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Bromate in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published on selected chemicals in 1998 and on microbiological aspects in 2002. The third edition of the GDWQ was published in 2004, and the first addendum to the third edition was published in 2005.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the documents for the third edition and addenda.

Under the oversight of a group of coordinators each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the

International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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The work of the following working group coordinators was crucial in the development of this document and others contributing to the first addendum to the third edition:

Dr J. Cotruvo, J. Cotruvo Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Working Group Meeting for the first addendum to the third edition of the GDWQ, held on 17–21 May 2004. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinator was Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters. Mr Robert Bos, Water Sanitation and Health Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
CT	concentration × time
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency (USA)
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (USA)
GDWQ	*Guidelines for Drinking-water Quality*
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MDL	method detection limit
NOAEL	no-observed-adverse-effect level
PQL	practical quantification level
TDI	tolerable daily intake
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

Compound	*CAS No.*	*Molecular formula*
Potassium bromate	7758-01-2	$KBrO_3$
Sodium bromate	7789-38-0	$NaBrO_3$

The bromate ion (BrO_3^-) may exist in a number of salts, the most common of which are potassium and sodium bromate.

1.2 Physicochemical properties *(Weast, 1986)*

Property	*Potassium bromate*	*Sodium bromate*
Boiling point (°C)	370 (decomposes)	–
Melting point (°C)	350	3.81
Density at 20 °C	3.27	3.34
Water solubility (g/litre)	133 (40 °C) 498 (100 °C)	275 (8 °C) 909 (100 °C)

1.3 Organoleptic properties

No information is available on the taste or odour threshold of bromate.

1.4 Major uses and sources in drinking-water

Bromate may be formed in water during ozonation when the bromide ion is present (Haag & Hoigné, 1983). Under certain conditions, bromate may also be formed in concentrated hypochlorite solutions used to disinfect drinking-water (IPCS, 2000). This reaction is due to the presence of bromide in the raw materials (chlorine and sodium hydroxide) used in the manufacture of sodium hypochlorite. Bromide is not oxidized by chlorine dioxide, so the use of chlorine dioxide will not generate hypobromous acid, hypobromite ion or bromate (Hoigné & Bader, 1994). (Although bromate can be formed on simultaneous exposure to chlorine dioxide and light [Rice & Gomez-Taylor, 1986; Gordon & Emmert, 1996], the reaction is thermodynamically unfavourable, and bromate is unlikely to be formed under water treatment conditions.) Bromate can also be formed in electrolytically generated hypochlorous acid solutions when bromide is present in the brine (Fielding & Hutchison, 1993).

Sodium and potassium bromate are powerful oxidizers used mainly in permanent wave neutralizing solutions and the dying of textiles using sulfur dyes (Mack, 1988). Potassium bromate is also used as a chemical reagent and as an oxidizer to mature flour during milling and to condition dough during baking (US FDA, 1994; IARC, 1999). As well, it is used in treating barley in beer making and has been used for the improvement of the quality of fish paste products in Japan (Ministry of Health and Welfare, 1979; JECFA, 1995). However, JECFA (1995) concluded that the use of

potassium bromate in food processing was not appropriate and that, as a general principle, bromate should not be present in food as consumed.

1.5 Environmental fate

Bromate does not volatilize and is only slightly adsorbed onto soil or sediment. Because it is a strong oxidant, its most likely fate is reaction with organic matter, leading to the formation of bromide ion.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Water

Bromate is not normally found in water. Conversion of bromide to bromate upon ozonation may be affected by natural organic matter, pH and temperature, among other factors. The relative increase of bromate depends on measures used for comparison (over time or as a function of concentration × time, or CT). The use of CT has been suggested as a more useful indicator to describe the relative rate of bromate formation because it also gives a simultaneous descriptor for disinfection efficiency (von Gunten et al., 2001). The rate of formation of bromate ion may increase with temperature (AWWARF, 1991; Siddiqui & Amy, 1993). In addition, many studies on the effect of alkalinity on the formation of bromate during ozonation indicate that increased alkalinity increases bromate formation (Siddiqui et al., 1995). However, the rate of formation of bromate during ozonation is also affected by ozone characteristics. Thus, a smaller CT might result because ozone becomes less stable with increasing temperature and/or alkalinity. All factors being equal, bromide concentration and ozone dose are the best predictors of bromate formation during ozonation (IPCS, 2000).

