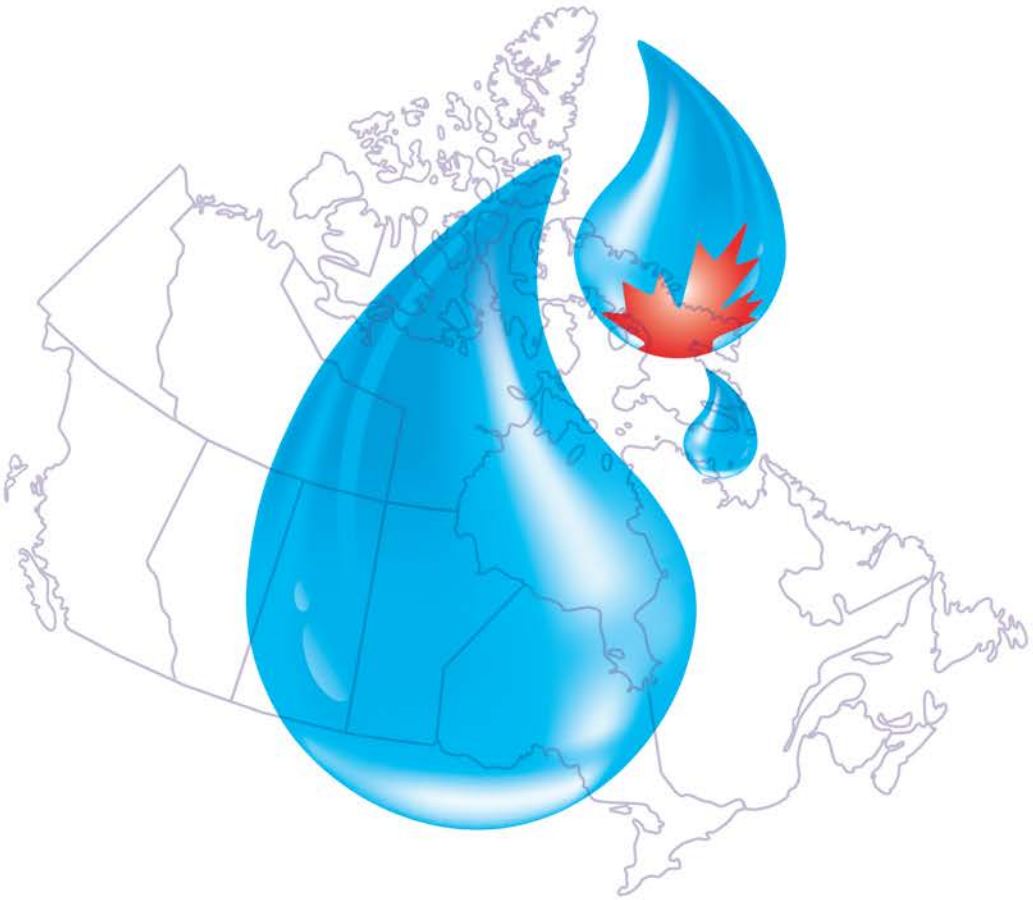
Health Canada Santé Canada

Your health and safety… our priority. *Votre santé et votre sécurité… notre priorité.*

Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Bromate



Canada

October 1998
(edited January 1999)

Bromate

Guideline

The maximum acceptable concentration (MAC) for bromate in drinking water is 0.01 mg/L (10 µg/L).

Identity, Use and Sources in the Environment

The bromate ion (BrO_3^-) exists in a number of salts, the most common of which are potassium bromate and sodium bromate. Potassium bromate is soluble in water (7.5 g/100 mL) at 25°C and is highly stable in water at room temperature. Bromate does not volatilize and adsorbs only slightly to soil or sediment. Because it is a strong oxidant, it reacts with organic matter, which ultimately leads to the formation of bromide ion.

Potassium bromate is used primarily as a maturing agent in flour and as a dough conditioner in bread making. In Japan, it was formerly used in fish paste products.[1] It may be used in the production of cheese and beer. Potassium bromate and sodium bromate are also components of neutralizing solutions in home permanent wave kits.[2]

Although bromate is unlikely to be formed during water chlorination, evidence has been found in U.S. and British studies that water treatment grade sodium hypochlorite solutions may contain bromate as a contaminant. Data collected suggest that bromate concentrations range from <2 to 51 mg/L in the United States.[3] In the United Kingdom, ranges from 50 to 1150 mg/L were noted.[4] Other researchers have found bromate concentrations much greater than 10 µg/L in sodium hypochlorite solutions.[5] Since chlorination activity of the solution decreases with time, it may be necessary to use larger quantities of the sodium hypochlorite solution in order to obtain the required level of disinfection. As a result, bromate levels could be high as a result of bromate's stability during long-term storage (as occurs in smaller municipalities).

Bromate is not a natural component of water but may be formed during the disinfection of drinking water using ozone[6] or a combination of ozone and hydrogen peroxide.[7] The concentration of bromide in raw water is a major factor in the formation of bromate. The bromine in well waters is primarily inorganic. The major natural sources of bromide in groundwater are saltwater intrusion and bromide dissolution from sedimentary rocks.[8] Sewage and industrial effluent as well as road and agricultural runoff may also contribute to elevated bromide levels in surface waters.[8]

Exposure

For most Canadians, exposure to bromate is unlikely to be significant, because relatively few Canadian treatment plants (except in Quebec) use ozone for disinfection. This situation may change as water utilities seek alternatives to chlorination, which may lead to the formation of other toxic disinfection by-products (DBPs).

Bromides must be present in the water for bromate formation to occur. Bromide in water causes a catalytic disintegration of ozone and forms hypobromite (OBr^-) as an intermediate product. Hypobromite is predominantly present at higher pH values (pH > 8); at lower pH values, increasingly more hypobromous acid (HOBr) is formed. Hypobromite reacts further with an overdose of ozone to form bromate. Hypobromous acid does not react further with ozone; therefore, at low pH, no bromate is formed. In the presence of organic matter, HOBr does lead to the formation of brominated organic compounds, such as bromoform, mono- and dibromoacetic acid, dibromoacetonitrile, bromopicrin and especially cyanogen bromide.[6,9]

No monitoring data on bromides in Canadian raw water or drinking water were found. Krasner *et al.*[10] measured bromide concentrations in the incoming water (after final disinfection but prior to distribution) of 35 drinking water companies in the United States. Quarterly median values ranged between 0.07 and 0.1 mg/L (overall range from <0.01 to 3.00 mg/L). In general, a good correlation existed between bromide concentration and chloride concentration, with the concentration of bromide approximately 0.0031 times the concentration of chloride.[10] In another study, bromide levels ranged from 0.33 to 0.48 mg/L in raw water from northern California where there was seawater infiltration and from 0.03 to 0.07 mg/L in Colorado River water.[11]

There is little information available on concentrations of bromate in drinking water following chlorination, but bromate does not appear to be formed by this process, which favours the formation of brominated organics. Ozonation of water containing bromide concentrations of ≥0.18–0.37 mg/L resulted in the formation of bromate at concentrations of ≥5 µg/L (the detection limit) in pilot plant research in the United States.[9,11] Bromate was measured at concentrations of 8–180 µg/L, depending on temperature, pH, ozone and peroxone dose, ammonia-nitrogen concentration and bromide concentrations in raw water (0.3–1.4 mg/L).

