tetanic potentiation) in the SCG (in situ); prevented the increase in Ca^{2+} that was observed in pre- and post-synaptic organelles in the control group following stimulation. These results indicate that NaBr treatment inhibited the development of post-tetanic potentiation (PTP) in the rat SCG, which is likely Ca^{2+}-dependent since NaBr also prevented the increase in the number of calcium containing pre- and postsynaptic organelles in the SCG with PTP.
In vitro investigation of rat cerebral cortex Sodium bromide Wistar rat embryos PMRA# 2642881	**Supplemental** Reversal potential investigations revealed the relative permeability ratio of the $GABA_A$-coupled channels to Br^- with respect to Cl^- is 1.51. **≥10 mM Br^-:** enhanced GABA-activated outward currents **≥20 mM Br^-:** enhanced GABA-induced hyperpolarization These results demonstrate that bromide (at therapeutic concentrations; 10-20 mM) potentiated GABA-activated currents, and also elicited a larger amount of anion influx, causing a larger GABA-induced hyperpolarization. Bromide may exert its antiepileptic effects via potentiation of inhibitory postsynaptic potentials elicited by GABA
In vivo investigation of cerebral cortex (drinking water) Sodium bromide Adult rat (strain not specified) PMRA# 2642096	**Supplemental** **27 mM NaBr (108 mg Br^-/kg bw/day) or 27 mM NaCl (48 mg Cl^-/kg bw/day):** No effects were noted on any of the endpoints examined in cerebral cortex, including high-affinity GABA uptake in cortical slices, GABA metabolism in cortical homogenates, GABA levels in tissue and GABA binding to washed particulate fractions containing neuronal membranes.

In vivo investigations of the effects on neural neuroplasticity in rat neonates (drinking water) Sodium bromide Sprague Dawley rat PMRA# 2642883	**Supplemental** **Note:** Both eyes were enucleated in pups on PND 1, 15 or 30, and then at 3-4 months of age, evoked potential in response to electrical stimulation were mapped. **2800 mL NaBr (equivalent to 217 mg Br^-/kg bw/day):** **PND 1 enucleation:** Similar expansion of somatosensory responsive area in controls and NaBr; no effect of NaBr treatment noted. **PND 15 enucleation:** No modification of somatosensory responsive area in controls, while treatment with NaBr caused an expansion of cortical areas responsive to electrical stimulation, which was similar to that observed in rats enucleated at PND 1. **PND 30 enucleation:** No modification of somatosensory responsive area in controls or in rats treated with NaBr (results not shown in article) The above results suggest that the developmental period during which enucleation induces cortical plasticity is restricted to the first post-natal week in untreated animals. NaBr treatment may extend or shift the critical period of neuroplasticity during which somatosensory projections can be modified by visual deafferentation, at least up to 15 days after birth. **Limitations:** Dosing regime is unclear; it appears that the NaBr was administered to nursing dams, and this was the source of NaBr for pups until they were consuming treated water directly.
In vitro investigations of effects on epileptic activity of rat cortex slices Sodium bromide Wistar rat PMRA# 2637298	**Supplemental** Combined rat hippocampus-entorhinal cortex slices were used to investigate the effects of NaBr on different types of epileptiform discharges in two models of epilepsy (low-Ca^{2+} and low-Mg^{2+}). Effects on GABAergic inhibition were tested in a paired-pulse stimulation protocol (in the stratum pyramidale), and on spontaneous inhibitory postsynaptic currents (IPSC) in cultured hippocampal neurons in whole-cell patch clamp configurations **≥3 mM NaBr:** ↓ frequency of seizure-like events in entorhinal cortex **≥5 mM NaBr:** ↓ frequency and/or blocked low-Ca^{2+} and low-Mg^{2+} discharges in a dose-dependent manner **≥7 mM NaBr:** blocked seizure-like events in entorhinal cortex **≥10**mM NaBr: ↓ late recurrent discharges in entorhinal cortex **30 mM NaBr:** blocked ↓ late recurrent discharges in entorhinal cortex NaBr did not cause a change in extracellular pH. NaBr increased paired-pulse inhibition in the stratum pyramidale, and also increased inhibitory postsynaptic current amplitude in hippocampal neurons. The results suggest that sodium bromide exerts a 'broad-spectrum' anti-convulsant activity, likely mediated via effects on membrane excitability, via an increase in GABAergic inhibition, and less likely to be caused by effects on extracellular pH.