A study of European water utilities found bromate levels ranging from less than the detection limit (2 µg/litre) to 16 µg/litre in finished water (IPCS, 2000). Health Canada (1999) reported an average level of 1.71 µg/litre, with a range of 0.55–4.42 µg/litre; in another survey, it reported an average concentration of 3.17 µg/litre, with a range of 0.73–8.00 µg/litre. In ozonated bottled water, the average level of bromate was 18 µg/litre, with a range of 4.3–37.3 µg/litre (Health Canada, 1999). Haag & Hoigné (1983) and McGuire et al. (1990) reported a range of 60–90 µg/litre in ozonated water. In IPCS (2000), the range of bromate concentrations reported in drinking-water with a variety of source water characteristics after ozonation was <2–293 µg/litre, depending on bromide ion concentration, ozone dosage, pH, alkalinity and dissolved organic carbon. AWWA (2000) reported a mean level of bromate in finished waters of 3.06 µg/litre and a median level of 3.64 µg/litre. The mean level in the distribution system was 2.5 µg/litre, and the median level was 0.05 µg/litre. It should be noted that some of the studies demonstrating high rates of conversion of bromide to bromate are pure laboratory studies with very high bromide levels and thus may not be representative of conversion rates at environmentally relevant doses.

In the USA, the annual mean bromate concentration in finished surface water determined using the EPA methods was 2.9 µg/litre, with a range of <0.2–25 µg/litre; the annual mean concentration of bromate in the same waters determined using the utility method was 2.1 µg/litre, with a range of <5–50 µg/litre. It is difficult to compare values obtained by the EPA and utility methods because the minimum reporting level using the utility method is 5 µg/litre, while for the EPA method it is 0.2 µg/litre. At this time, there are no data for groundwater plants (US EPA, 2001a).

2.2 Food

Bromates may be added to beer or fish paste (IARC, 1986; JECFA, 1995). Small amounts of bromate (≤30 mg/kg) may be added to flour or dough during the preparation of bread, but this is broken down to bromide during baking (IARC, 1986). However, when bread was made from flour doughs containing >50 mg of potassium bromate per kg of dough, either by bulk fermentation or by mechanical development, increasing amounts of residual potassium bromate were detected, with bulk fermentation giving higher residual levels than mechanical development (Thewlis, 1974). JECFA (1995) reported that the previous acceptable level of treatment of flours for bread making (0–60 mg of bromate per kg of flour) has been withdrawn, and the use of potassium bromate as a flour treatment agent is not appropriate. In the USA, the Code of Federal Regulations allows up to 50 mg/kg in finished bromated flour and up to 75 mg/kg in finished bromated whole wheat flour if this addition improves the baking qualities (US FDA, 1994). However, the US FDA has suggested that bakers voluntarily decrease potassium bromate use, and, if bromate is used, it must be indicated on packages.

2.3 Estimated total exposure and relative contribution of drinking-water

For most people, exposure to bromate is unlikely to be significant. If ozone is used to disinfect drinking-water, intake of bromate might range from 120 to 180 µg/day (McGuire et al., 1990). In the USA, the amount of residual inorganic bromides in fermented malt beverages may not exceed 25 µg/litre (calculated as bromine) (US FDA, 1994). The levels in baked goods and products made from bromated flour are expected to be low, since bromates are broken down to bromide during baking (IARC, 1986).

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Following oral administration, bromate is absorbed from the gastrointestinal tract in both humans and animals. A 2-year-old male child accidentally ingested 30–60 ml of a permanent wave solution containing 10–12 g of bromate per 100 ml, resulting in an estimated dose of 230–460 mg of bromate per kg of body weight. Serum bromide levels peaked 12 h following ingestion. Approximately 60–70% of the bromate ingested was recovered from dialysate and urine (Lichtenberg et al., 1989).

Peak plasma concentration occurred 15 min after gavage administration of a dose of 100 mg of potassium bromate per kg of body weight to male Wistar rats; peak urine concentration occurred 1 h after dosing (Fujii et al., 1984). Neither bromide nor bromine was released following incubation of normal human gastric juice with potassium bromate at 38 °C for 3 days, suggesting that bromate is absorbed unchanged (Parker & Barr, 1951). However, other investigators report that bromate may be converted to hydrobromic acid by the hydrochloric acid in the stomach (Kutom et al., 1990).