Results from a small survey, in the summer of 1996, of 12 Quebec drinking water systems that use ozone indicated that bromate levels increased significantly in distributed water compared with raw water at seven of 12 sites. Bromate levels for distributed water ranged from 0.55 to 4.42 µg/L, with an average value of 1.71 µg/L. In many instances, bromate levels reached their maximum at the treatment plant and decreased in the distribution system.[12] In a follow-up survey in the summer of 1997 at these same sites, significantly increased bromate levels in distributed water compared with raw water were again seen. Bromate levels in distributed water ranged from 0.73 to 8.00 µg/L, with an average value of 3.17 µg/L. With the exception of two sites, bromate levels were found to be highest in the distribution system.[12]

Another limited survey of the 12 municipal water supplies using ozonation in Quebec was conducted in the winter of 1998. This study found that bromate concentrations generally increased from raw to treated to distributed water, although concentrations in distributed water were occasionally the same as or lower than those in treated water. Concentrations of bromate ranged from <0.20 to 1.79 µg/L in raw water, from 0.43 to 5.98 µg/L in treated water and from 0.42 to 6.80 µg/L in distributed water.[13] Spatial and temporal variations have been found to affect levels of chlorinated disinfection by-products (CDBPs) and may account for the differences in results of these three surveys.[14]

A limited survey of bromate concentrations in ozonated treated waters in the United Kingdom detected concentrations of bromate of 10–20 µg/L at two of four sites sampled, whereas bromate concentrations ranging from 3 to 28 µg/L were found in final waters from treatment works using commercial sodium hypochlorite as a disinfectant.[15]

Bottled water was also tested in two limited surveys carried out in 1995 and 1996. In 1995, 27 types of bottled water were tested, with bromate concentrations ranging from below detection (0.3 µg/L) to 19.7 µg/L. The 1996 testing of eight bottled water samples that used ozone as a disinfectant showed bromate concentrations ranging from 2.0 to 33.0 µg/L.[16]

In 1996, a bottled water survey of 18 different brands of bottled spring water, all bottled in Canada, was carried out.[12] Eleven of these samples were ozonated, and the results showed that most samples had bromate levels that were much higher than in non-ozonated samples. The average bromate concentration in the non-ozonated bottled waters was 3.72 µg/L, with a range of <0.20–12.90 µg/L, whereas the average concentration for the ozonated bottled waters was 18.14 µg/L, with a range of 4.28–37.30 µg/L. Although this procedure was used to determine bromate in bottled water, this type of water is regulated under the *Food and Drugs Act* and thus is not subject to Canadian drinking water guidelines.

Another bottled water survey was carried out in 1998 by the Food Directorate of Health Canada. In this survey, bromate levels of 206 bottled waters were tested, with bromate concentrations ranging from below detection (0.5 ppb) to 144 ppb. An overall average of 6.88 ppb was calculated. There was no apparent correlation between bromate levels and bromide or use of ozone.[17]

A small amount of potassium bromate is added to flour during the preparation of bread; however, it breaks down to bromide during baking.[2] The recommended maximal potassium bromate doses are 30 and 50 mg/kg flour for Japan[1] and the United States, respectively.[18]

Analytical Methods and Treatment Technology

Bromate has seldom been monitored in drinking water until recently. In most cases, only bromide concentrations are measured. The National Testing Laboratories network performs bromate analysis via EPA Method 300.0,[19] the only EPA-approved method for bromate analysis in drinking water to date. The current detection level of 5 µg/L is difficult to attain; there are not many accredited laboratories in the United States, and very few are capable of reaching this low a level. Samples with high chloride levels must often be diluted, thus increasing the detection level to 10 µg/L for this method.

Analytical methods with increasingly lower limits of detection are being developed for the measurement of bromate in drinking water. Ion chromatography is a potentially useful detection method; however, it is subject to significant interferences from chlorides, sulphates and bicarbonate/carbon dioxide. The practical quantitation level (PQL) achievable by most certified laboratories is 5 µg/L; however, it can be as high as 20 µg/L, as any significant level of interference requires sample dilution, thus doubling or tripling the PQL. As well, the method has not been properly validated through round-robin testing. No performance evaluation sample testing has been done; thus, the method's scientific validity is considered unreliable at this time. Although it shows promise, this

method is not widely used, is complex and requires very experienced chromatographers. In addition, it is not sufficiently available to all parties concerned with maintaining regulatory compliance.

Ion chromatography can isolate a large number of anions using specific ion exchange columns. A number of inorganic DBPs, such as chlorate, chlorite and bromate, can be analysed within one sample cycle of 25 minutes by this method.[20,21] The detection limit depends on the presence of major components, especially the concentration of chloride present. Pfaff and Brockhoff[20] tested the recovery of bromate from Cincinnati tap water and deionized water spiked with bromate at different concentrations. The method detection limit for bromate was 0.01 mg/L in tap water and 0.02 mg/L in deionized water. This detection limit was subsequently lowered to 0.005 mg/L.[22]

Selective anion concentration has been demonstrated to be quite an effective technique for analysing bromate at lower levels. This new application of ion chromatography performs multi-column separation with automated peak fractionation of high-volume injections.[23] The method detection limit was reported as 0.18 µg/L and 0.25 µg/L for deionized water and river water, respectively. However, this technique is complex and may not be amenable to utilities with inexperienced ion chromatographers.[24]

Another application of selective ion chromatography performed by multi-column separation of pretreated samples also appears to be a promising technique.[25] Surface water samples were analysed with and without pre-treatment to determine the effect on the chromatographic resolution of the bromate peak. Pretreatment of the sample prior to ion chromatography was shown to minimize interference from chloride and sulphate ions as well as reduce the carbonate level. The method detection limit was reported as 0.2 µg/L for surface water. This method is preferred to the Sorrell and Hautman[24] method owing to its success in minimizing or eliminating interference by other DBPs; however, it, too, is a complex technique requiring experienced chromatographers.

A simple concentration technique for the analysis of bromate at low levels in drinking water has been reported by Sorrell and Hautman.[24] A rotary evaporator is used to remove the excess water from the sample (sample volume reduced from 750–1000 mL to 10 mL); for a 1000-mL sample, the concentration of bromate has been increased by a factor of 100. The method detection limit is 0.1 µg/L. The average recovery of bromate was 96 ± 4% and 94 ± 2% from deionized water samples fortified with bromate at 2 µg/L and 5 µg/L, respectively, and 94 ± 17% from raw surface water fortified with bromate at 4 µg/L. This technique, however, has not been incorporated in the approved ion chromatography technique currently used by many laboratories. The method requires proper validation through round-robin testing and performance evaluation sample testing.

There are no practical methods currently available to remove bromate from water. Advanced treatment processes that have been suggested as warranting further evaluation include ion exchange and membrane filtration.[21] Bromate in ozonated drinking water supplies is best controlled by limiting its formation, which is influenced by the bromide concentration (≥0.18 mg/L),[22] the source and concentration of organic precursors, pH, temperature, alkalinity and ozone dose.[26] For example, reductions in bromate formation can be achieved by lowering the pH to less than 8, adding ammonia or controlling the ozone reaction time and the ozone/dissolved organic carbon ratio.[21,27,28] These and other measures have both advantages and disadvantages; a low pH, while reducing bromate formation, increases the formation of bromoform and other brominated organic byproducts, in addition to being undesirable from the point of view of corrosion control; addition of ammonia results in the conversion of HOBr to monobromamine, which in turn may be oxidized to nitrate.[28] Because of the large number of factors that influence bromate production, it will be necessary to optimize treatment by balancing the advantages and disadvantages of various measures on an individual basis for each water supply.