In vivo neurological investigations (dietary) Potassium bromide Beagle Dogs PMRA# 1460750	**Supplemental** **30 mg/kg bw/day (20 mg Br^-/kg bw/day):** No adverse neurologic effects from Days 0-115; following a dose adjustment to increase serum bromide levels to target of 400 mg/L (Days 115-121), two dogs exhibited caudal paresis and ataxia (characterized by wide-based and/or crouched pelvic limb stance, difficulty rising from sitting position, and ↓ hemi-standing and flexor withdrawal reflexes in the pelvic limbs) and two dogs were agitated/hyperexcitable; BAERs measurements revealed significant ↑ in latencies of waves I and V (Days 0 to 9) and a significant ↑ I-V interpeak latency (Days 0 to 121); examination of individual data showed correlations between neurologic deficits and changes in BAERs and/or SSEP parameters; serum bromide concentrations did not correlate well with signs of neurotoxicity in most cases The above BAER findings suggest that conduction along peripheral and central sensory pathways may be delayed when serum and CSF bromide concentrations are elevated. It is noted that slowed neural conduction may be related to the hyperpolarizing effect of bromide on neuronal membrane potential and that serum bromide concentrations may not be reliable indicators of impending toxicity. **Limitations:** Single dose tested; purity not specified.
Human clinical studies	
Human study Bromine levels in adults with thyroid disorders PMRA# 2588921	**Supplemental** Plasma bromine concentrations were measured in 799 patients being examined for thyroid disorders. Bromine plasma concentration in 'normal' subjects was previously established to be 4.1 ± 0.9 mg/L (0.051 mmol/L); therefore, bromine concentrations above 6 mg/L (0.08 mmol/L) were considered above the normal range. Of the patients being seen for thyroid disorders, 22% had plasma bromine concentrations above 6 mg/L (0.08 mmol/L). The percentage of patients with high TSH values, but normal free T_4 levels, was significantly increased in the group with higher than normal plasma bromine levels (i.e. > 6 mg/L = 0.08 mmol/L). Also, the mean plasma bromine concentration in patients with normal TSH and T_4 levels was 13 mg/L (0.16 mmol/L), compared to 38 mg/L (0.48 mmol/L) in patients with high TSH, but normal T_4 levels.
Human clinical study (oral) Potassium bromide Adult patients with Graves' disease PMRA# 2637295	**Supplemental** Graves' disease is an autoimmune disease of the thyroid gland characterized by excessive production of thyroid hormone, goiter, protrusion of the eyeballs and symptoms of hyperthyroidism. Methimazole is used to treat this disease, and inhibits the synthesis of thyroid hormone without blocking the absorption of iodine, and has no effect on the release of thyroid hormone from the thyroid gland. **1 g/day (approximately equivalent to 29 mg Br^-/kg bw/day):** Combined treatment with methimazole resulted in improved clinical hyperthyroidism symptoms significantly faster (10 days earlier) than methimazole treatment alone; combined treatment with methimazole further decreased FT_3 and FT_4 levels and further increased TSH levels compared to treatment with methimazole alone; 28/30 patients had FT_3 and FT_4 levels within normal ranges in the combined potassium bromide and methimazole group, compared to 5/30 in the methimazole only group.

Human case studies - Newborns/infants (<1 year) and pregnant mothers	
PMRA# 1460724	2-month old ♀: Medecitral (contains sodium bromide) for 1 month to treat abdominal pain. Dose not specified. Serum Br^- levels not reported. Several large vegetative plaques with an erythematous base (bromoderma)
PMRA# 1460735	7-day old ♀ and mother: 24 h prior to delivery, the mother consumed approximately 0.95 L of a sedative consisting of sodium bromide, potassium bromide, and ammonium bromide. The mother had been ingesting lesser amounts regularly throughout her 39-week pregnancy. Serum bromide levels: Child: 365 mg/dL = 45.7 mmol/L; Mother: 320 mg/dL = 40.1 mmol/L Child's symptoms: lethargic, poor suck, non-existent spontaneous movement, moderately dilated pupils that reacted very slowly, minimal response to painful stimuli, poor grasp reflexes, no tendon or abdominal reflexes Mother's symptom: delirium
PMRA# 1460748	Preterm ♂ (37 weeks gestation) and mother: The mother had been taking dextroamphetamine and chlorpromazine. During the week prior to delivery, liquid bromide mixture [(containing 72 g ammonium bromide and 72 g potassium bromide per pint (=0.3 g total bromide/mL)] was prescribed. The mother had taken 6 g/day for 4 days until the day prior to delivery. Serum bromide levels: Child: 200 mg/dL = 25 mmol/L; Mother: 310 mg/dL = 38.8 mmol/L Child's symptoms: Hypotonic, quiet, weak and high pitched cry, poor suck, partial moro reflex, diminished tone, absence of deep tendon reflexes
PMRA#1460749	4-day old ♀ and mother: The mother was employed in a photographic laboratory throughout her entire pregnancy up until 5 weeks prior to delivery. Bromide levels: Child: Urine Br^- level: 33 mg/dL = 4.1 mmol/L (day 11); Serum Br^- level: 15 mg/dL = 1.88 mmol/L (day 18) Mother: Serum Br^- level: 19 mg/dL = 2.38 mmol/L (day 18) Child's symptoms: Sudden development of cyanotic episode, frontal bossing, inner canthal distance of the 97^{th} percentile, broad nasal bridge, prominent gingivae, clinodactyly of fifth finger, weak cry, suck and grasp, hyporeflexia, profound generalized hypotonia