Bromide, but not bromate, was detected in the kidney, pancreas, stomach, small intestine, red blood cells and plasma of rats 24 h following gavage dosing with 100 mg of potassium bromate per kg of body weight (Fujii et al., 1984). *In vitro* studies suggest that bromate is reduced to bromide in body tissues, probably by glutathione or another sulfhydryl-containing compound (Tanaka et al., 1984); however, other studies suggest that bromate is very stable in the body and only small amounts are reduced to bromide (Kutom et al., 1990). Bromate is excreted mainly in the urine, partly as bromate and partly as bromide. A dose-related increase in urinary bromate was observed in rats following a single gavage dose of 5–100 mg/kg of body weight. Twenty-four hours after the administration of a single gavage dose of potassium bromate (50 mg of bromate ion per kg of body weight) to male rats, approximately 30% of the dose was detected in the urine (Fujii et al., 1984).

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO *TEST SYSTEMS*

4.1 Acute exposure

LD_{50}s of 223–363 and 136 mg of bromate per kg of body weight, respectively, were determined for mice administered potassium bromate orally (Nakajima et al., 1989) and intraperitoneally (Hayashi et al., 1989). LD_{50}s of 280–495 mg/kg of body weight were obtained for rats, mice and hamsters given potassium bromate by gavage (Kurokawa et al., 1990).

A single dose of potassium bromate at 0, 129, 192, 257 or 385 mg of bromate per kg of body weight was given to male Long-Evans rats (five per dose) by gavage. Rats in the highest dose group exhibited diarrhoea and signs of sedation at 6 h following bromate administration (Fujie et al., 1988).

Young adult F344 rats (five per dose) were given a single gavage dose of 0, 50, 300, 600 or 1200 mg of potassium bromate per kg of body weight (0, 38.5, 231, 462 or 924 mg of bromate per kg of body weight). All rats given 924 mg/kg of body weight and four of five rats given 462 mg/kg of body weight died within 24 h, and one rat given 231 mg/kg of body weight died on day 6. Proximal tubule necrosis was observed in these animals. In surviving animals necropsied at 4 weeks, an increase in relative kidney weights was noted in rats in the two highest dose groups, and basophilic regeneration and accumulation of eosinophilic droplets were observed in the renal tubules of rats given 231 mg of bromate per kg of body weight (Kurata et al., 1992).

4.2 Short-term exposure

Male SPF mice (nine per dose) were given potassium bromate in drinking-water at concentrations of 0, 0.1, 0.5, 1.0, 2.5 or 5 g/litre (0, 10.8, 54, 108, 270 or 540 mg of bromate per kg of body weight per day) for 2 weeks. Decreased body weight was observed in the highest dose group. Relative kidney, lung and liver weights were increased in treated groups compared with controls, but no dose–response was observed. Alkaline phosphatase, γ-glutamyl transpeptidase and α-fetoprotein levels were significantly increased in the two highest dose groups. The NOAEL for this study was 108 mg of bromate per kg of body weight per day, based on changes in enzyme activities observed at doses of 270 mg/kg of body weight per day and above (Kawana et al., 1991).

Potassium bromate was administered to groups of F344 rats (10 per sex per dose) in water at concentrations of 0, 0.15, 0.3, 0.6, 1.25, 2.5, 5.0 or 10 g/litre (approximately 0, 16, 32, 63, 140, 270, 540 or 1080 mg of bromate per kg of body weight per day) for 13 weeks. All animals exposed to 270 mg of bromate per kg of body weight per day and higher died within 7 weeks. Observed signs of toxicity included significant inhibition of body weight gain in males at 63 mg of bromate per kg of body weight per day and higher. Significant increases in blood serum parameters indicative of liver and kidney toxicity (including glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase, cholinesterase and blood urea nitrogen) were seen in both sexes at 63 mg of bromate per kg of body weight per day. This study identified 63 mg of bromate per kg of body weight per day as an adverse effect level, but insufficient data were provided to determine whether these effects occurred at lower doses (Kurokawa et al., 1990).

4.3 Long-term exposure

The systemic toxicity of bromate (administered as the potassium salt) has been reported from long-term studies designed to evaluate bromate carcinogenicity in F344 rats and $B6C3F_1$ mice (Kurokawa et al., 1983, 1986a,b; Nakano et al., 1989; DeAngelo et al., 1998). The data show that the kidney is the major target organ of bromate-associated toxicity and that rats are more sensitive than mice to bromate treatment.

Male Wistar rats were exposed to 0.04% potassium bromate in drinking-water (approximately 30 mg of bromate per kg of body weight per day) for up to 15 months. Effects observed included markedly inhibited body weight gain in all exposed animals, karyopyknotic foci (shrunken cell nuclei) in tubules of the inner kidney medulla, increased blood urea nitrogen and structural abnormalities of the renal cortical tubules. Based on body weight and renal effects, the LOAEL for this study was the only dose tested, 30 mg of bromate per kg of body weight per day (Nakano et al., 1989).