Health Effects

Toxicokinetics

Fujii *et al.*[29] studied the absorption, degradation and excretion of bromate given orally as potassium bromate. In a preliminary study, male Wistar rats were given an aqueous solution of potassium bromate (dose 50 mg/mL as bromate) by gavage. Urine and faeces were collected for 24 hours, and bromate and bromide were determined. The animals were then sacrificed, and bromate and bromide were determined in the plasma, red blood cells, spleen, kidney, pancreas, stomach and small intestine. No bromate was detected in any tissues, although substantial amounts were found in urine (detection limits 2.5 µg/mL in urine and plasma and 5.0 µg/g in tissues). Bromide was found in significant amounts, up to six times control values ($p < 0.01$), in treated rats in the urine, red blood cells, plasma, stomach, kidney, small intestine and pancreas (in descending order).

A single dose of aqueous potassium bromate (100 mg/kg) was administered orally to groups of four Wistar rats. Animals were sacrificed after 15 minutes, 30 minutes, one hour, two hours, four hours or eight hours, and bromate was measured in stomach, small intestine, plasma and urine in the bladder. Bromate disappeared gradually from the stomach and reached a peak in the small intestine after 30 minutes, then

decreased rapidly, reaching an undetectable level within four hours. The plasma concentration was at a maximum after 15 minutes (approx. 4 µg/mL), decreasing rapidly until it was no longer detectable after two hours. Bromate was at a peak after one hour in urine and then decreased rapidly; no urinary excretion was detected after four hours.[29]

Groups of four male Wistar rats were administered an aqueous solution of potassium bromate by oral gavage at doses of 0, 0.625, 1.25, 2.5, 5, 10, 20, 40, 60, 80 or 100 mg/kg bw, and bromate and bromide were determined in the urine in the 24 hours following dosing. No bromate was detected in urine of rats who received 2.5 mg/kg bw or less. At higher dose levels, bromate excretion was observed in increasing amounts in proportion to the dose. The excretion of bromide parallelled that of controls up to the 5 mg/kg bw dose. The excretion of bromide also increased in rats that received potassium bromate at 10 mg/kg bw or more.[29]

Bromate is therefore rapidly absorbed from the gastrointestinal tract, partially converted to bromide in the tissues and excreted rapidly. As unchanged bromate could be determined in urine at doses of 5 mg/kg bw and above, it must come into contact with renal tissues at this or higher dose levels.[1,29]

To understand the transformation of bromate into bromide, various isolated tissues and organs (liver, kidney, spleen, stomach, small intestine, plasma, red blood cells, saliva and stomach tissues) were incubated with bromate (10 ppm). All tissues except saliva and plasma degraded bromate to bromide with >84% efficiency. SH compounds, including cysteine and glutathione (GSH), were shown to be responsible at least in part for the breakdown of potassium bromate and the simultaneous formation of bromide ion. GSH had the highest degradative action and plays a major role in the reduction of bromate.[30]

Acute and Short-term Exposure

Bromate is a highly toxic substance that has caused irreversible renal failure,[31] deafness[32–34] and death[33] subsequent to accidental poisoning. A case report indicated that a single oral dose of sodium bromate in adults (14 g/person) can cause vomiting, epigastralgia, watery diarrhoea and anuria within 30 minutes and deafness within 12 hours.[35] Bromate intoxication commonly occurs in hairdressers, as many permanent wave neutralizers still contain a 2% potassium bromate or a 10% sodium bromate solution. Serious poisoning in children has been reported subsequent to ingestion of 2–4 ounces of a 2% solution of potassium bromate (equal to 1.2–2.4 g of potassium bromate).[33] Oral lethal doses for adults are reported to be between 5 and 50 mg/kg bw.[36] Potassium bromate is more toxic than sodium bromate.[32]

Mack[37] reviewed the reported cases of bromate poisoning and found that acute toxic effects usually manifest within one hour of ingestion with gastrointestinal symptoms, including nausea, vomiting, abdominal pain and diarrhoea. This is followed by central nervous system depression, varying from lethargy to coma. Both these conditions are reversible.

Potassium bromate administered orally and intraperitoneally to mice gave LD_{50}s (as bromate) of 289–471 and 177 mg/kg bw, respectively.[38] In another study, rats, mice and hamsters were administered potassium bromate by gavage, resulting in LD_{50}s of 400–495 mg/kg bw, 280–355 mg/kg bw and 388–460 mg/kg bw, respectively.[1]

In a study in which potassium bromate doses of 250–4000 mg/L were administered in drinking water to male and female $B6C3F_1$ mice (10 per sex per dose) for a period of 10 weeks, no lethal or histopathological effects occurred at doses below 1000 mg/L that might be associated with the uptake of potassium bromate.[1] In a 13-week study, potassium bromate was administered to groups of F344 rats (10 per sex per group) in water at concentrations of 0, 150, 300, 600 or 1250 mg/L. Doses of 2500, 5000 and 10 000 mg/L were also attempted; however, they were unpalatable. All rats exposed to 1250 mg/L died within seven weeks, and the remaining animals survived for 13 weeks. Significant inhibition of body weight gain was seen in males dosed at 600 and 1250 mg/L. A significant increase in levels of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen, serum sodium and cholinesterase was observed in both males and females given 600 mg/L. Droplets were observed in the cytoplasm of the proximal tubular epithelium in treated males (no doses were specified). Extensive regenerative changes were reported in the renal tubules. In another study in which groups of five male F344 rats were orally given potassium bromate at 600 mg/L for 12 weeks, the droplets in the renal tubules were found as early as four weeks after the start and decreased to control levels four weeks after treatment ended. From the morphological characteristics, they were identified as eosinophilic bodies rather than hyaline droplets. Full details of recovery were not provided.[1]

Carcinogenicity

Groups of 53 male and 53 female F344 rats, 4–6 weeks old, were given drinking water containing potassium bromate at concentrations of 0, 250 or 500 mg/L (calculated by the authors as average potassium bromate doses of 0, 12.5 and 27.7 mg/kg bw per day for males and 0, 12.5 and 25.5 mg/kg bw per day for females) for a period of 110 weeks. Because the highest dose caused a significant reduction in body weight gain in males, the

dose was lowered to 400 mg/L at week 60 for male rats. Mean survival time in male rats given 500 mg/L was shorter than that in controls. In females, the survival rates of treated and control rats were comparable. The incidence of renal cell tumours in the control group, low-dose group and high-dose group was determined to be 3/53 (6%), 32/53 (60%) and 46/52 (88%) for males and 0/47 (0%), 28/50 (56%) and 39/49 (80%) for females. Effects were statistically significant ($p < 0.001$) for all exposed groups. The renal cell tumours were observed in weeks 111, 77 and 14 in control, low-dose and high-dose males, respectively, and in weeks 89 and 85 in low-dose and high-dose females, respectively. Most renal cell tumours were microscopic in size, although some were visible as round, yellowish-white or greyish projections from the renal cortex. Histologically, these tumours were classified as adenocarcinomas and adenomas. The incidence of peritoneal mesotheliomas in males was 6/53 (11%) for the control group, 17/52 (33%) for the low-dose group ($p < 0.05$) and 28/46 (59%) for the high-dose group ($p < 0.001$). No peritoneal mesotheliomas were observed in female rats. Potassium bromate was found to be carcinogenic in both male and female rats.[39]