PMRA# 1460763	Newborn ♀ and 27-year old mother: The mother had been taking Miles Nervine in the last 1-2 months of her pregnancy [reported to contain 615.4 mg of sodium, potassium, and ammonium bromides (153.7 mg Br^-) per capsule (25 capsules per bottle)]. Three empty bottles had been found in her home (11.5 g Br^- total). Serum bromide levels: Child: 242 mg/dL = 30.3 mmol/L; Mother: 295 mg/dL = 36.9 mmol/L Child's symptoms: hypotonic, only aroused with vigorous stimulation. Mother's symptoms (prior to delivery): headaches, sleeplessness, progressive lethargy, visual hallucinations, semiconscious, hyper-reflexes, excessive secretions, cyanosis
PMRA# 1460770	Newborn ♀: Source of exposure, dose, or duration not stated, only that "the mother had ingested large amounts of bromide during pregnancy". Serum bromide levels not reported Extremely irritable, high-pitched cry and very difficult to feed.
Human case studies - Children (2-18 years)	
PMRA# 1463092	17-year old ♀: Ingested bromide medication (containing 80 mg/mL each of sodium bromide, ammonium bromide, and potassium bromide; 60 mg/kg bw/day) for 7 years, with yearly bromide levels maintained within 150-200 mg/dL (18.8-25 mmol/L). Other medications included phenytoin (4.5 mg/kg bw/day) and valproate (31.6 mg/kg bw/day). Serum bromide levels: 390.7 mg/dL = 48.9 mmol/L Progressive deterioration in mental status, increasingly irritable, confused, anorexic, slurred and high pitched speech, generally weak, tremors, hyperactive reflexes.
PMRA# 1460761	Two boys, examined around 7-8 years of age: Exposure to bromide in utero (see mother's exposure under same PMRA # below). Serum bromide levels not reported Boys were below the 3rd percentile for height and weight. The younger son also had enamel hypoplasia, malocclusion and congenital heart disease (see mother's symptoms under same PMRA # below).
Human case studies - Adults (19-69 years)	
PMRA# 1463192	69-year old ♀: Codeine, valium, and antibiotics ingested; details regarding bromide exposure not specified. Serum bromide levels: 7 mg/dL = 0.88 mmol/L Bromoderma: ulcerated lesions on the hands with epithelial hyperplasia, necrosis, polymorphic inflammatory infiltrate, and pseudocarcinomatous dysplasia

PMRA# 1463192	60-year old ♂: Taking digitalis for a heart condition and "tonic" medications (unlabeled) for nervous tension and sleeplessness; details regarding bromide exposure not specified. Serum bromide levels: 12 mg/dL = 1.5 mmol/L Bromoderma: necrotic and granulomatous lesion on left arm with pseudocarcinomatous epithelium over a central necrotic ulcer.
PMRA#1463154	53-year old ♀: Only known medication was atenolol (a beta-blocker, no Br^- ion; 50 mg/day); details regarding bromide exposure not specified. Serum bromide levels: 31 mg/dL = 3.88 mmol/L upon admission. After initial recovery, the serum Br^- levels were 22 mg/dL = 3.13 mmol/L. Depression, drowsiness, mild memory impairment, dysarthria, fine finger tremor, unsteady gait, bilateral extensor plantar responses were reported. Patient was treated and recovered from these symptoms, but later developed dysarthria and ataxia.
PMRA# 1460753	23-year old ♂: Details of bromide exposure not specified. Serum bromide levels: 5.5 mg/dL = 0.689 mmol/L (also had barbiturates and salicylates in blood) Comatose febrile state
PMRA# 1460753	42-year old ♂: History of daily use of bromides (Bromo-Seltzer and Alva Tranquil). Duration and dose levels not specified. Serum bromide levels: 36.2 mg/dL = 4.53 mmol/L Hallucinations, thickened speech, twitching facial and lip movements, paranoid delusions
PMRA# 1460753	44-year old ♀: Details of bromide exposure not specified. Serum bromide levels: 20 mg/dL = 2.5 mmol/L Aggressive behaviour, rambling speech, ataxia
PMRA# 1460775	49-year old ♀: Patient had been taking a homeopathic preparation (Alveolan, containing 1.5 g potassium bromide and 30 g sodium bromide per 100 mL) for six weeks. A daily ingestion of 6 mL corresponded to 1468 mg bromide per day, with a total dose of 60 g bromide after six weeks. Serum bromide levels: 33 mg/dL = 4.1 mmol/L Fatigue, attention and concentration disorders, disorientation, distorted speech, uncertain gait, dysarthria, memory deficits
PMRA# 1463081	49-year old ♂: Patient reported an excessive intake of bromide sedative for the previous two weeks; dosage was not reported. Serum bromide levels: 123 mg/dL = 15.4 mmol/L Completely disorientated and agitated, global confusion, aggressive outbursts, metabolic encephalopathy