Male and female F344 rats (53 per sex per dose) were given potassium bromate in drinking-water at concentrations of 0, 0.25 or 0.5 (reduced to 0.4 at week 60) g/litre

(approximately 0, 12 or 33 mg of bromate per kg of body weight per day) for 110 weeks. Survival was reduced in males in the high-dose group beginning at week 60 and in the low-dose group beginning at week 100. Body weight was significantly reduced in high-dose males. Non-neoplastic changes included renal tubular degeneration and necrosis, formation of hyaline droplets in the renal proximal tubules, thickening of the transitional epithelium of the renal pelvis and papillary hyperplasia. No information was provided on the incidence or statistical significance of these changes. A NOAEL could not be determined for this study (Kurokawa et al., 1983).

Male F344 rats (20–24 per dose) were administered potassium bromate in drinking-water at concentrations of 0, 0.015, 0.03, 0.06, 0.125, 0.25 or 0.5 g/litre (corresponding to 0, 0.7, 1.3, 2.5, 5.6, 12 or 33 mg of bromate per kg of body weight per day) for 104 weeks. Males in the highest dose group had decreased survival and decreased body weight beginning at week 70, compared with controls. The only non-neoplastic effect reported was a dose-related increase in the severity of nephropathy that is characteristic of aging F344 rats. No information was given on the doses at which these effects occurred. A NOAEL could not be determined for this study (Kurokawa et al., 1986a).

Potassium bromate was administered to male and female F344 rats in drinking-water at time-weighted average daily doses of 0, 9.6 or 21.3 mg of bromate per kg of body weight for males and 0, 9.6 or 19.6 mg of bromate per kg of body weight for females for 104 weeks. Decreased survival and body weight were observed in male rats in the high-dose group beginning at week 70, effects that may have been due to early onset of tumours. Significant decreases in serum chemistry values (including glutamate pyruvate transaminase, albumin to globulin ratio, potassium and cholinesterase) were observed in females in the high-dose group. Other effects included the formation of hyaline droplets, eosinophilic bodies and brown pigments in the renal tubular epithelium. No quantitative information was provided on the incidence and severity of these lesions or on the statistical significance of the findings. Furthermore, early onset of tumours is likely to have contributed to the decreased survival and body weight. A NOAEL for this study could not be determined (Kurokawa et al., 1986b).

No effects were reported for female $B6C3F_1$ mice given potassium bromate in drinking-water for 78 weeks at time-weighted average doses of 0, 43.5 or 91.6 mg of bromate per kg of body weight per day (Kurokawa et al., 1986b).

Potassium bromate was administered to male F344 rats (78 per dose) in drinking-water at concentrations of 0, 0.02, 0.1, 0.2 or 0.4 g/litre (approximately 0, 1.1, 6.1, 12.9 or 28.7 mg of bromate per kg of body weight per day) for 100 weeks (DeAngelo et al., 1998). In male rats, decreased survival and body weight were observed in the highest dose group starting at week 79 and in the next lower dose group at week 88, attributed to an excessive tumour burden (D.C. Wolf, personal communication, 1998). Non-neoplastic kidney lesions were observed in rats. Although the severity of chronic nephropathy was comparable between control and treated animals, a dose-dependent increase in the incidence of urothelial hyperplasia was noted at 6.1 mg of bromate per kg of body weight per day and higher. Kidney effects in treated animals were reported

to include mineralized foci in the renal papilla and eosinophilic droplets in the proximal tubule epithelium, although the authors did not indicate the dose levels at which these findings occurred. In this study, a NOAEL of 1.1 mg of bromate per kg of body weight per day was identified, based on kidney effects in male rats (DeAngelo et al., 1998). In a companion study, potassium bromate was administered to male $B6C3F_1$ mice (78 per dose) in drinking-water at concentrations of 0, 0.08, 0.4 or 0.8 g/litre (approximately 0, 6.9, 32.5 and 59.6 mg of bromate per kg of body weight per day) for 100 weeks. No effects on survival, body weight, organ weights, serum chemistry or the incidence of non-neoplastic lesions were observed. The NOAEL for this study was 59.6 mg of bromate per kg of body weight per day (DeAngelo et al., 1998).

