WHO/HSE/WSH/09.01/6
English only

Bromide in drinking-water

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

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Printed by the WHO Document Production Services, Geneva, Switzerland

Preface

One of the primary goals of the World Health Organization (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 in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

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, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

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.

Acknowledgements

The first draft of Bromide in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality* (GDWQ), was prepared by Dr J. Cotruvo, J. Cotruvo Associates, USA, to whom special thanks are due.

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

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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held on 19–23 June 2008. 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 at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. 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 comments are greatly appreciated.

Acronyms and abbreviations used in the text

ADI	acceptable daily intake
at.%	atomic per cent
EEG	electroencephalogram
FAO	Food and Agriculture Organization of the United Nations
FSH	follicle stimulating hormone
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD_{50}	median lethal dose
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
TRH	thyrotropin releasing hormone
TSH	thyroid stimulating hormone
WHO	World Health Organization

Table of contents

The following is a short background document to provide guidance on bromide in drinking-water. This will be of particular interest to those with waters with naturally elevated bromide levels and desalinated water supplies, which may have higher bromide levels than are typically found in fresh water. Most of the toxicological text is taken from FAO/WHO (1989).

1. GENERAL DESCRIPTION

Bromide (Br^-) is the anion of the element bromine, which is a member of the common halogen element series that includes fluorine, chlorine, bromine and iodine. These elements have chemical similarities, but also important differences. They are oxidizing agents, and all form anions by accepting an electron. The elements below fluorine in the periodic table also form numerous oxyanions. The atomic weight of bromine is 79.909. Naturally occurring bromine consists of 50.57% ^{79}Br and 49.43% ^{81}Br. Bromine is a dense mobile dark liquid at room temperature that freezes at −7 °C and boils at 58 °C (Cotton & Wilkinson, 1962).

Bromide commonly exists as salts with sodium, potassium and other cations, which are usually very soluble in water. It also forms the strong acid, hydrobromic acid (HBr), and the weaker hypobromous (HOBr), bromous ($HBrO_2$) and bromic ($HBrO_3$) oxyacids. Basic solutions of OBr^- are stable at 0 °C but rapidly disproportionate to Br^- and BrO_3^- at temperatures of about 50 °C and above (Cotton & Wilkinson, 1962).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Bromide is commonly found in nature along with sodium chloride, owing to their similar physical and chemical properties, but in smaller quantities. Bromide concentrations in seawater are generally in the range of 65 mg/l to well over 80 mg/l in some confined sea areas; chloride, on the other hand, is present at concentrations ranging from 18 980 mg/l to over 23 000 mg/l (Al-Mutaz, 2000). Concentrations of bromide in fresh water typically range from trace amounts to about 0.5 mg/l. Concentrations of bromide in desalinated waters may approach 1 mg/l.

The typical daily dietary intake of bromide in the United States of America is 2–8 mg (Nielsen & Dunn, 2009) from grains, nuts and fish. The average bromide intake from dietary sources in the Netherlands is reported as 8.4–9.4 mg/day (EMEA, 1997). The intake of bromide from food would be lower in bottle-fed infants.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Bromide and chloride are always present in body fluids in animals in steady state at levels dependent upon intake, and both are excreted readily. Increased chloride intake will increase the excretion of bromide. Reported example levels of bromide in blood plasma in rats on a laboratory chow diet were 0.55 ± 0.46 mmol/l (~43.5 mg/l); in humans, blood plasma levels of 0.08 ± 0.01 mmol/l (~6.4 mg/l) were reported.

4. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute toxicity

The acute toxicity of bromide to mice and rats is summarized in Table 1. Bromide shows very low acute toxicity upon oral administration.

Table 1. Acute toxicity of bromide

Species	Route	LD_{50} (mg/kg body weight)	Reference
Mouse	Oral	5020	Vose, Haskell & Gartenberg (1961)
Mouse	Oral	7000	Groff, Tripod & Meyer (1955)
Rat	Oral	3500	Smith & Hambourger (1925)

LD_{50}, median lethal dose

4.2 Short-term toxicity

In a range-finding study, five groups of four female Wistar rats received sodium bromide (purity 99.5%) at 0, 300, 1200, 4800 or 19 200 mg/kg diet for 4 weeks. High dose level rats did not groom themselves sufficiently and showed lack of motor coordination in their hind legs. No clear influence on growth, food or water intake was observed. There was a dose-related replacement of chloride in plasma and organs by bromide. The plasma bromide concentration reached a plateau by the third week of treatment. Compound-related histopathological changes were not observed (van Logten et al., 1973a, 1973b).

In another range-finding study, groups of five male and five female Wistar rats received sodium bromide at 0, 75, 300, 1200, 4800 or 19 200 mg/kg in a low-chloride diet (by leaving out sodium chloride and potassium chloride, but adding 1% potassium sulfate) for 4 weeks. The chloride content was about 3 g/kg diet, whereas the normal diet contained 11 g/kg. All high dose level rats and three male and two female rats at 4800 mg/kg diet died within 12 and 22 days, respectively. Food intake and growth were significantly decreased at 4800 and 19 200 mg/kg diet. Kidney weight was significantly increased in males in all dose groups (Kroes et al., 1974).