In order to study carcinogenic effects at low concentrations, six-week-old male F344 rats (20–24 per group) were given potassium bromate in drinking water for a period of 104 weeks at concentrations of 0, 15, 30, 60, 125, 250 or 500 mg/L (average potassium bromate doses were 0, 0.9, 1.7, 3.3, 7.3, 16.0 and 43.4 mg/kg bw per day). Significant decreases in survival period (82.8 ± 11.7 weeks vs. 103.1 ± 3.3 weeks) and body weight gain (330.7 g vs. 398.8 g) were observed in the group administered 500 mg potassium bromate/L when compared with the control group. Statistically significant increases were observed in the incidence of renal cell tumours in rats treated with a dose of 125 mg/L or more (≥7.3 mg/kg bw per day). The incidence of renal cell tumours increased significantly in a dose-related manner — 5/24 (21%; $p < 0.05$), 5/20 (25%; $p < 0.05$) and 9/20 (45%; $p < 0.001$) — in groups given 125, 250 and 500 mg potassium bromate/L, respectively. A significant increase in occurrence of dysplastic foci in kidneys was observed in animals receiving potassium bromate doses of 30 mg/L or more (≥1.7 mg/kg bw per day). Follicular adenomas and adenocarcinomas of the thyroid were found in rats treated at 60, 250 and 500 mg/L ($p < 0.05$). Although peritoneal mesotheliomas were found in rats receiving doses of 30 mg/L or more, these were significant ($p < 0.001$) only in animals receiving the highest dose.[40,41]

Groups of female $B6C3F_1$ mice (approximately 50 per group) were administered potassium bromate at concentrations of 0, 500 or 1000 mg/L in drinking water for 78 weeks (average dose of 0, 56.5 and 119.8 mg/kg bw per day) followed by tap water for 26 weeks and subsequently killed. No significant increase in the number of tumours was observed macroscopically or microscopically at any site. Body weight increase was markedly reduced in the high-dose group.[39]

In a review article by Kurokawa *et al.*,[1] the authors discussed a 1987 study by Kurokawa *et al.*[42] in which groups of 27 male mice of $B6C3F_1$, BDF_1 and CDF_1 strains were given potassium bromate at 750 mg/L in drinking water (intake was in the range of 60–90 mg/kg bw per day for all three strains) for 88 weeks and compared with groups of 15 controls given drinking water only. No significant differences were found in growth rate and survival time between experimental and control animals. The incidence of renal cell tumours, which were histologically identical to those seen in rats, was 3/26, 1/27 and 1/27 in $B6C3F_1$, BDF_1 and CDF_1 mice, respectively, compared with no incidence in controls (it is noted that the number of animals in the control group was low, and no statistical analysis was presented). Dysplastic foci were found in two of 26 $B6C3F_1$ mice and four of 27 BDF_1 mice, but the incidence was not statistically significant, with dysplastic foci occurring in one of 15 mice in $B6C3F_1$ and BDF_1 control groups.[1] The authors concluded that potassium bromate induced renal cell tumours in mice. This conclusion was supported by the fact that spontaneous induction of renal cell tumours is historically very low in mice (0.1% or 3/2543 in $B6C3F_1$ males and 0.08% or 2/2522 in $B6C3F_1$ females) and that the renal tumours observed in mice were identical to those observed in rats. As well, significant increases in the occurrence of adenomas of the small intestine (14/21, $p < 0.01$) in CDF_1 mice and adenomas of the liver (7/26, $p < 0.05$) in $B6C3F_1$ mice were also observed.

Kurokawa *et al.*[1] discussed a study by Takamura *et al.*[43] that examined species differences in the carcinogenicity of potassium bromate. Groups of 20 male Syrian golden hamsters were administered potassium bromate in drinking water at 0, 125, 250, 500 or 2000 mg/L for a period of 89 weeks.[43] No difference was noted in survival times. The mean final body weights of animals treated with 2000 mg potassium bromate/L were significantly reduced, and the mean absolute and relative kidney weights were significantly higher in animals that received 2000 or 250 mg/L than in controls. Renal adenomas were developed in one, two and four hamsters in groups given 250, 500 and 2000 mg/L, respectively, and dysplastic foci were also seen. No renal cell tumours were found in control animals (no statistical analyses were presented). The structural and cellular morphological characteristics of renal cell tumours and dysplastic foci were quite similar to those observed in rats. The spontaneous development of renal cell tumours in hamsters was noted to be

extremely low in historical controls from other laboratories, giving some limited support to the hypothesis that the observed lesions, although of low incidence, were induced by potassium bromate.[1]

In order to better understand the mechanisms underlying the carcinogenicity and organ specificity of potassium bromate, the promoting effects of this compound were tested using N-ethyl-N-hydroxyethylnitrosamine (EHEN), a potent initiator. In this study, groups of seven-week-old male Fischer 344 rats were given drinking water as 1) distilled water alone for 26 weeks (group 1); 2) distilled water containing EHEN at 500 or 1000 mg/L for two weeks followed by distilled water for 24 weeks (groups 2 and 3); 3) distilled water containing EHEN at 500 or 1000 mg/L for two weeks followed by distilled water containing potassium bromate (99.5% pure) at 500 mg/L for 24 weeks (groups 4 and 5); or 4) distilled water for two weeks followed by distilled water contain- ing potassium bromate at 500 mg/L for 24 weeks (group 6). All animals were killed at the end of 26 weeks. Significant increases in the number of renal tumours ($p < 0.05$) and dysplastic foci ($p < 0.01$) were found in animals administered potassium bromate following initiation with EHEN (groups 4 and 5), compared with the animals administered EHEN only (groups 2 and 3), potassium bromate only (group 6) or controls (group 1) (there were no tumours in the latter two). This demonstrates some promoting activity of potassium bromate on kidney lesion development. The incidences of renal cell tumours were as follows: group 1 (controls), 0/19; group 2, 9/22 (41%); group 3, 4/23 (17%); group 4, 9/19 (47%); group 5, 10/20 (50%); and group 6, 0/20. No tumours other than renal tumours were found in these animals.[44] Potassium bromate showed no initiating action in this test. A follow-up study to determine whether a threshold level of potassium bromate treatment exists for the enhancement of renal tumorigenesis was undertaken, still using EHEN as the initiator.[45] Groups of six-week-old F344 rats (15 per sex) were treated with 1) EHEN for the first two weeks and then potassium bromate (at concentrations of 15, 30, 60, 125, 250 or 500 mg/L) for the subsequent 24 weeks; 2) EHEN for the first two weeks and then distilled water for the subsequent 24 weeks; or 3) distilled water for the first two weeks and then potassium bromate (500 mg/L) for the subsequent 24 weeks. Results confirmed those found previously; no dysplastic foci or tumours were observed with controls (distilled water only) or potassium bromate only. A non-significant increase was seen in the EHEN group and in the EHEN plus 15 mg potassium bromate/L group. Significant increases were observed in all other groups ($p < 0.05$ at 30 mg potassium bromate/L; $p < 0.01$ at 60 mg/L or more). This appeared to indicate a threshold level between 15 and 30 mg/L for promotion of renal tumorigenesis under the conditions of this experiment.