4.4 Reproductive and developmental toxicity

In a reproductive and developmental toxicity screening assay, Sprague-Dawley rats were administered sodium bromate in drinking-water at concentrations of 0, 0.025, 0.08 or 0.25 g/litre (approximately 0, 2.2, 7.7 and 22 mg of bromate per kg of body weight per day) over a 35-day period. One group of female rats (10 per dose) was given sodium bromate from study day 1 to study day 34 to test for effects during conception and gestation. Another group of females (13 per dose) was dosed from gestation day 6 to postnatal day 1 to test for effects during mid to late gestation and birth. Untreated male rats (10 per dose) were cohabited with the second group of females for 5 days before dosing (study days 1–5) and were subsequently dosed from study day 6 to study day 34–35. No effects on adult survival, organ weights, reproductive performance or histopathology were observed in any group. At 22 mg of bromate per kg of body weight per day, males showed a statistically significant decrease (approximately 18%) in epididymal sperm density. For this study, the NOAEL was 7.7 mg of bromate per kg of body weight per day, based on changes in sperm density (Wolf & Kaiser, 1996).

Rats and mice fed diets containing bread baked from flour treated with 15 mg of potassium bromate per kg over five and eight generations, respectively, did not exhibit any effects on reproductive function or survival (Kurokawa et al., 1990). However, because most bromate added to flour is converted to bromide during the bread baking process (Kurokawa et al., 1986b), it is unlikely that the animals in these multigeneration studies were actually exposed to bromate.

4.5 Mutagenicity and related end-points

Bromate was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of S9 activation and produced chromosomal aberrations in cultured Chinese hamster fibroblast cells (Ishidate et al., 1984). In assays using V79 Chinese hamster ovary cells, bromate increased the frequency of cells with micronuclei, the number of chromosomal aberrations and the number of DNA strand breaks and induced gene mutations at the HPRT locus (Speit et al., 1999). Positive results were also observed in *in vivo* studies. The number of aberrant metaphase cells was increased following single oral doses of potassium bromate in Long-Evans rats (Fujie et al., 1988).

Following either intraperitoneal injection or gavage dosing, the number of micronuclei was elevated in mouse micronucleus tests with MS/Ae and CD-1 mice strains (Hayashi et al., 1988, 1989; Nakajima et al., 1989; Awogi et al., 1992). Intraperitoneal injection of bromate in F344 rats significantly increased the number of micronuclei in reticulocytes (Sai et al., 1992). Evidence of DNA damage, as indicated by elevated levels of 8-hydroxy-deoxyguanosine, has been observed in rats orally administered potassium bromate (Kasai et al., 1987). The weight of evidence demonstrates that bromate is clearly mutagenic in *in vitro* assays. The positive findings in *in vivo* studies show that this mutagenicity is also expressed *in vivo*. Thus, bromate should be considered a mutagenic disinfection by-product.

4.6 Carcinogenicity

Several reports of bromate-induced cancer in experimental animals are available. The clearest evidence comes from studies in F344 rats (Kurokawa et al., 1983, 1986a,b, 1987; DeAngelo et al., 1998).

F344 rats (53 per sex per dose group) were given drinking-water containing 0, 0.25 or 0.5 (reduced to 0.4 at week 60) mg of potassium bromate per litre (reported as 0, 12 and 33 mg of bromate per kg of body weight per day) for 110 weeks. Statistically significantly increased incidence of renal tumours (both adenomas and adenocarcinomas) was noted in treated males and females in both dose groups. The incidence of peritoneal mesotheliomas (tissue of origin not identified) was significantly increased in males in both dose groups, compared with controls. The authors concluded that potassium bromate was carcinogenic in both male and female rats (Kurokawa et al., 1983).

F344 rats were given drinking-water containing potassium bromate (time-weighted average doses of 0, 9.6 and 21.3 mg of bromate per kg of body weight per day in males and 0, 9.6 and 19.6 mg of bromate per kg of body weight per day in females) for 110 weeks. The incidence of renal tumours (adenomas and carcinomas combined) in the three groups was 6%, 60% and 88% in males and 0%, 56% and 80% in females in the control, low-dose and high-dose groups, respectively. In males, the incidence of peritoneal mesotheliomas was also significantly elevated (11%, 33% and 61%, respectively) (Kurokawa et al., 1986a).

