



Bromine

Toxicological Overview

Key Points

Kinetics and metabolism

- Bromine is rapidly absorbed by the lungs.
- Ingestion of liquid bromine results in rapid and complete absorption from the intestine.
- Bromine is distributed widely into tissues. Majority of bromine is distributed into the extracellular fluid of the body.
- Bromine is not metabolised by the body.

Health effects of acute exposure

- The major route of exposure is by inhalation.
- Acute inhalation exposure to bromine vapour may cause upper respiratory effects, cough, headache, CNS effects and lacrimation.
- Acute oral exposure to bromine results in central nervous system effects.
- Deep partial skin loss and skin discolouration have been reported following acute dermal exposure to bromine.
- Ocular exposure to bromine causes lacrimation, photophobia and blepharospasm.

Health effects of chronic exposure

- Inhalation exposure to bromine vapour causes disturbances of the respiratory, nervous and endocrine systems.
- Chronic oral exposure to liquid bromine results in dermal effects, changes in conditioned reflexes and blood indexes.

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Summary of Health Effects

Following acute inhalation exposure to bromine in humans, irritation of the eyes, nose and throat and lacrimation of the eyes may occur in a concentration-dependent manner [1]. Exposure to lower doses may result in irritation of the eyes, nose and throat, while exposure to higher doses may result in upper respiratory symptoms, cough and headache. These effects are likely to last for up to 3 days. Some individuals may experience gastrointestinal effects, which may include diarrhoea, nausea, vomiting and abdominal pain [2].

Following acute inhalation exposure to low levels of bromine, irritation of the upper respiratory tract was the most observed effect in experimental animals. At high levels of bromine exposure disturbances to central nervous system (CNS) function was noted [1-3].

Acute oral exposure to high doses of bromine in humans may result in adverse effects in the kidneys [2]. However, in the majority of cases, except for a rise in blood plasma levels, no other effects were observed [4, 5].

Bromine is of low acute oral toxicity in experimental animals [4, 5].

Acute dermal exposure to bromine in humans results in a cooling sensation on the skin followed by deep partial skin loss injuries and skin discolouration [1]. Acute ocular exposure to bromine may result in lacrimation at low doses and, at higher doses photophobia and blepharospasm may occur [6]. Acute dermal exposure to bromine may cause irritation of the skin and, may be highly corrosive and cause severe burns [5].

No data could be located on the human health effects following chronic inhalation, dermal or ocular exposure to bromine.

In experimental animals chronic inhalation exposure to bromine results in disturbances of the respiratory, nervous and endocrine systems [5].

Chronic oral exposure to bromine results in the replacement of 50% of the chloride in plasma, brain, kidneys and liver in experimental rats [4]. Other effects of chronic ingestion of bromine at high doses include decreased body weight gain and decreased thymus weight in males and females, respectively. Increases in thyroid weight were observed in females at high doses. Decreased grooming, motor in-coordination of the hind limbs and effects on the gonadotropic hormones were seen in rats.

Liquid bromine is mutagenic in the Ames test employing *Salmonella typhimurium* [7]. No other data could be located on the genotoxicity of bromine.

Bromine is not listed as a carcinogen by the International Agency for Research on Cancer (IARC) [8].

Kinetics and Metabolism

Bromine is a gas and, therefore, inhalation exposure is the most relevant route of exposure to humans [6]. Other routes of exposure are minimal.

Following inhalation, bromine is absorbed by the lungs and the physical characteristics of bromine determine the depth and site of penetration into the lung tissue and therefore the rate of absorption. Bromine deposition in the lungs is primarily determined by the water solubility of bromine. Bromine is relatively more water soluble than chlorine and thus tends to produce effects on the upper respiratory tract. However, inhalation of high concentrations, e.g. in confined spaces, may also cause marked irritant effects on the lower airways [6].

No data could be located regarding the absorption of bromine vapours via the ocular or dermal routes of exposure.

Following ingestion, bromine liquid is rapidly and completely absorbed from the intestine by passive, paracellular transport. Bromine crosses blood cell membranes in an electrically neutral form [1].

Bromine is distributed widely into various tissues and mainly into the extracellular fluid of the body [1].