In a more recent study,[46] levels of 8-hydroxydeoxyguanosine (8-OH-dG) — a substance formed following the damage of DNA by oxygen radical-forming compounds — and cumulative replicating fractions (CRFs) were measured in the kidneys and livers of F344 rats receiving a single gavage dose of 100, 200 or 400 mg potassium bromate/kg bw. In addition, female rats were given 0.05% EHEN initiator followed by 500 mg potassium bromate/L for 30 weeks. Levels of 8-OH-dG in the kidneys were significantly increased at 200 and 400 mg/kg bw and correlated with increased in CRFs of proximal tubules. The study suggests that oxidative stress generated by potassium bromate exposure may be associated with induction of cell proliferation and associated promoting activity.

In a 104-week study in male F344 rats to test the initiating potential of potassium bromate, potassium bromate given by gavage as a single dose of 300 mg/kg bw (the maximum tolerated dose, which induced regenerative changes in kidney) was ineffective as a renal tumour initiator when followed from weeks 2 to 104 by a diet containing 4000 mg barbital sodium/L, a recognized rodent renal tumour promoter. Dysplastic foci of renal tubular cells (putative pre-neoplastic lesions) were observed in 16/27 (59%) animals given potassium bromate plus barbital sodium and in 16/23 (69%) animals given barbital sodium alone, compared with 3/27 (11%) given potassium bromate only and 1/23 (4%) in controls (significant differences between first two groups and last two groups at $p < 0.001$). No statistically significant increase in tubular cell adenomas or carcinomas was observed in any group, although a trend towards increased adenomas was evident in the two barbital sodium groups, with and without the initiating dose of potassium bromate. Nephropathy was significantly increased after 30 and 52 weeks in the same two groups. It was noted that the 300 mg/kg bw dose given here was lower than the 400 mg/kg bw dose given in a study by Kasai *et al.*[47] in which potassium bromate initiation by production of oxygen radicals was observed, thus suggesting that there may be a threshold dose at which oxygen radicals are produced, leading to initiation of carcinogenesis.[48]

In a recent study,[49] the carcinogenicity and chronic toxicity of potassium bromate were studied in male $B6C3F_1$ mice and F344/N rats. Mice were treated with 0, 80, 400 or 800 mg potassium bromate/L (0, 9.1, 42.4 and 77.8 mg/kg bw per day) in drinking water for up to 100 weeks. Rats were provided with 0, 20, 100, 200 or 400 mg potassium bromate/L (0, 1.5, 7.9, 16.9 and 37.5 mg/kg bw per day). No significant differences were seen in survival times, body weight gain or feed consumption. However, a decrease in water consumption with increasing potassium bromate concentration was noted when compared with controls. The study confirmed that potassium bromate results in an increased

incidence of renal tumours, thyroid follicular tumours and mesotheliomas in a dose-dependent fashion in male rats. Although rat renal cell tumours were seen at 100 mg/L (6/47), 200 mg/L (3/39) and 400 mg/L (12/32), they were statistically significant only at the highest dose. An increased incidence of renal cell tumours was also noted in mice and found to be treatment related. These kidney tumours were seen at all dose levels in male mice — 800 mg/L (1/44), 80 mg/L (5/38) and 40 mg/L (3/41) — but they were statistically significant only at the 80 mg/L dose ($p < 0.05$).

Although renal nephrosis was not associated with treatment in rats and mice, a treatment-related increase in the presence of eosinophilic droplets within the cytoplasm of proximal tubule epithelium was noted in rats in the same study.[49] The presence of these eosinophilic droplets was shown to be a result of oxidative damage. The transitional cells within the renal pelvis were markedly hyperplastic in rats at potassium bromate doses greater than 20 mg/L, but no urothelial hyperplasia was noted in the mouse renal pelvis. No hyperplastic response was seen in the urinary bladder, and no treatment-related hyperplasia of the urinary bladder was associated with urothelial hyperplasia of the renal pelvis. Mesothelioma originating from the tunica vaginalis testis was induced in the rat in a dose-dependent manner at all dose levels. The mesotheliomas spread to other sites by direct implantation or seeding from the primary tumour and were frequently found scattered throughout the peritoneal cavity on the serosal surfaces of many organs. The frequency of multiple sites for this tumour did not appear to be dose dependent. Thyroid follicular tumours were increased in rats in a treatment- and dose-related manner. An increased incidence of thyroid follicular proliferative lesions was noted at all doses; however, tumours were statistically increased only at doses of 200 and 400 mg/L. This study shows that potassium bromate is carcinogenic in the rat kidney, thyroid and mesothelium and in the kidney of the male mouse. Potassium bromate was carcinogenic in rodents in drinking water at concentrations as low as 20 mg/L (1.5 mg/kg bw per day).[49]

Special Studies

Lipid peroxidation (LPO) in the kidney of male F344 rats was significantly increased ($p < 0.01$) after intravenous administration of potassium bromate at doses of 77, 96, 120 and 150 mg/kg bw. The increases were dose and time dependent. When an exogenous source of cysteine was provided by pre-treating with 400 mg/kg bw, LPO remained at the control level. Administration of diethylmaleate, a GSH depletor, prior to intravenous treatment with a potassium bromate dose as low as 20 mg/kg bw significantly increased LPO, and eosinophilic droplets were noted in the tubular epithelium of the kidney. No equivalent increase in LPO was seen in kidneys of two strains of mice and hamsters treated intravenously with potassium bromate at 120 mg/kg bw, although LPO was slightly increased in a third strain of mouse. A possible relationship was suggested between LPO in the kidney and the differences in species susceptibility to tumour formation noted in a previous study.[50]

A significant increase in 8-OH-dG was noted in kidney DNA of male F344 rats after a single intragastric dose of 400 mg potassium bromate/kg bw, and a positive significant correlation between formation of this substance within DNA and induction of renal cell tumours was also found. No increase was apparent in the liver.[47]

After a single intravenous potassium bromate dose of 70 mg/kg bw was given to male F344 rats, LPO was significantly increased after six hours and continued to increase until a plateau was reached at 48–96 hours; 8-OH-dG rose sharply at 24 hours, then decreased somewhat, as did the relative kidney weight. This suggested that the LPO rise in the cell is closely related to, and precedes, the 8-OH-dG rise, which is indicative of DNA damage. A dose–response study at potassium bromate concentrations of 0, 20, 40 and 80 mg/kg bw indicated no effects on LPO or 8-OH-dG at 20 mg/kg bw, slight but significant effects at 40 mg/kg bw and marked effects at 80 mg/kg bw.[51] A study by Chipman *et al.*[52] confirms these findings; when combined with studies by Sai *et al.*,[51,53] it suggests that DNA oxidation is concomitant with LPO and toxicity at high doses and that there is a secondary mechanism for DNA oxidation in renal carcinogenesis.