Male F344 rats (20–24 per dose group) were administered drinking-water containing potassium bromate at 0, 0.015, 0.03, 0.06, 0.125, 0.25 or 0.5 g/litre (corresponding to 0, 0.7, 1.3, 2.5, 5.6, 12 and 33 mg of bromate per kg of body weight per day) for 104 weeks. The incidence of combined renal adenomas and carcinomas in these dose groups was 0%, 0%, 0%, 4%, 21%, 25% and 45%, respectively. This increase was statistically significant at 5.6 mg of bromate per kg of body weight per day and higher. The incidence of dysplastic foci in the kidney (considered to be preneoplastic lesions) was 0%, 5%, 25%, 25%, 50%, 95% and 95% in these groups, respectively, and was statistically significantly increased at 1.3 mg of bromate per kg of body weight per day and higher. The incidences of follicular tumours of the thyroid gland (0%, 0%, 0%, 4%, 0%, 15% and 37% in treated groups, respectively) and of

peritoneal mesotheliomas (0%, 0%, 15%, 17%, 8%, 15% and 75% in treated groups, respectively) were significantly elevated only in the highest dose group (Kurokawa et al., 1986b).

Male F344 rats (78 per dose group) were given potassium bromate in drinking-water at concentrations of 0, 0.02, 0.1, 0.2 or 0.4 g/litre (approximately 0, 1.1, 6.1, 12.9 or 28.7 mg of bromate per kg of body weight per day) for 100 weeks. A statistically significant, dose-dependent increase in the combined incidence of renal adenomas and carcinomas was observed at terminal sacrifice (2%, 2%, 13%, 8% and 40% in the groups, respectively). The incidence of combined adenomas and carcinomas of the thyroid gland (0%, 10%, 2%, 11% and 47% in dosed groups, respectively) and the incidence of mesotheliomas (*tunica vaginalis testes*) (0%, 8%, 10%, 21% and 63% in dosed groups, respectively) were also significantly increased. Renal tumours and mesotheliomas were first observed at 52 weeks, and tumours of the thyroid gland were first noted at 26 weeks (DeAngelo et al., 1998).

The carcinogenic potential of potassium bromate was investigated in female $B6C3F_1$ mice (50 per dose group) supplied with drinking-water containing 0, 0.5 or 1 g of potassium bromate per litre (0, 43.5 or 91.6 mg of bromate per kg of body weight per day) for 78 weeks. Based on histological examination of tissues at week 104 (26 weeks following termination of dosing), no significant increases in the incidence of tumours were observed in treated animals compared with controls. The authors concluded that potassium bromate was not carcinogenic in female mice (Kurokawa et al., 1986a).

Male $B6C3F_1$ mice (78 per dose group) were given potassium bromate in drinking-water at concentrations of 0, 0.08, 0.4 or 0.8 g/litre (approximately 0, 6.9, 32.5 and 59.6 mg of bromate per kg of body weight per day) for 100 weeks. A significant increase in the combined incidence of renal adenomas and carcinomas was observed in mice given 6.9 mg of bromate per kg of body weight per day (13% incidence) compared with controls, but there was no increase in renal tumours in mice treated with either 32.5 or 59.6 mg of bromate per kg of body weight per day (DeAngelo et al., 1998).

To assess the time course of renal tumour induction, male F344 rats were given drinking-water containing 0 or 0.5 g/litre of potassium bromate (0 and 32.3 mg of bromate per kg of body weight per day) for up to 104 weeks. Groups of rats were sacrificed and necropsied after 13, 26, 39, 52 or 104 weeks of treatment. Dysplastic foci (considered to be a preneoplastic lesion) and renal adenomas were first observed in dosed animals after 26 weeks of treatment, but the incidence was not statistically significantly increased over the controls. Dysplastic foci and renal adenomas were significantly increased relative to controls by 52 weeks of treatment. After 104 weeks, renal adenocarcinomas were observed in 3 of 20 dosed rats (15%) and adenomas in 6 of 20 (30%). The combined incidence of follicular adenomas and adenocarcinomas of the thyroid gland (7/35 [35%]) was significantly increased after 104 weeks of treatment. The authors concluded that the minimum induction time for the development of renal adenomas was 26 weeks (Kurokawa et al., 1987).

In the same study, the minimum treatment period and total cumulative dose required for the development of renal tumours was assessed by giving F344 rats potassium bromate in drinking-water containing 0.5 g of potassium bromate per litre (approximately 29.6–35.3 mg of bromate per kg of body weight per day) for up to 104 weeks. Groups of rats were treated for 13, 26, 39 or 52 weeks and subsequently maintained on distilled water until sacrifice at week 104. The incidence of renal dysplastic foci was 65% in animals exposed for 1–13 weeks and increased to 100% in animals exposed for 39–52 weeks (the incidence was 0% in controls). The combined incidence of adenomas and adenocarcinomas in rats exposed for 13–52 weeks ranged from 47% to 74%, which was similar to or higher than that observed in animals exposed continuously for 104 weeks (45%). The authors concluded that the minimum treatment period and total cumulative dose for the induction of renal adenomas and adenocarcinomas were 13 weeks and 4 g of potassium bromate per kg of body weight (approximately 3.1 g of bromate per kg of body weight), respectively (Kurokawa et al., 1987).