There are no data regarding the metabolism of inhaled bromine, however bromine has been known to quickly form bromide in living tissue [6]. Bromide is partitioned in the body similarly to chloride and acts by replacing chloride. Bromide ion is a CNS depressant and its adverse effects are as a result of overdoses, however due to the extreme irritant nature of bromine, the duration of exposure is generally severely limited, reducing any likely body burden of bromide [1].

No data could be located regarding the biological half-life of inhaled bromine. The biological half-life of ingested bromine has been reported to be between 12 and 30 days in humans [6]. The biological half-life in rats is markedly shorter, being approximately 3 days.

Bromine reacts with water resulting in the formation of hydrobromous acid, which slowly decomposes to hydrogen bromide and O₂ [7]. The mechanism of action of bromine is by liberation of nascent oxygen or oxygen free radicals from the water present in mucous membranes. It is the nascent oxygen, a potent oxidiser, which is responsible for bromine-induced tissue damage [2, 6].

No data could be located regarding the excretion of bromine from the body.

Sources and Route of Human Exposure

Bromine is a halogen element found naturally occurring in the earth's crust and seawater in various chemical forms [6].

Exposure to bromine usually occurs as a result of accidental spill or leak during transportation or manufacturing. One of the major routes of exposure in humans is through inhalation of bromine vapour, with other routes of exposure being minimal [6].

Exposure to bromine may occur via inhalation, oral, dermal or ocular routes [6]. Bromine is a gas and therefore, inhalation exposure is the most relevant route to humans.

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A small number of the population may also be exposed to bromine through their occupation in industry involved in the manufacture and use of bromine [9].

In the UK, the long-term exposure limit (LTEL) for bromine is 0.66 mg/m³ (8-hour time weighted average (TWA) exposure reference period). The short-term exposure limit (STEL) is 1.3 mg/m³ (15-minute reference period) [10]. In the EU, the Scientific Committee on Occupational Exposure Limits (SCOEL) has set an Indicative Occupational Exposure Limit Value (IOEL) of 0.7 mg/m³ [11].

In the UK, the Expert Panel on Air Quality Standards has recommended that a concentration of bromine gas or mass equivalent to aerosol not exceeding 0.07 mg/m³ (equivalent to 0.01 ppm) over a 1-hour averaging period should protect against irritant and inflammatory responses to the skin, eyes and breathing airways [12].

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has set a Tolerable Daily Intake (TDI) of 1 mg/kg bw/day [13]. This TDI was based on a short-term toxicity study in rats and a human study [4].

Health Effects of Acute / Single Exposure

Human Data

Inhalation

Initial irritant symptoms of inhalation of bromine vapour include shortage of breath, cough, choking and wheezing, bronchoconstriction, inflammation of the oesophagus, and laryngeal spasm. Such respiratory distress can lead to hypoxaemia, metabolic acidosis and death [12].

Low concentrations of bromine vapour have also caused inflammation of the eyelids, lacrimation, nosebleeds, a feeling of oppression, dizziness and headache [7]. Inhalation may also cause gastrointestinal effects including diarrhoea, nausea, vomiting and abdominal pain, and dermal effects such as a measles-like eruption on the trunk and extremities and dermatitis [2, 7].

Inhalation of high concentrations of bromine vapour have resulted in brown colouration of the eyes, tongue, and mucous membranes of the mouth as well as catarrh, salivation, coughing, feeling of suffocation, glottis cramps, hoarseness, bronchitis and bronchial asthma [7]

A worker was exposed to bromine vapour (unknown concentration) during an industrial incident. Bromine burns to 20% of the body, extensive pulmonary and tracheal damage, and effects on the kidneys and liver were found at autopsy. In a separate incident, several workers were exposed to bromine vapour (unknown concentration) and developed bronchopneumonia, one developed blepharospasm, and the remainder developed laryngitis. One worker died as a result of circulatory failure associated with bronchopneumonia [7].