PMRA# 1460753	64-year old ♀: Patient had been taking a bromide-containing drug (Miles Nervine); dose and duration not specified. Serum bromide levels: 135 mg/dL = 16.9 mmol/L Tremulous state with dystonic tongue movements
PMRA# 1463085	30-year old ♀: Medications (over several months) containing 200 mg bromvalerylurea (=71.6 mg Br^-) per tablet, as well as cold medication (3x daily for one month) containing 20 mg dextromethorphan hydrobromide (=4.32 mg Br^-) per tablet. Serum bromide levels: 157 mg/dL = 19.7 mmol/L Mental confusion, lethargy, fever, acneiform eruption on face, gradual onset of memory impairment, anorexia and drowsiness over a two week period.
PMRA# 1463131	51-year old ♀: Details of bromide exposure not specified. Serum bromide levels: 186 mg/dL = 23.3 mmol/L Excessively tired, poor memory, insomnia, irritability, tearfulness, failure to gain weight
PMRA# 1460761	33-year old ♀: Chronic ingestion of large amounts of 'Bromo-Seltzer' (approximately 5 years); dose not specified. Serum bromide levels: 135 mg/dL = 16.9 mmol/L Progressive weakness, anorexia, weight loss, constipation, difficulty swallowing, dry mouth, severe toxic encephalopathy, chronic somnolence, disorientation, hallucination, profound weakness with muscle pain, incontinence (see children's symptoms under same PMRA # above).
PMRA# 1460776	48-year old ♀: Overdose; an empty 400 mL bottle of 250 mg/mL sodium bromide (=194 mg Br^-/mL) was found by a family member. Serum bromide levels: 170 mg/dL = 21.3 mmol/L (day 6 after admission) Altered mental status, severe pseudohyperchloremia, minimally responsive
PMRA# 1463149	40-year old ♀: Sedative syrup ingested daily [containing 40 g sodium bromide (31 g Br^-), 500 mg sodium phenobarbital, sirupus simplex, and menthol extract per 300 mL]; duration unknown. Serum bromide levels: 265 mg/dL = 33.2 mmol/L Disorientated, confused, agitated, in a stuporous state, brisk tendon reflexes, disturbed consciousness with lack of cooperation
PMRA# 1463205	60-year old ♀: Bromide medication ingested (at least 4 teaspoons daily) for the last 7 years; amount of Br^- not specified. Serum bromide levels: 356 mg/dL = 44.6 mmol/L Extreme drowsiness, bizarre behaviour, hallucinations

PMRA# 1460753	42-year old ♀: Bromide overdose (had taken 25 Miles Nervine tablets). Serum bromide levels: 360 mg/dL = 45.1 mmol/L Irritable, tremulous, disoriented, in an ataxic state, auditory and visual hallucinations
PMRA# 1460753	49-year old ♀: Patient had taken a bromide-containing drug (Miles Nervine); dose and duration not specified. Serum bromide levels: 345 mg/dL = 43.2 mmol/L Rambling speech, hallucinations, ataxia
PMRA# 1460753	60-year old ♀: Patient had taken bromide-containing drug (Miles Nervine); dose and duration not stated. Serum bromide levels: 355 mg/dL = 44.4 mmol/L Confusion, disorientation, hallucinations, lethargy, thickened speech
PMRA# 1463131	59-year old ♀: Patient had taken sleeping medication for many years (containing 3.9 g ammonium bromide; 3.2 g Br^-). Serum bromide levels: 380 mg/dL = 47.6 mmol/L Constipation, fatigue, confusion, slurred speech, poor memory, drowsy, emaciated, incontinent, dry and furred tongue, bilateral ptosis, constricted pupils, extreme muscular weakness, depressed tendon reflexes
PMRA# 1463131	59-year old ♂: Patient had taken a bromide-chloral mixture for 18 years; dose (not specified) had been doubled in the week before admission. Serum bromide levels: 202 mg/dL = 25.3 mmol/L Progressive mental deterioration, dragging of right foot, paranoid and violent prior to lapsing into a semicoma, dysarthric, constricted pupils, diminished tendon reflexes in legs, sordes in mouth, acneiform rash on chest, dysphasia, dysarthria, disorientation, mild incoordination of left arm and leg.
PMRA# 1460753	41-year old ♀: History of multiple drug abuse, including a bromide-containing drug (Miles Nervine); dose and duration not stated. Serum bromide levels: 514 mg/dL = 64.4 mmol/L Lethargic, disoriented
PMRA# 1460768	44-year old ♂: Patient had ingested medications for approximately one month including a sodium bromide-containing drug (Normgastryl); up to 25 pills/day of Normgastryl consisting of 250 mg sodium bromide/pill, 6.25 g/day (=4.86 g Br^-/day) were taken. Serum bromide levels: 1222 mg/dL = 153 mmol/L Confusion, hallucinations, depressed mood, epigastric pain (duodenal ulcer), bronze discoloration of teguments, cephalic rash of monomorphic acne, foul breath, disoriented.