No significant differences were observed in the incidence of tumours in male or female newborn F344 rats or ICT mice when a single dose of potassium bromate was administered subcutaneously 24 h after birth and the tissues were examined histologically for neoplastic lesions at 78–82 weeks following dosing (Matsushima et al., 1986). Potassium bromate given as a single gavage dose of 300 mg/kg of body weight (231 mg of bromate per kg of body weight) to male F344 rats, followed by dietary ingestion of sodium barbital (a promoting agent), did not initiate renal tumours within a 104-week observation period (Kurata et al., 1992).

In summary, bromate produces tumours at multiple sites in male rats, including the kidney (adenomas and carcinomas), the thyroid gland (follicular cell adenomas and carcinomas) and the peritoneum (mesotheliomas) (Kurokawa et al., 1986a,b, 1987; DeAngelo et al., 1998). In the female rat, only kidney tumours are observed (Kurokawa et al., 1986a). Further, a clear dose–response relationship exists in tumour incidence and the severity/progression of tumours. The weight of evidence from the rat bioassays clearly indicates that bromate has the potential to be a human carcinogen.

5. EFFECTS ON HUMANS

Most cases of human poisoning from bromate are due to the accidental or intentional ingestion of home permanent wave solutions, which usually contain either 2% potassium bromate or 10% sodium bromate. In children, serious poisonings have been reported following ingestion of 60–120 ml of 2% potassium bromate (equivalent to 46–92 mg of bromate per kg of body weight per day for a 20-kg child). Lethal doses of potassium bromate are estimated to be 200–500 mg/kg of body weight (150–385 mg of bromate per kg of body weight) (Mack, 1988).

Toxic effects of bromate salts include nausea, vomiting, abdominal pain, anuria and diarrhoea, varying degrees of central nervous system depression, haemolytic anaemia

and pulmonary oedema. Most of these effects are reversible. Irreversible effects include renal failure and deafness, both of which have been observed following the ingestion of 240–500 mg of potassium bromate per kg of body weight (185–385 mg of bromate per kg of body weight) (Quick, 1975).

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

Bromate in drinking-water may be measured by ion chromatography using conductivity detection (EPA Method 300.1), ultraviolet/visible absorbance detection (EPA Method 317.0) or detection by inductively coupled plasma–mass spectrometry (EPA Method 328.1). For samples with high chloride ion content, a silver cartridge can be used to remove chloride prior to ion chromatographic analysis to minimize its interference with bromate measurement (IPCS, 2000). However, it should be noted that for natural sources and waters with high total organic carbon levels, detection limits will be slightly different because of the masking effect of natural organic matter and high concentrations of carbonate/bicarbonate ions that may interfere with bromate measurement (IPCS, 2000). The method detection limit (MDL) for bromate in EPA Method 300.1 is <1.5 μg/litre, and the practical quantification level (PQL) is approximately 5 μg/litre. The MDLs for bromate in EPA Methods 317.0 and 328.1 are <0.2 μg/litre and 0.3 μg/litre, respectively, and the PQL for both methods is as low as 1 μg/litre.

6.2 Treatment and control methods and technical achievability

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 (Kruithof et al., 1992). Bromate in ozonated drinking-water supplies is best controlled by limiting its formation, which is influenced by the bromide concentration (≥0.18 mg/litre) (Krasner et al., 1993), the source and concentration of organic precursors, pH, temperature, alkalinity and ozone dose (AWWA, 1993). 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 (Kruithof et al., 1992; von Gunten & Hoigné, 1992; Siddiqui & Amy, 1993). 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 by-products, in addition to being undesirable from the point of view of corrosion control; addition of ammonia results in the conversion of hypobromous acid to monobromamine, which in turn may be oxidized to nitrate (Siddiqui & Amy, 1993). 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.