Table 1 – Calculated LC_{50S} for humans exposed to bromine vapour [7].

| Population | 10-minute LC ₅₀ | | 30-minute LC ₅₀ | |
|--------------------------------|----------------------------|-----|----------------------------|-----|
| | mg/m ³ | ppm | mg/m ³ | ppm |
| Regular | 2124 | 325 | 2451 | 375 |
| Vulnerable | 850 | 130 | 980 | 150 |
| Average (regular + vulnerable) | 1359 | 208 | 2059 | 315 |

A group of healthy volunteers were exposed to bromine concentrations of 0.07-6.7 mg/m³ (0.01-1.0 ppm) for 0.5 h. A concentration-dependent increase in the number affected and severity of irritation was observed in the subjects. Bromine caused irritation of the eyes, nose and throat at a concentration of 1.3 mg/m³ (0.2 ppm), while levels of 3.3 mg/m³ (0.5 ppm) and above were not tolerable. The most common symptoms of exposure to bromine at concentrations of 1.3-3.3 mg/m³ (0.2-0.5 ppm) for 4 hours were upper respiratory symptoms, cough and headache, with symptoms lasting for up to 3 days in some individuals [1, 12].

Exposure to high levels of bromine vapour (actual concentration unknown) generated from a widely used water disinfectant employed in hot tubs was implicated in the development of reactive airways dysfunction syndrome in two exposed patients [1]. No further details were available. Table 2 outlines the health effects in humans following exposure to bromine vapour.

Table 2 - Human health effects of bromine vapour at various concentrations [6].

| Bromine | | Effects |
|-------------------|-----------|--|
| Mg/m ³ | ppm | |
| 0.04 | 0.006 | Irritation to eyes |
| 1.3 – 3.3 | 0.2 – 0.5 | Irritation to eyes, nose and throat; cough, headache |
| >3.33 | >0.5 | Intolerable |
| 261 - 392 | 40 - 60 | Toxic pneumonitis & pulmonary oedema |
| 6536 | 1000 | Fatal within a few minutes |

Ingestion

Haemorrhagic nephritis, with oliguria or anuria, may develop within 1 to 2 days following ingestion of liquid bromine (concentration not stated) [2]. No further data were available.

Dermal / ocular exposure

The initial effect of dermal exposure to bromine is a cooling sensation on the skin. Signs of dermal exposure to bromine are deep partial skin loss injuries and skin discolouration [1].

Exposure to bromine vapour at 3 mg/m³ (0.5 ppm) has been reported to cause a stinging and burning sensation of the conjunctiva [7].

Irritation of the eye, with lacrimation were seen following exposure to low levels of bromine and at higher levels (concentrations not stated) photophobia and blepharospasm were observed [6].

Delayed effects following an acute exposure

A feature of dermal exposure to bromine is the delay in the appearance of injury [1]. The delayed effects include upper respiratory effects as well as dermal effects, since bromine vapour is capable of causing skin lesions/blisters.

Animal and In-Vitro Data

Inhalation

An LC₅₀ of 1569 mg/m³ (240 ppm) has been reported in mice (strain and sex not specified) exposed to bromine for 2 hours [2].

Rats (strain and sex not specified) were exposed to 0.8-503 mg/m³ (approximately 0.12-77 ppm) bromine vapour for 4 hours. Decreased respiratory frequency was noted at a concentration of 10 mg/m³ (1.5 ppm). Olfactory sharpness was decreased and the number of 'free cells' in the upper respiratory pathways was increased. At a concentration of 50

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mg/m³ (8 ppm) respiratory, cardiac, vascular, neural and endocrine systems were affected. Spermatogenesis was affected at 100 mg/m³ (15 ppm) [7].

Inhalation LC_{50s} of 2.7 mg/l (equivalent to 17.65 mg/m³ or 2.7 ppm) for an unspecified exposure time has been reported in rats (strain and sex not specified). In mice (strain and sex not specified), LC_{50s} of 4902 mg/m³ (750 ppm) and 1569-4902 mg/m³ (240-750 ppm) for 9 and 270 minutes, respectively, have been reported [5].