PMRA# 2642098	22-year old ♀: Suicide attempt; patient had taken a single dose containing approximately 10 g of sodium bromides and potassium bromides, as well as 50 mg of biperiden hydrochloride. Serum bromide levels not reported. Coma, with no response to deep pain and symmetrically hypoactive tendon reflexes. Conscious status slowly improved and was clear by day 10; however, other symptoms appeared including excitement, memory defect, hallucination, complete deafness, slight enlargement of thyroid
PMRA# 1463130	Observations based on a series of 70 cases that were examined. Serum bromide levels not reported. Eye symptoms included disturbances of colour, and object form and outline perception, hypersensitivity to light, and visual hallucinations.
Human case studies - Elderly (≥70 years)	
PMRA# 1463154	77-year old ♂: A teaspoon of potassium bromide granules at least weekly for the previous 30 years; dose not specified. Serum bromide levels: 40 mg/dL = 5 mmol/L Tingling in legs, hallucinations, garrulous and euphoric mood, fine finger tremor, wide-based unsteady gait (diagnosed with paranoid psychosis associated with bromism)
PMRA# 1463131	76-year old ♀: Patient had taken a medication (“mist, gelsem. et hyoscy. co. B.N.F.”; 650 mg bromide per 15 mL) for trigeminal neuralgia. Serum bromide levels: 285 mg/dL = 35.7 mmol/L Incoherent, incontinence of urine, paranoid delusions
PMRA# 1463075	74-year old ♀: Patient had taken a sedative for 4 weeks that contained 1 g potassium bromide (=0.67 g Br^-) in 15 mL; dose was 60 mL/day (=2.68 g Br^-/day). Serum bromide levels: 352 mg/dL = 44 mmol/L Confusion, auditory and visual hallucinations, loss of short-term memory, disorientation, impaired attention and concentration
PMRA# 1463180	73-year old ♂: Patient had taken an analgesic for more than a decade containing 200 mg bromvalerylurea, 350 mg ethoxybenzamide, 200 mg acetaminophen, and 50 mg caffeine anhydrous/g. Dose equivalent to 3 g bromvalerylurea/day (1.07 g Br^-/day) for the previous six months. Serum bromide levels: 101 mg/dL = 12.7 mmol/L Mental deterioration, impaired short-term memory, occasional incoherent speech, dysarthria, dysphagia, body weight loss, poor attention span with fluctuating consciousness, ataxia, wide-based gait, visual and auditory hallucination, persecutory delusions, moderate to severe diffuse cortical dysfunction

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Bromate

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Short-term dermal[2]	Short-term drinking water and reproductive toxicity studies in rats	NOAEL: 8 mg bromate/kg bw/day Renal toxicity and decreased sperm density	1000
Non-dietary oral ingestion (short-term)	Short-term drinking water and reproductive toxicity studies in rats	NOAEL: 8 mg bromate/kg bw/day Renal toxicity and decreased sperm density	1000
Long-term dermal[2]	Chronic drinking water rat study	NOAEL: 1.1 mg bromate/kg bw/day Renal toxicity	1000
Non-dietary oral ingestion (long-term)	Chronic drinking water rat study	NOAEL: 1.1 mg bromate/kg bw/day Renal toxicity	1000
Cancer	Low-dose linear extrapolation approach; q_1* value of 0.115 [mg/kg bw/day]$^{-1}$ for testicular tumours in male rats		

[1] MOE refers to a target margin of exposure for occupational and residential assessments
[2] Since an oral NOAEL was selected, a dermal absorption factor will be used in any route-to-route extrapolation

Appendix III Environmental Risk Assessment

Table 1 USEPA Tier Ic modelling EEC results for hypobromous acid, measured as bromine

Use site classification	Reasonable worst case exposure scenario[1]	Typical exposure scenario[2]
Food processing	0.450 mg/L	0.00063 mg/L
Pulp and paper	0.450 mg/L	0.0012 mg/L
General industrial waste disposal, air washer systems, sewage systems	0.450 mg/L	0.00063 mg/L
Water cooling towers, evaporative condensers, heat exchangers	0.450 mg/L	0.00072 mg/L

[1] "Reasonable worst case" is based on the dilution factor for the 7Q10 flow rate at a given site where 90% of other like sites have a higher flow.
[2] Typical exposure scenario is based on the dilution factor for the median flow rate among a range of sites of the same industry.