4.3 Subchronic toxicity

Groups of Wistar-SPF rats (10 animals per sex per group) were fed low-chloride diets containing chloride at 0.4–0.7 g/kg and 1% potassium sulfate for 90 days and dosed with sodium bromide (purity 99.5%) at 0, 8, 31, 125, 500 or 2000 mg/kg diet. Observations included body weight, food intake, clinical chemical determinations in blood, urine and liver, bromide and total halide levels in plasma and several organs, organ weights and histopathology. In the highest dose group, three male and three female rats died during the experiment. At the same dose, grooming was depressed, motor incoordination of the hind legs was observed and weight gain was significantly decreased. The percentage and total number of neutrophilic granulocytes and the total leukocyte count were increased at the highest dose. Corticosterone in blood was lower at the two highest dose levels (significantly at 2000 mg/kg diet). At 2000 mg/kg diet, the relative weights of heart, brain, spleen, adrenals, thyroid and pituitary gland were increased in males, whereas the relative prostate weight was decreased. In high dose level females, relative heart and brain weights were increased, and relative pituitary and uterus weights were decreased. Activation of the thyroid, absence of

nephrocalcinosis in female rats, less vacuolization in the zona fasciculata of the adrenals and less zymogen granulae in the pancreas were observed at the two highest doses. In the highest dose groups, fewer corpora lutea, retardation in maturation of the uterus, inhibition of spermatogenesis and less secretory activity of the salivary glands were observed (van Logten et al., 1976; Rauws et al., 1977).

The toxicity of sodium bromide in rats on a low-chloride diet is about 10 times higher than the toxicity in rats on a normal diet. The highest dose in the low-chloride study (2000 mg/kg diet) is more toxic than the highest dose (19 200 mg/kg diet) in the study for rats on a normal diet (mortality: 6/20 and 1/20, respectively).

Male Wistar rats (10 animals per group per period) were fed diets containing sodium bromide (purity 99.5%) at 0, 20, 75, 300 or 1200 mg/kg feed for 4 or 12 weeks. An additional experiment was carried out using the same protocol with sodium bromide at 0 and 19 200 mg/kg feed. Significantly decreased body weight was observed at 19 200 mg/kg feed after 4 and 12 weeks. Relative thyroid weight was significantly increased at 1200 mg/kg diet after 4 weeks and at 19 200 mg/kg diet after both 4 and 12 weeks. Activation of the thyroid gland and decreased spermatogenesis in the testes were observed microscopically in the highest dose group after 4 and 12 weeks. Thyroxine levels were significantly decreased at 1200 and 19 200 mg/kg diet after 4 weeks and at the highest dose after 12 weeks. Thyroid stimulating hormone (TSH) levels were significantly increased at the highest dose after both 4 and 12 weeks (Loeber, Franken & van Leeuwen, 1983; van Leeuwen, Loeber & Franken, 1983).

A no-observed-adverse-effect level (NOAEL) for sodium bromide of 300 mg/kg diet (equivalent to 240 mg/kg diet as bromide; 12 mg/kg body weight per day) for effects on the thyroid was determined (FAO/WHO, 1989).

4.4 Reproductive toxicity

In a three-generation reproduction study (two litters per generation), groups of Wistar rats (10 males and 20 females per group) were fed a diet containing sodium bromide at 0, 75, 300, 1200, 4800 or 19 200 mg/kg. Observations included behaviour, growth, food and water consumption, leukocyte count and differentiation, triiodothyronine and thyroxine levels in serum, bromide levels in blood and thyroid, litter size and weight, reproduction parameters, such as fertility, viability and lactation index, organ weights and macroscopic examination. Complete infertility was observed at the highest dose, and fertility and the viability of the offspring were significantly reduced at 4800 mg/kg diet. No treatment-related effects were observed in reproductive performance, viability or body weight of the offspring in the second and third generations bred only from the groups dosed at up to and including 1200 mg/kg diet. Body and organ weight determinations did not reveal a clear pattern of dose-related effects in the successive generations. Only relative adrenal weight was significantly reduced in F_0 females at 4800 and 1200 mg/kg feed. To investigate the reversibility of the observed effects, an additional litter was bred with parent animals fed a diet containing sodium bromide at 19 200 mg/kg for 7 months followed by a control diet for 3 months before mating. No differences were observed in breeding results between control and exposed rats (van Logten et al., 1979; van Leeuwen, den Tonkelaar & van Logten, 1983).

4.5 Mutagenicity

Sodium and ammonium bromide were studied in an Ames test with *Salmonella typhimurium* strains TA98 and TA100. At dose levels of 0.001–10 mg/plate, both with and without metabolic activation, no mutagenic effect was observed (Voogd, 1988).

5. EFFECTS ON HUMANS

Bromide was once used as an anticonvulsant and sedative at doses as high as 6 g/day. Clinical symptoms of bromide intoxication have been reported from its medicinal uses. Large doses of bromide cause nausea and vomiting, abdominal pain, coma and paralysis. Doses of bromide giving plasma levels of 12 mmol/l (96 mg/l plasma) produce bromism (the chronic state of bromide intoxication), and plasma levels greater than 40 mmol/l (320 mg/l plasma) are sometimes fatal (EMEA, 1997). The signs and symptoms of bromism relate to the nervous system, skin, glandular secretions and gastrointestinal tract (van Leeuwen & Sangster, 1988).