7. PROVISIONAL GUIDELINE VALUE

Bromate is mutagenic both *in vitro* and *in vivo*. IARC (1986, 1999) has classified potassium bromate in Group 2B (possibly carcinogenic to humans), concluding that there is inadequate evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals. US EPA (2001b) has classified bromate as a probable human carcinogen by the oral route of exposure under the 1986 EPA Guidelines for Carcinogen Risk Assessment (US EPA, 1986) on the basis of adequate evidence of carcinogenicity in male and female rats. Under the 1999 EPA draft Guidelines for Carcinogen Risk Assessment (US EPA, 1999), bromate is likely to be a human carcinogen by the oral route; the data on the carcinogenicity of bromate via the inhalation route are inadequate for an assessment of its human carcinogenic potential. Health Canada (1999) has classified bromate as probably carcinogenic to humans (sufficient evidence in animals; no data in humans).

At this time, there is not sufficient evidence to conclude the mode of carcinogenic action for potassium bromate (Health Canada, 1999; IARC, 1999; IPCS, 2000; US EPA, 2001b). Observation of tumours at a relatively early time and the positive response of bromate in a variety of genotoxicity assays suggest that the predominant mode of action at low doses is due to DNA reactivity. Although there is limited evidence to suggest that the DNA reactivity in kidney tumours may have a non-linear dose–response relationship, there is no evidence to suggest that this same dose–response relationship operates in the development of mesotheliomas or thyroid tumours. Oxidative stress may play a role in the formation of kidney tumours, but the evidence is insufficient to establish lipid peroxidation and free radical production as key events responsible for induction of kidney tumours. Also, there are no data currently available to suggest that any single mechanism, including oxidative stress, is responsible for the production of thyroid and peritoneal tumours by bromate.

Because of insufficient information on the mode of carcinogenic action of bromate, IPCS (2000) developed both a carcinogenicity assessment based on the linearized multistage model as well as a TDI based on a non-linear approach for the carcinogenicity of bromate. A TDI of 1 µg/kg of body weight was calculated based on a no-effect level for the formation of renal cell tumours in rats at 1.3 mg/kg of body weight per day in the Kurokowa et al. (1986b) study and the use of an uncertainty factor of 1000 (10 each for inter- and intraspecies variation and 10 for possible carcinogenicity). The IPCS (2000) value of 0.1 µg/kg of body weight per day for a 10^{-5} excess lifetime cancer risk level was based on an increased incidence of renal tumours in male rats given potassium bromate in drinking-water for 2 years using the same study (Kurokawa et al., 1986b).

The more recent study by DeAngelo et al. (1998) has been selected for the derivation of a guideline value, because this study uses lower doses and more animals per group and the tumour findings are similar to those observed in the earlier study. To estimate cancer risks based on low-dose linear extrapolation, a one-stage Weibull time-to-tumour model is applied to the incidence of each tumour type (mesotheliomas, renal tubule tumours and thyroid follicular tumours) in male rats given potassium bromate

in drinking-water, using the 12-, 26-, 52- and 77-week interim kill data (DeAngelo et al., 1998). Individual cancer potency estimates are summed using Monte Carlo analysis (US EPA, 2001b). The upper-bound estimate of the cancer potency for bromate is 0.19 per mg/kg of body weight per day.[1] The concentrations in drinking-water associated with upper-bound excess lifetime cancer risks of 10^{-4}, 10^{-5} and 10^{-6} are 20, 2 and 0.2 µg/litre, respectively.

The concentration of bromate in drinking-water associated with an upper-bound excess lifetime cancer risk of 10^{-5}, 2 µg/litre, is similar to values that can be calculated based on the Kurokawa et al. (1986b) study. Using the IPCS (2000) value of 0.1 µg/kg of body weight per day for a 10^{-5} cancer risk and assuming a 60-kg person ingesting 2 litres of water per day, a value of 3 µg/litre can be derived (as was derived in the second edition of the Guidelines). Alternatively, if the TDI of 1 µg/kg of body weight given in IPCS (2000) were used, and assuming a 60-kg person drinking 2 litres of water per day and an allocation of 20% of the TDI to drinking-water, a value of 6 µg/litre would be obtained.

The PQL of 1 µg/litre may be difficult to achieve in many laboratories; a more attainable PQL is around 5 µg/litre. In addition, it is now considered that 10 µg/litre is a technically achievable value for the removal of bromate from drinking-water. The health-based value of 2 µg/litre should therefore be raised to 10 µg/litre, on the basis of analytical and technological feasibility. A provisional guideline value of 10 µg/litre is therefore recommended. This value is associated with an upper-bound excess lifetime cancer risk of 5×10^{-5}.

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[1] The slope factor given here does not incorporate a surface area to body weight correction.

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