Table 2 Summary of effects of hypobromous acid (measured as bromine) on freshwater and marine species

Species	Test chemical[1] (% active ingredient)	Study details	Toxicity endpoints (mg/L)	Toxicity category	Reference (EPA MRID or PMRA No.)
USEPA-reviewed studies; Freshwater:					
Bluegill sunfish (*Lepomis macrochirus*)	Bromine chloride, 100%	96-hr, static conditions	LC_{50}=0.52 mg/L as bromine NOEC = 0.30 mg/L as bromine	Highly toxic	406699-03, in USEPA RED 1993 (PMRA 1460777) PMRA 2700235 PMRA 1170609
Rainbow trout (*Salmo gairdneri*)	Bromine chloride, 100%	96-hr, static conditions	LC_{50}=0.31 mg/L as bromine NOEC = 0.10 mg/L as bromine	Highly toxic	406699-02, in USEPA RED 1993(PMRA 1460777) PMRA 2700235 PMRA 1170610
Freshwater invertebrate (*Daphnia magna*)	Bromine chloride, 99%	48-hr, static conditions	LC_{50}=1.07 mg/L as bromine	Highly toxic	406708-16, in USEPA RED 1993 (PMRA 1460777) PMRA 2700235 PMRA 1170611

Species	Test chemical[1] (% active ingredient)	Study details	Toxicity endpoints (mg/L)	Toxicity category	Reference (EPA MRID or PMRA No.)
USEPA-reviewed studies; Marine:					
Sheepshead minnow (*Cyprinodon variegatus*)	Sodium bromide, 46%	96-hr, flow through conditions	LC_{50}=0.19 mg/L as bromine NOEC = 0.11 mg/L as bromine	Highly toxic	407010-03, in USEPA RED 1993 (PMRA 1460777) PMRA 2700235 PMRA 1232624
Mysid shrimp (*Mysidopsis bahia*)	Sodium bromide, 46%	96-hr, flow through conditions	LC_{50}=0.18 mg/L as bromine NOEC < 0.037 mg/L as bromine	Highly toxic	407010-01, in USEPA RED 1993(PMRA 1460777) PMRA 2700235 PMRA 1170614
Eastern oyster (*Crassostrea virginica*)	Sodium bromide, 46%	96-hr, shell deposition, flow through conditions	EC_{50}=0.47 mg/L as bromine NOEC < 0.068 mg/L as bromine	Highly toxic	407010-02, in USEPA RED 1993(PMRA 1460777) PMRA 2700235 PMRA 1170613
Other Data available in PMRA database:					
Freshwater fish: Golden shiner	Sodium bromide	96-hr continuous exposure	LC50 = 0.29 mg/L as bromine	Highly toxic	1463214
Freshwater fish: Rainbow trout	Sodium bromide	96-hr flow through	LC50 = 0.068 mg/L as bromine	Very highly toxic	1463221
Freshwater invertebrate: Cloeon sp.	Not stated, assumed sodium bromide	48-hr, renewal	LC50 = 0.46 mg/L as bromine	Highly toxic	1463228
Freshwater invertebrate: *Daphnia manga*	Sodium bromide	48-hr flow through	LC50 < 0.038 mg/L as bromine	Very highly toxic	1463235
Marine invertebrate: Mysid shrimp	Sodium bromide	96-hr flow through	LC50 = 0.092 mg/L as bromine	Very highly toxic	1463239
Marine fish: inland silverside	Sodium bormide	96-hr flow through	LC50 = 0.065 mg/L as bromine	Very highly toxic	1463242

[1] The test substance in the test system is hypobromous acid, which was generated from either bromine chloride or sodium bromide. Both are considered acceptable as starting materials to produce hypobromous acid.