Induction of LPO and 8-OH-dG and increases in relative liver weight by an intraperitoneal dose of potassium bromate at 80 mg/kg bw were significantly inhibited by the antioxidants GSH or cysteine given intraperitoneally at 2 × 800 and 2 × 400 mg/kg bw, respectively, pre- and post-injection. The antioxidant vitamin C also acted as an inhibitor at a daily intragastric dose of 200 mg/kg bw per day for five days prior to bromate dosing. Superoxide dismutase (18 000 U/kg) and vitamin E (100 mg/kg bw for five days), also antioxidants, were ineffective.[54] Micronucleus induction in peripheral blood reticulocytes by a potassium bromate dose of 60 mg/kg bw was similarly inhibited in male rats, in the same protocol as the preceding study.[55]

Genotoxicity

Weakly positive results were obtained for the mutagenicity of potassium bromate in the Ames test using *Salmonella typhimurium* strain TA100 at a concentration of 3 mg/plate following metabolic activation.[56] However, negative results were found with other strains: TA98, TA1535, TA1537 and TA1538.[1,57] Negative results were also found in tests with *Escherichia coli*[56,58] and in *Bacillus subtilis* both with and without metabolic

activation.[57] In a repeat of earlier Ames tests, potassium bromate again showed weak positive activity with TA100 with and without activation and with TA102 and TA104 with activation only. The latter two strains are known to be sensitive to chemicals that generate oxygen radicals.[1] Sodium bromate and silver bromate were also found to be negative in Ames tests with TA97, TA98, TA100 and TA102 strains in concentrations of 5 mg/plate and 25 µg/plate, respectively.[1]

Potassium bromate induced chromosomal aberrations in cultured Chinese hamster fibroblast cells at concentrations of 0.0625–0.25 mg/mL in both the presence and absence of metabolic activation. The incidence of structural aberrations in cells was 100% after 24 hours at the maximum dose.[58] Chromatid breaks were also induced in CH DON-6 cells at a potassium bromate concentration of 0.084 mg/mL.[1]

Positive results were also obtained in an *in vivo* study of the acute cytogenetic effects of potassium bromate on bone marrow cells in male Long-Evans rats following oral or intraperitoneal administration of 334.0 and 250.5 mg/kg bw, respectively (it is noted that these doses were close to the LD_{50} values). In both cases, the number of aberrant cells increased progressively, reaching a maximum of 10.5% at 12 hours (intraperitoneal) and 10.8% at 18 hours (oral) after administration. Significant differences were observed at three, six and 12 hours following intraperitoneal administration and at 12 and 18 hours following oral administration.[59] Potassium bromate gave positive dose-dependent responses in mouse micronucleus tests with two strains of male mice (Ms/Ae and CD-1) using femoral bone marrow polychromatic erythrocytes following intraperitoneal or oral gavage administration of doses between 18.8 and 150 mg/kg bw (intraperitoneal) or between 37.5 and 300 mg/kg bw (oral).[38] Similar results were reported for male ddY mice at doses above 100 mg/kg bw for the oral route and above 25 mg/kg bw for the intraperitoneal route.[60] These results were also found using peripheral blood reticulocytes with intraperitoneal dosing at 18.8–212 mg/kg bw in male CD-1 mice.[61]

Reproductive Effects

No reproductive studies were found that tested bromate directly, via water or gavage. A study has been conducted[62] on groups of rats given bread made from flour treated with potassium bromate; however, as bromate is changed to bromide during the baking process,[2] this study would not be relevant here.

Classification and Assessment

No information is available on the induction of tumours by bromate in humans. Potassium bromate induced a dose-related increase in benign and malignant renal cell tumours in both sexes of F344 rats when administered in drinking water. Limited evidence of the induction of benign renal cell tumours was found in hamsters and in three strains of mice. Benign and malignant thyroid tumours and peritoneal mesotheliomas were also seen in male rats, and a significant increase in adenomas of the small intestine and liver was reported in mice. There is some evidence that bromate is detoxi- fied by metabolism with GSH to bromide, although intermediate reactions with cell components also take place, releasing lipid peroxidases, which cause genotoxic effects. Bromate gave largely negative results in bacterial mutagenicity tests, whereas positive results were obtained for clastogenic effects and DNA damage in all *in vivo* tests to date. Bromate has therefore been classified as probably carcinogenic to humans (sufficient evidence in animals; no data in humans).

Cancer risks have been estimated on the basis of renal cell tumours from two bioassays: one conducted in male and female F344 rats,[39] and a second conducted at a lower range of doses in the same laboratory on males only.[40,41] Given that these studies show that bromate is a non-threshold carcinogen, the model-free extrapolation method[63] can be used. Using this method, one can calculate that the unit lifetime excess cancer risk associated with the ingestion of bromate at a concentration of 1 µg/L in drinking water ranges from 1.55×10^{-6} to 2.19×10^{-6} based on renal cell tumours in rats. The estimated range of bromate concentrations in drinking water corresponding to lifetime excess cancer risks of $l0^{-4}$, 10^{-5} and 10^{-6} for renal cell tumours based on three data sets from studies by Kurokawa and colleagues is as follows:

Lifetime risk	Concentration in drinking water (µg/L)
10^{-4}	46 – 65
10^{-5}	4.6 – 6.5
10^{-6}	0.46 – 0.65

There is some discussion as to whether bromate carcinogenesis is a result of a threshold effect. A study conducted in male F344 rats on the promoting effects of potassium bromate with and without initiation by EHEN[44,45] appears to indicate a threshold level for promotion of renal tumorigenesis. This suggests that data obtained from studies of rats exposed at high doses may not be relevant to humans exposed at low doses; thus, the mathematical models for risk assessment may not be appropriate in this case. There is also concern about the relevance of the rat toxicity data to humans given that bromate may be genotoxic via an indirect mechanism (LPO) with a threshold, thus again suggesting that data obtained from studies of rats exposed at high doses are not relevant to humans exposed at low doses. However, bromate must be considered a non-threshold carcinogen until additional research provides sufficient evidence to prove otherwise.

It should be noted that peritoneal mesotheliomas that were observed[39,40] may originate in rat-specific tissue (tunica vaginalis covering testis in male rats) and then spread to other tissues. As a result, this tumour would not be relevant to humans and as such was not used in determining lifetime excess cancer risk.

Although there was a third study[49] from which the lifetime cancer risk could have been calculated, it was not available at the time the calculation was made. Given that the effect level for the study from which the risk was calculated was 1.7 mg/kg bw per day and that of the DeAngelo *et al.*[49] study was 1.5 mg/kg bw per day, the risk is expected to be of the same order of magnitude.

Rationale

Because bromate has been classified as being probably carcinogenic to humans, the maximum acceptable concentration (MAC) is derived based on estimated lifetime cancer risk and available practicable treatment technology. As the MAC must also be measurable by available analytical methods, the PQL is also taken into consideration in its derivation.

A maximum acceptable concentration (MAC) of 10 µg/L for bromate was established on the basis of the following considerations:

(1) The MAC must be measurable and achievable at reasonable cost. No treatment technology is available to remove bromate from drinking water; however, careful application of ozone treatment technology can minimize its formation in waters containing high bromide concentrations without compromising the level of disinfection.

(2) The PQL (based on the ability of laboratories to measure bromate within reasonable limits of precision and accuracy) for bromate in drinking water is 2 µg/L and well below the MAC. It is based on the method reported by Lo and Subramanian,[25] which has been successful in eliminating or minimizing interference by other DBPs. It is the recommended method for analysis of bromate in drinking water; however, it is a complex technique requiring experienced chromatographers. Currently, however, EPA Method 300.0[19] appears to be the most practical and widely available method, with a PQL of 10 µg/L.