Mice exposed via inhalation to bromine concentrations of >147 mg/m³ resulted in mortality. The majority of animals died within the first 4 days and the remainder died between 8 and 10 days when exposed to 1158 mg/m³ (174 ppm). Death was caused by either bronchospasm or oedema of the lungs and by peribronchitis, with abscess formation. Exposure to bromine at 33 and 67 mg/m³ (5 and 10 ppm) for 8 hours/day for 3 days did not cause mortality, but body weights were decreased, thought to be due to irritation of the upper respiratory tract. A Lowest Observed Adverse Effect Level (LOAEL) of 147 mg/m³ (5 ppm) was identified from this study [1].

Cats, rabbits and guinea pigs (strain and sex not specified) exposed to 150 mg/m³ (approximately 23 ppm) bromine for 7 hours provoked a slight irritation of the respiratory tract, while 1176 mg/m³ (180 ppm) caused CNS function disturbances [2, 3]. A LOAEL of 150 mg/m³ was identified.

Ingestion

Oral LD_{50s} of 2600-3500 mg/kg bw/day in rats; 3100-7000 mg/kg bw/day in mice, 4160 mg/kg bw/day in rabbits and 5500 mg/kg bw/day in guinea pigs have been reported [4, 5]. Strain and sex of animals were not specified for these studies.

Oral Lowest Lethal Concentrations (LCLo) have been reported as 5.4 mg/kg bw/day for 6.5 hours, 7 mg/kg bw/day for 7 hours and 5.6 mg/kg bw/day for 7 hours in rabbits, cats and guinea pigs, respectively [5].

Dermal / ocular exposure

Bromine is a skin irritant in rats, no further information was available. It is also reported to be highly corrosive to the skin and causes severe burns, no further information available [5].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

No data could be located regarding effects in humans following chronic inhalation exposure to bromine.

Ingestion

No data could be located regarding effects in humans following chronic oral exposure to bromine.

Dermal / ocular exposure

No data could be located regarding dermal/ocular effects in humans following chronic exposure to bromine.

Genotoxicity

No data could be located regarding genotoxicity in humans following chronic exposure to bromine.

Carcinogenicity

Bromine is not listed as a carcinogen by the International Agency for Research on Cancer (IARC) [8]. No data are available to assess the carcinogenicity of bromine in humans.

Reproductive and developmental toxicity

No data could be located regarding reproductive and developmental effects in humans following exposure to bromine.

Animal and In-Vitro Data

Inhalation

Rats (strain and sex not specified) were exposed continually to bromine vapour via inhalation for 4 months at a dose of 12.4 mg/m³ (1.9 ppm). Disturbances of the respiratory, nervous and endocrine systems were observed in the animals [5].

Rats, mice and rabbits (strain and sex not specified) were exposed via inhalation to bromine vapour continually for 4 months at doses of 0.13-1.31 mg/m³ (approximately 0.02-0.2 ppm). At the highest dose, animals developed disturbances in respiratory, nervous and endocrine functions. No adverse effects were observed at the lowest dose employed. A no observed adverse effect level (NOAEL) of 0.13 mg/m³ could be identified from this study [5].

Ingestion

Rats (strain and sex not specified) were fed liquid bromine at 20 mg/kg bw/day in a 28 day feeding study. Clinical signs of salivation and decreased activity were observed, with

increased red blood cell count, haemoglobin and packed cell volume, increased serum glucose and increased urinary volume with protein also being reported [7].

Rats (strain and sex not specified) received oral 0.01 mg/kg bw continually for 6 months. Changes in conditioned reflexes and several blood indexes were observed in the animals. No further details about this study were available [5].

Genotoxicity

Liquid bromine was mutagenic in the Ames test employing *Salmonella typhimurium* strains TA1537 and TA100 in the absence of a metabolic activation system, and with TA1537 in the presence of a metabolic activation system [7].

Carcinogenicity

Male and female Fischer 344 rats were fed bromine in their diet continually for 2 years at doses of 0, 80, 200 and 500 mg/kg bw (equivalent to 0, 80, 200 or 500 ppm). The No Observed Effect Level (NOEL) in this study was stated to be 6.77 mg/kg bw/day (200 ppm) in males and the maximum NOEL could not be determined for females [5].

There was no evidence to suggest that bromine was carcinogenic in experimental animals [5].

Reproductive and developmental toxicity

No data could be located regarding reproductive and developmental effects of bromine in experimental animals.

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