Table 3 Toxicity endpoints used in the aquatic risk assessment of hypobromous acid

Organism	Exposure	Toxicity endpoint	Adjusted Toxicity Endpoint[1]	Uncertainty factor (UF) applied
USEPA-reviewed studies:				
Freshwater invertebrate (*Daphnia magna*)	Acute	48-hr LC_{50}=1.07 mg/L as bromine	48-hr LC_{50}=0.535 mg/L as bromine	2
Bluegill sunfish (*Lepomis macrochirus*)	Acute	96-hr LC_{50}=0.52 mg/L as bromine 96-hr NOEC = 0.30 mg/L as bromine	96-hr LC_{50}=0.052 mg/L as bromine 96-hr NOEC = 0.30 mg/L as bromine	10
Rainbow trout (*Salmo gairdneri*)	Acute	96-hr LC_{50}=0.31 mg/L as bromine 96-hr NOEC = 0.10 mg/L as bromine	96-hr LC_{50}=0.031 mg/L as bromine 96-hr NOEC = 0.10 mg/L as bromine	10
Amphibians - Rainbow trout (*Salmo gairdneri*) used as a surrogate	Acute	96-hr LC_{50}=0.31 mg/L as bromine	96-hr LC_{50}=0.031 mg/L as bromine	10
Mysid shrimp (*Mysidopsis bahia*)	Acute	96-hr LC_{50}=0.18 mg/L as bromine 96-hr NOEC < 0.037 mg/L as bromine	96-hr LC_{50}=0.09 mg/L as bromine	2
Eastern oyster (*Crassostrea virginica*)	Acute	96-hr EC_{50}=0.47 mg/L as bromine 96-hr NOEC < 0.068 mg/L as bromine	96-hr EC_{50}=0.47 mg/L as bromine 96-hr NOEC < 0.068 mg/L as bromin	1
Sheepshead minnow (*Cyprinodon variegatus*)	Acute	96-hr LC_{50}=0.19 mg/L as bromine NOEC = 0.11 mg/L as bromine	96-hr LC_{50}=0.019 mg/L as bromine NOEC = 0.11 mg/L as bromine	10
Study summaries available in PMRA database:				
Freshwater fish: Golden shiner	Acute	96-hr LC50 = 0.29 mg/L as bromine	96-hr LC50 = 0.029 mg/L as bromine	10
Freshwater fish: Rainbow trout	Acute	96-hr LC50 = 0.068 mg/L as bromine	96-hr LC50 = 0.0068 mg/L as bromine	10
Freshwater invertebrate: Cloen sp.	Acute	48-hr LC50 = 0.46 mg/L as bromine	48-hr LC50 = 0.23 mg/L as bromine	2
Freshwater invertebrate: *Daphnia manga*	Acute	48-hr LC50 < 0.038 mg/L as bromine	48-hr LC50 < 0.010 mg/L as bromine	2
Marine invertebrate: Mysid shrimp	Acute	96-hr LC50 = 0.092 mg/L as bromine	96-hr LC50 = 0.046 mg/L as bromine	2
Marine fish: inland silverside	Acute	96-hr LC50 = 0.065 mg/L as bromine	96-hr LC50 = 0.0065 mg/L as bromine	10

[1] Adjusted toxicity value = (Toxicity endpoint value / UF)

Table 4 Summary of risk to aquatic organisms

Organism	Exposure	Adjusted Toxicity value mg/L	EEC[1] (mg/L)		RQ[3]		LOC Exceeded[4]	
			High[2]	Typical	High[2]	Typical	High[2]	Typical
USEPA reviewed studies; Freshwater species								
Daphnia magna	Acute	0.535	0.45	0.0012	0.8	0.002	No	No
Rainbow trout	Acute	0.031	0.45	0.0012	**14.5**	0.04	**Yes**	No
Bluegill sunfish	Acute	0.052	0.45	0.0012	**8.7**	0.02	**Yes**	No
Amphibians	Acute	0.031	0.45	0.0012	**14.5**	0.04	**Yes**	No
USEPA reviewed studies; Marine species								
Crustacean	Acute	0.09	0.45	0.0012	**5**	0.01	**Yes**	No
Mollusk	Acute	0.47	0.45	0.0012	0.96	0.003	No	No
Fish	Acute	0.019	0.45	0.0012	**24**	0.06	**Yes**	No
Study summaries available in PMRA database								
Freshwater fish: Golden shiner	Acute	0.029	0.45	0.0012	**16**	0.04	**Yes**	No
Freshwater fish: Rainbow trout	Acute	0.0068	0.45	0.0012	**66**	0.18	**Yes**	No
Freshwater invertebrate: Cloeon sp.	Acute	0.23	0.45	0.0012	**1.9**	0.005	**Yes**	No
Freshwater invertebrate: *Daphnia manga*	Acute	0.01	0.45	0.0012	**24**	0.06	**Yes**	No
Marine invertebrate: Mysid shrimp	Acute	0.046	0.45	0.0012	**9.8**	0.03	**Yes**	No
Marine fish: inland silverside	Acute	0.0065	0.45	0.0012	**69**	0.2	**Yes**	No