(3) The lifetime renal cancer risk associated with the ingestion of drinking water containing bromate at the MAC is greater than the range that is considered generally to be essentially negligible. Based on the incidence of renal tumours in rats, the lifetime renal cancer risk associated with the ingestion of drinking water containing bromate at the MAC of 10 µg/L is 2.19×10^{-4}.

References

1. Kurokawa, Y., Maekawa, A., Takahashi, M. and Hayashi, Y. Toxicity and carcinogenicity of potassium bromate — a new renal carcinogen. Environ. Health Perspect., 87: 309–335 (1990).

2. International Agency for Research on Cancer. Some naturally occurring and synthetic food components, furocumarins and ultraviolet radiation. IARC Monogr. Eval. Carcinog. Risk Chem. Hum., 40: 207–220 (1986).

3. Bolyard, M. and Snyder Fair, P. Occurrence of chlorate in hypochlorite solutions used for drinking water disinfection. Environ. Sci. Technol., 26: 1663–1665 (1992).

4. Ellison, D. Personal communication. Canadian Water and Wastewater Association, Ottawa, letter dated July 10 (1998).

5. Koudjonou, B. and Prévost, M. Personal communication. École polytechnique de Montréal, Montreal, letter dated July 3 (1998).

6. Haag, W.R. and Hoigné, J. Ozonation of bromide-containing waters: kinetics of formation of hypobromous acid and bromide. Environ. Sci. Technol., 17: 261–267 (1983).

7. Pontius, F.W. (ed.). Water quality and treatment — A handbook of community water supplies. 4th edition. American Water Works Association. McGraw-Hill, New York, NY. 1194 pp. (1990).

8. Luong, T.V., Peters, C.J. and Perry, R. Occurrence of bromide in source and treated waters. Effluent Water Treat. J., (May): 192–197 (1983).

9. Krasner, S.W., Gramith, J.T. and Means, E.G. Formation and control of brominated ozone by-products. Presented at the 1991 Annual American Water Works Association Conference, Philadelphia, PA (1991).

10. Krasner, S.W., McGuire, M.J., Jacangelo, J.G., Patania, N.L., Reagan, K.M. and Aieta, E.M. The occurrence of disinfection by-products in US drinking water. J. Am. Water Works Assoc., 81: 41 (1989).

11. Ferguson, D.W., McGuire, M.J., Koch, B., Wolfe, R.L. and Aieta, E.M. Comparing peroxone and ozone for controlling taste and odor compounds, disinfection by-products and micro-organisms. J. Am. Water Works Assoc., 82: 181–191 (1990).

12. Lo, B., Williams D.T. and Subramanian, K.S. Bromate levels in Canadian municipal and bottled water. American Laboratory News (in press).

13. Ministère de l'environnement et de la faune du Québec. Winter 1998 survey of drinking water in raw, treated and distributed water. Unpublished data (1988).

14. Health Canada. A one-year survey of halogenated disinfection by-products in the distribution system of treatment plants using three different disinfection processes. Environmental Health Directorate, Health Protection Branch, Ottawa (1996).

15. Hutchinson, J., Bailey, K., Lunt, D., Ofgen, T. and Fielding, M. Effects of disinfectants on organic substances in water. National Centre for Environmental Toxicology, Water Research Centre, Medmenham, UK (1995).

16. Federal–Provincial Subcommittee on Drinking Water. Agenda package for the May 12–14, 1997, meeting, Ottawa (1997).

17. Health Canada. Survey of bromide and bromate found in various types of bottled water. Unpublished data. Food Division, Food Directorate, Ottawa (1998).

18. U.S. Food and Drug Administration. Foods and drugs. U.S. Code Fed. Regul., Title 21, Parts 137.155, 172.730 (1984).

19. Pfaff, J.D. Method 300.0. Determination of inorganic anions in drinking water by ion chromatography. Office of Research and Development, National Exposure Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH (1993).

20. Pfaff, J.D. and Brockhoff, C.A. Determining inorganic disinfection by-products by ion chromatography. J. Am. Water Works Assoc., 82: 192–195 (1990).

21. Kruithof, J.C., van Dijk-Looyaard, A.M., van Genderen, J., van der Jagt, H. and Schippers, J.C. Formation of bromate by ozonation and application of other chemical disinfectants. The Netherlands Waterworks Testing and Research Institute (KIWA), Nieuwegein, The Netherlands (1992).

22. Krasner, S.W., Glaze, W.H., Weinberg, H.S., Daniel, D.A. and Najm, I.M. Formation and control of bromate during ozonation of waters containing bromide. J. Am. Water Works Assoc., (January): 71–83 (1993).

23. Hautman, D.P. Analysis of trace bromate in drinking water using "selective anion concentration and ion chromatography." Paper presented at the American Water Works Association Water Quality Technology Conference, Toronto, November 15–19 (1992).

24. Sorrell, R.K. and Hautman, D.P. A simple concentration technique for the analysis of bromate at low levels in drinking water. Paper presented at the American Water Works Association Water Quality Technology Conference, Toronto, November 15–19 (1992).

25. Lo, B. and Subramanian, K.S. Bromate in drinking water: Trace level determination by ion-chromatography. Proceedings of the 7th National Conference on Drinking Water (in press).

26. American Water Works Association. Brominated DBPs [editorial]. J. Am. Water Works Assoc., (January): 41 (1993).

27. von Gunten, U. and Hoigné, J. Factors controlling the formation of bromate during ozonation of bromide-containing waters. J. Water SRT – Aqua, 41: 299–304 (1992).

28. Siddiqui, M.S. and Amy, G.L. Factors affecting DBP formation during ozone–bromide reactions. J. Am. Water Works Assoc., (January): 63–72 (1993).

29. Fujii, M., Oikawa, K., Saito, H., Fukuhara, C., Onosaka, S. and Tanaka, T. Metabolism of potassium bromate in rats. *In vivo* studies. Chemosphere, 13: 1207–1212 (1984).

30. Tanaka, T., Oikawa, K., Fukuhara, C., Saito, H., Onosaka, S., Min, K.S. and Fujii, M. Metabolism of potassium bromate in rats. II. *In vitro* studies. Chemosphere, 13: 1213–1219 (1984).

31. Warshaw, B.L., Carter, M.C., Hymes, L.C., Bruner, B.S. and Rauber, A.P. Bromate poisoning from hair permanent preparations. Pediatrics, 76: 975–978 (1985).

32. Quick, C.A., Chole, R.A. and Mauer, S.M. Deafness and renal failure due to potassium bromate poisoning. Arch. Otolaryngol., 101: 494–495 (1975).

33. Matsumoto, I., Morizono, T. and Paparella, M.M. Hearing loss following potassium bromate: two case reports. Otolaryngol. Head Neck Surg., 88: 625–629 (1980).

34. Gradus, D.B., Rhoads, M., Bergstrom, L.B. and Jordan, S.C. Acute bromate poisoning associated with renal failure and deafness presenting as hemolytic uremic syndrome. Am. J. Nephrol., 4: 188–191 (1984).

35. Matsuyama, Z., Katayama, S. and Nadamura, S. A case of sodium bromate intoxication with cerebral lesion. Rinsho Shinkeigaku, 33: 535–540 (1993).

36. Gosselin, R.E., Hodge, H.C., Smith, R.P. and Gleason, M.N. Clinical toxicology of commercial products: acute poisoning. 4th edition. Williams & Wilkins, Baltimore, MD. p. 66 (1976).