Sodium bromide at 1 mg/kg body weight per day (as bromide) was administered orally to 20 healthy volunteers (10 females not using oral contraceptives and not pregnant and 10 males) for 8 weeks. In the females, bromide was administered during two full menstrual cycles. There were no differences observed in physical examinations before and after the exposures; haematological, biochemical and urine parameters did not change. Plasma bromide concentrations rose in females and males from 0.08 ± 0.01 mmol/l to 0.97 ± 0.18 mmol/l and from 0.08 ± 0.01 mmol/l to 0.83 ± 0.09 mmol/l, respectively. No changes were observed in the serum concentrations of thyroxine, free thyroxine, thyroxine-binding globulin, triiodothyronine, cortisol, testosterone, estradiol or progesterone. There were also no changes in the serum concentrations of TSH, prolactin, luteinizing hormone (LH) and follicle stimulating hormone (FSH) measured before as well as 20 and 60 min after the administration of thyrotropin releasing hormone (TRH) and LH releasing hormone (LHRH) (Sangster et al., 1981, 1982a).

In another study, healthy volunteers were repeatedly given sodium bromide at oral bromide doses of 0, 4 or 9 mg/kg body weight per day in a double-blind study. Groups of seven males received the treatment for 12 weeks, and groups of seven non-pregnant females (not using oral contraceptives) received it over three full estrous cycles. At the beginning and end of the study, a full medical history, the results of physical examination, haematological studies and standard clinical chemistry and urine analyses were recorded for each subject. Except for incidental nausea, no changes were observed. Mean plasma bromide concentrations at the end of treatment were 0.07, 2.14 and 4.30 mmol/l for males and 0.07, 3.05 and 4.93 mmol/l for females of the 0, 4 and 9 mg/kg body weight per day bromide dose groups, respectively. Only in the females receiving bromide at 9 mg/kg body weight per day was there a significant increase in serum thyroxine and triiodothyronine at the end compared with pre-administration values, but all concentrations remained within normal limits. No changes were observed in serum concentrations of free thyroxine, thyroxine-binding globulin, cortisol, estradiol, progesterone or testosterone, or of thyrotropin, prolactin, LH and FSH before or after the administration of TRH and LHRH. Analysis of neurophysiological data (electroencephalogram [EEG] and visual evoked response)

showed shifts in the power of various spectral bands and a shift in mean frequency in the groups on bromide at 9 mg/kg body weight per day, but all values were within normal limits (Sangster et al., 1982b, 1983). A limited replication study did not show effects on the thyroid or on the central nervous system. Analysis of the EEGs showed only a marginal effect in females receiving bromide at 9 mg/kg body weight per day (Sangster et al., 1986).

6. RECOMMENDATION

Bromide ion has a low degree of toxicity; thus, bromide is not of toxicological concern in nutrition. Limited findings suggest that bromide may be nutritionally beneficial; for example, insomnia exhibited by some haemodialysis patients has been associated with bromide deficiency (Nielsen & Dunn, 2009).

Inorganic bromide was evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1966, which recommended an acceptable daily intake (ADI) for humans of 0–1 mg/kg body weight, based on a minimum pharmacologically effective dosage in humans of about 900 mg of potassium bromide, equivalent to 600 mg of bromide ion. The JMPR ADI of 0–1 mg/kg body weight was reaffirmed with new data in 1988.

EMEA (1997) noted that JMPR took account of the Sangster et al. (1986) human study, but that at the time of the JMPR evaluation (FAO/WHO, 1989), the study was provisional and in need of confirmation. Since the JMPR evaluation, this result has been confirmed in a second human study. A conservative no-observed-effect level (NOEL) (for marginal effect within normal limits of EEGs in females at 9 mg/kg body weight per day) of 4 mg/kg body weight per day (Sangster et al., 1986) suggests an ADI of 0.4 mg/kg body weight (EMEA, 1997), including a safety factor of 10 for population diversity.

The ADI of 0.4 mg/kg body weight yields an acceptable total daily intake of 24 mg/person for a 60 kg person. Assuming a relative source contribution of 50%, the drinking-water value for a 60 kg adult consuming 2 litres/day would be up to 6 mg/l; for a 10 kg child consuming 1 litre/day, the value would be up to 2 mg/l. However, the dietary bromide contribution for a 10 kg child would probably be less than that for an adult. These are reasonably conservative values, and they are unlikely to be encountered in drinking-water supplies.

Bromide can be involved in the reaction between chlorine and naturally occurring organic matter in drinking-water, forming brominated and mixed chloro-bromo by-products, such as trihalomethanes or halogenated acetic acids, or it can react with ozone to form bromate. The levels of bromide that can result in the formation of these substances are well below the health-based values suggested above. This guidance applies specifically to inorganic bromide ion and not to bromate or organohalogen compounds, for which individual health-based guideline values have been developed.

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