[1] Estimated environmental concentration
[2] "High" exposure refers to "reasonable worst case" scenario under the USEPA Tier Ic modeling results
[3] Risk quotient (RQ) = [EEC / Toxicity Value]
[4] Level of Concern (LOC) = 1 for aquatic organisms

Table 5 Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion Value		Active Ingredient Endpoints	
			Hypobromous Acid	Sodium Bromide
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	N/A
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	N/A	N/A
	Water	Half-life ≥ 182 days	Half-life, 125 hours	N/A
	Sediment	Half-life ≥ 365 days	N/A	N/A
	Air	Half-life ≥ 2 days or evidence of long range transport	N/A	N/A
Bioaccumulation[4]	Log $K_{OW} \geq 5$		Value not available	N/A
	BCF ≥ 5000		Value not available	N/A
	BAF ≥ 5000		Value not available	N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{OW}).

Appendix IV Proposed Label Amendments for Products Containing Sodium Bromide

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements below.

1. **Label Amendments for Technical Grade Active Ingredients and End-use Products that are Repackaged Technical Grade Sodium Bromide:**

   For the protection of human health:
   - Add the signal words "WARNING POISON" to the primary display panel.
   - Add "May be fatal if inhaled. DO NOT inhale dusts." to the PRECAUTIONS section.

2. **Label Amendments for Products Containing Sodium Bromide with Industrial Uses:**

   For the protection of human health:

   "Wear protective eyewear, chemical-resistant coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves and footwear when handling the concentrate and contacting treated process fluids."

   "For use with closed loading and transfer systems only."

   For the protection of the environment:

   "Toxic to aquatic organisms."

   "DO NOT discharge effluent containing this product or the biocide produced into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters unless the effluent has been detoxified by suitable means."

3. **Label Amendments for Chlorine Swimming Pool or Spa Electrolysis Device Products:**

   For the protection of human health:

   "Do not use this device with bromide products."

4. Label Amendments for Products Containing Sodium Bromide with Pool and Spa Uses:

For the protection of human health:

"Do not use this product with an electrolysis device (for example, a chlorine generator)."

"Do not use this product with ozonation."

"Do not use this product with ultraviolet (UV) disinfection."

References

A. Information Considered in the Chemistry Assessment

A.1 List of Studies/Information Submitted by the Registrant

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1261469	Cambrian Chemicals Inc. Cambrex NaBr Manufacturing Summary, DACO: 2.11.1
1261470	Cambrian Chemicals Inc. Cambrex NaBr Description of Starting Material, DACO: 2.11.2
1261474	Cambrian Chemicals Inc. Cambrex NaBr Summary of Batch Data, Certificate of Analysis, DACO: 2.13.3
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2490092	Final Report for the Chemical Characterization Analytical of Albemarle Corporations Sanibrom 40 (Lot# 9667-85-1, 9667-85-2, 9667-85-3, 9667-85-4, and 9667-85-5) and Sanibrom 45 (Lot# 9661-86-l, 9667-86-2, 9667-86-3, 9667-86-4, and 9667-86-5) Biocides, DACO: 2.13.3
2490093	Sanibrom 40 Raw Data for Final Report for the Chemical Characterization Analytical of Albemarle Corporations Sanibrom 40 (Lot# 9667-85-1, 9667-85-2, 9667-85-3, 9667-85-4, and 9667-85-5) and Sanibrom 45 (Lot# 9661-86-l, 9667-86-2, 9667-86-3, 9667-86-4, and 9667-86-5) Biocides, DACO: 2.13.3
2514895	Restatement of [Removed CBI] Data for Lots of Albemarle Corporations Sanibrom 40 (LOT# 9667-85-1, 9667-85-2, 9667-85-3, 9667-85-4, and 9667-85-5) and Sanibrom 45 (LOT# 9667-86-r, 9667-86-2, 9667-86-3, 9667-86-4, and 9667-86-5) Biocides, DACO: 2.13.1, 2.13.3
2514896	Manufacturing Date Information of Albemarle Corporations Sanibrom 40 (LOT# 9667-85-1, 9667-85-2, 9667-85-3, 9667-85-4, and 9667-85-5) and Sanibrom 45 (LOT# 9667-86-1, 9667-86-2, 9667-86-3, 9667-86-4, and 9667-86-5) Biocides, DACO: 2.13.3

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B.1 List of Studies/Information Submitted by the Registrant

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B.2 Additional Information Considered

Published Information

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C. Information Considered in the Occupational and Non-Occupational Assessment

C.1 List of Studies/Information Submitted by the Registrant

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C.2 Additional Information Considered

Published Information

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PMRA Document Number	Reference
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PMRA Document Number	Reference
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D. Information Considered in the Environmental Assessment

D.1 List of Studies/Information Submitted by the Registrant

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D.2 Additional Information Considered

Published Information

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