37. Mack, R.B. Round up the usual suspects. Potassium bromate poisoning. N. C. Med. J., 49: 243–245 (1988).

38. Nakajima, M., Kitazawa, M., Oba, K., Kitagawa, Y. and Toyoda, Y. Effect of route of administration in the micronucleus test with potassium bromate. Mutat. Res., 223: 399–402 (1989).

39. Kurokawa, Y., Takayama, S., Konishi, Y., Hiasa, Y., Asahina, S., Takahashi, M., Maekawa, A. and Hayashi, Y. Long-term *in vivo* carcinogenicity test of potassium bromate, sodium hypochlorite and sodium chlorite conducted in Japan. Environ. Health Perspect., 69: 221–235 (1986).

40. Kurokawa, Y., Aoki, S., Matsushima, Y., Takamura, N., Imazawa, T. and Hayashi, Y. Dose–response studies on the carcinogenicity of potassium bromate in F344 rats after long-term oral administration. J. Natl. Cancer Inst., 77: 977–982 (1986).

41. Kurokawa, Y., Matsushima, Y., Takamura, N., Imazawa, T. and Hayashi, Y. Relationship between the duration of treatment and the incidence of renal cell tumors in male F344 rats administered potassium bromate. Jpn. J. Cancer Res. (Gann), 78: 358–364 (1987).

42. Kurokawa, Y., Matsushima, Y. and Hayashi, Y. Long-term oral administration of potassium bromate in mice. In: Proceedings of the 46th Annual Meeting of the Japanese Cancer Association, Tokyo (1987), cited in reference 1.

43. Takamura, N., Kurokawa, Y., Matsushima, Y., Imazawa, T., Onodera, H. and Hayashi, Y. Long-term oral administration of potassium bromate in male Syrian golden hamsters. Sci. Rep. Res. Inst. Tohoku Univ., Ser. C., 32: 43–46 (1985), cited in reference 1.

44. Kurokawa, Y., Takahashi, M., Kokubo, T., Ohno, Y. and Hayashi, Y. Enhancement by potassium bromate of renal tumorigenesis initiated by N-ethyl-N-hydroxyethylnitrosamine in F344 rats. Gann, 74: 607–610 (1983).

45. Kurokawa, Y., Auki, S., Imazawa, T., Hayashi, Y., Matsushima, Y. and Takamura, N. Dose-related enhancing effect of potassium bromate on renal tumorigenesis in rats initiated with N-ethyl-N-hydroxyethylnitrosamine. Jpn. J. Cancer Res. (Gann), 76: 583–589 (1985).

46. Umemura, T., Sai, K., Takagi, A., Hasegawa, R. and Kurokawa, Y. A possible role for oxidative stress in potassium bromate ($KBrO_3$) carcinogenesis. Carcinogenesis, 16(3): 593–597 (1995).

47. Kasai, H., Nishimura, S., Kurokawa, Y. and Hayashi, Y. Oral administration of the renal carcinogen, potassium bromate, specifically produces 8-hydroxydeoxyguanosine in rat target organ DNA. Carcinogenesis, 18: 1959–1961 (1987).

48. Kurata, Y., Diwan, B.D. and Ward, J.M. Lack of renal tumour-initiating activity of a single dose of potassium bromate, a genotoxic renal carcinogen in male F344/NCr rats. Food Chem. Toxicol., 30: 251–259 (1992).

49. DeAngelo, A.B., George, M.H., Kilburn, S.R., Moore, T.M. and Wolf, D.C. Carcinogenicity of potassium bromate administered in the drinking water to male B6C3F1 mice and F344/N rats. Toxicol. Pathol., 26(5): 587–594 (1998).

50. Kurokawa, Y., Takamura, N., Matsuoka, C., Imazawa, T., Matsushima, Y., Onodera, H. and Hayashi, Y. Comparative studies on lipid peroxidation in the kidney of rats, mice, and hamsters and on the effect of cysteine, glutathione, and diethyl maleate treatment on mortality and nephrotoxicity after administration of potassium bromate. J. Am. Coll. Toxicol., 6: 489–501 (1987).

51. Sai, K., Takagi, A., Umemura, T., Hasegawa, R. and Kurokawa, Y. Relation of 8-hydroxydeoxyguanosine formation in rat kidney to lipid peroxidation, glutathione level and relative organ weight after a single administration of potassium bromate. Jpn. J. Cancer Res., 82: 165–169 (1991).

52. Chipman, J.K., Davies, J.E., Parsons, J.L., Nair, J., O'Neill, G. and Fawell, J.K. DNA oxidation by potassium bromate; a direct mechanism or linked to lipid peroxidation. Toxicology, 126: 93–102 (1997).

53. Sai, K., Tyson, C.A., Thomas, D.W., Dabbs, J.E., Hasegawa, R. and Kurokawa, Y. Oxidative DNA damage induced by potassium bromate in isolated rat renal proximal tubules and renal nuclei. Cancer Lett., 87: 1–7 (1994).

54. Sai, K., Umemura, T., Takagi, A., Hasegawa, R. and Kurokawa, Y. The protective role of glutathione, cysteine and vitamin C against oxidative DNA damage induced in rat kidney by potassium bromate. Jpn. J. Cancer Res., 83: 45–51 (1992).

55. Sai, K., Hayashi, M., Takagi, A., Hasegawa, R., Sofuni, T. and Kurokawa, Y. Effect of antioxidants on induction of micronuclei in rat peripheral blood reticulocyte by potassium bromate. Mutat. Res., 269: 113–118 (1992).

56. Ishidate, M., Jr., Yoshikawa, K. and Sofuni, T. Studies on the mutagenicity of potassium bromate and other oxidizing chemicals. In: Proceedings of the 41st Annual Meeting of the Japanese Cancer Association (1982), cited in reference 1.

57. Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. and Sugiyama, T. Cooperative programme on short-term assays for carcinogenicity in Japan. Proceedings of a meeting organized by the International Agency for Research on Cancer and the Commission of the European Communities and held in Hanover, Federal Republic of Germany, June 4–9, 1979. In: Molecular and cellular aspects of carcinogen screening tests. R. Montesano, H. Bartsch and L. Tomatis (eds.). IARC Scientific Publications Series No. 27, Lyon, France. pp. 324–330 (1980).

58. Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M. and Matsuoka, A. Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol., 22: 623–636 (1984).

59. Fujie, K., Shimazu, H., Matsuda, M. and Sugiyama, T. Acute cytogenetic effects of potassium bromate on rat bone marrow cells *in vivo*. Mutat. Res., 206: 455–458 (1988).

60. Hayashi, M., Kishi, M., Sofuni, T. and Ishidate, M., Jr. Micronucleus test with mice on 39 food additives and 3 miscellaneous chemical substances. Food Chem. Toxicol., 26: 487–500 (1989).

61. Awogi, T., Murata, K., Uejima, M., Kuwahara, T., Asanami, S., Shimono, K. and Morita, T. Induction of micronucleated reticulocyte by potassium bromate and potassium chromate in CD-1 male mice. Mutat. Res., 278: 181–185 (1992).

62. World Health Organization. Seventh report of the Expert Committee on Food Additives on the specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents. World Health Organization Technical Report Series No. 281, Geneva. p. 164 (1964).

63. Krewski, D., Gaylor, D. and Szyszkowicz, M. A model-free approach to low-dose extrapolation. Environ. Health Perspect., 90: 279–285 (1991).