

Bromide

Bromide (Br^-) is the anion of the element bromine (Br_2), 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 atom % ^{79}Br and 49.43 atom % ^{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 HBr , and 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 at about 50°C and above (Cotton & Wilkinson, 1962). Bromide is commonly found in nature in smaller quantities along with sodium chloride owing to their similar physical and chemical properties. Bromide concentrations in seawater are generally in the range of 65 mg/l to well over 80 mg/l in some confined sea areas, compared with chloride, which is present at 18 980 mg/l to over 23 000 mg/l (Al-Mutaz, 2000). Freshwater concentrations range typically from a trace to about 0.5 mg/l.

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 blood plasma levels in rats on a lab chow diet were 0.55 ± 0.46 mmol/l (~ 43.5 mg/l), and in humans, 0.08 ± 0.01 mmol/l (~ 6.4 mg/l) in some studies.

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 of plasma) produce bromism, and plasma levels greater than 40 mmol/l (320 mg/l of plasma) are sometimes fatal (EMEA, 1997). The signs and symptoms relate to the nervous system, skin, glandular secretions and gastrointestinal tract (van Leeuwen & Sangster, 1988).

The following summaries are derived from JMPR (1988), with exceptions.

Acute toxicity

The acute toxicity 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 bw)	Reference
Mouse	Oral	5020	Vose et al. (1961)
Mouse	Oral	7000	Groff et al. (1955)
Rat	Oral	3500	Smith et al. (1925)

Short-term toxicity

In a range-finding study, five groups of four female Wistar rats received NaBr (purity 99.5%) at 0, 300, 1200, 4800 or 19 200 mg/kg 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. Plasma bromide concentration plateaued by the 3rd 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 NaBr doses of 0, 75, 300, 1200, 4800 or 19 200 mg/kg in a low chloride diet (by leaving out NaCl and KCl, but adding 1% potassium sulfate) for 4 weeks. The chloride content was about 3 g/kg, whereas the normal diet contained 11 g/kg. All high dose level rats and three male and two female rats at 4800 ppm died within 12 and 22 days, respectively. Food intake and growth were significantly decreased at 4800 and 19 200 ppm. Kidney weight was significantly increased in males at all dose groups (Kroes et al., 1974).

Subchronic toxicity

Groups of Wistar-SPF rats (10 animals per sex per group) were fed low-chloride diets containing 0.4–0.7 g Cl⁻ and 1% potassium sulfate/kg for 90 days and dosed with 0, 8, 31, 125, 500 or 2000 mg/kg NaBr (purity 99.5%). Observations included body weight, food intake, clinical chemical determinations in blood, urine and liver, bromide and total halide 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 2000 mg NaBr/kg, grooming was depressed, motor incoordination of the hind legs was observed and weight gain was significantly decreased. 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). At 2000 mg/kg, 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 in 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 NaBr in rats on a low-chloride diet is about 10 times higher than the toxicity for rats on a normal diet. The highest dose in the low-chloride study (2000 mg/kg) is more toxic than the highest dose (19 200 mg/kg) in the study for rats on a normal diet (mortality: 6/20 and 1/20, respectively).

Reproduction

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 0, 75, 300, 1200, 4800 or 19 200 mg NaBr/kg. Observations included behaviour, growth, food and water

consumption, leukocyte count and differentiation, triiodothyronine and thyroxine levels in serum, bromide 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. No treatment-related effects were observed in reproductive performance, viability and 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.

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 F₀ females at 4800 and 1200 mg/kg food. To investigate the reversibility of the observed effects, an additional litter was bred with parent animals fed a diet containing 19 200 mg NaBr/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 et al., 1983a). A no-effect level for bromide ion of 240 mg/kg diet was determined.

Mutagenicity

Sodium and ammonium bromide were studied in an Ames test with *Salmonella typhimurium* strains TA-98 and TA-100. At dose levels of 0.001–10 mg/plate, both with and without metabolic activation, no mutagenic effect was observed (Voogd, 1988).

Human studies

Sodium bromide at 1 mg Br⁻/kg bw per day was administered orally to 20 healthy volunteers (10 females not using oral contraceptives and not pregnant and 10 males) during 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 thyroid-stimulating hormone (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 in oral doses of 0, 4 or 9 mg Br/kg bw 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) over three full estrus 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 Br/kg bw per day groups, respectively. Only in the females receiving 9 mg Br/kg bw 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 thyrotropin-releasing hormone 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 9 mg Br⁻/kg bw 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 9 mg Br/kg bw per day (Sangster et al., 1986).

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 0–1.0 mg/kg bw, based on a minimum pharmacologically effective dosage in humans of about 900 mg of KBr, equivalent to 600 mg of bromide ion. Although some effects were observed, no adverse effects were observed in the 12 week humans studies at up to 9 mg/kg bw per day.

Recommendation

The JMPR ADI of 0–1 mg/kg bw for bromide was set in 1966 and reaffirmed with new data in 1988. The typical daily dietary intake of bromide in the United States is 2–8 mg (Nielsen & Dunn, 2008) from grains, nuts and fish; the average bromide intake in the United Kingdom is reported as 8.4 mg/day. The intake of bromide from food would be smaller in bottle-fed infants. Bromide ion has a low degree of toxicity; thus, bromine 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. A conservative no-observed-effect level (NOEL) (for marginal effect within normal limits of EEGs in females at 9 mg/l) of 4 mg/kg bw per day gives an ADI of 0.4 mg/kg bw per day (EMEA, 1997; Sangster et al., 1986), including a safety factor of 10 for population diversity. This yields an acceptable total daily intake of 24 mg/person per day, or a drinking-water equivalent value of 12 mg/l. 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. These values apply specifically to inorganic bromide ion and not to organobromine compounds, which have individual guideline values.

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