METHYL BROMIDE

Identity

Name (parent)	Methyl bromide
UN number	1062
CAS number	74-83-9
Intervention value (AGW in mg/m^3)	200
Structure	CH_3Br

Occurrence

Chemical state (at 20°C)	Gas
Physical appearances	Colorless gas
Industrial products	Methyl bromide is used to fight pests, e.g. rats, insects, fungus and is used for production of brominated chemicals

Physicochemical properties

Molecular weight	95.0
Vapor pressure (mbar at 20°C)	1900
Octanol/water partition coefficient (log Po/w)	1.19 [1]
Water solubility (in g/100mL at 20 °C)	1.5

Toxicokinetics (parent)

Uptake by inhalation	In rats, approximately 50% is absorbed at low concentrations (50 – 300 nmol/L). At higher concentrations 37% (5700 nmol/L) and 27% (10400 nmol/L) were absorbed [2].
Uptake by skin absorption	In humans accidental reports indicate skin absorption [3]. In rats a rapid increase in the concentration of plasma bromide ion was observed in upon topical treatment [4].
Uptake via gastrointestinal tract	Rats given [^{14}C]–methyl bromide in corn oil absorbed nearly all methyl bromide, < 3% of radioactivity was excreted in feces [5].
Distribution	After absorption, methyl bromide is distributed throughout the body [6].
Metabolism	Conjugation with glutathione, both non-enzymatic and catalyzed by glutathione-S-transferase to methylglutathion. Methylgluthation is transformed in S-methylcysteine by transpeptidases [7].
Excretion via lungs	In rats 66 h following inhalation exposure <4% of the dose was exhaled 50% as methyl bromide and 50 % as CO_2 [2]. In rats 72 h following oral administration 4 % of the dose was exhaled as methyl bromide and 32% as CO_2 [5]. In rats 72 h following intraperitoneal administration 20% of the dose was exhaled as methyl bromide and 45% as CO_2 [5]
Excretion via urine	In rats 66 h following inhalation exposure 50 % of the dose was excreted in urine [2]. In rats 72 h following oral administration 43 % of the dose was excreted in urine [5]. In rats 72 h following intraperitoneal administration 16% of the dose was excreted in urine [5]. [5]
Excretion via feces	Minor excretion route, independent of route of administration. In rats, 66 h following inhalation exposure or 72 h following oral or intraperitoneal administration <3% of the dose was excreted in feces [2, 5].

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Toxicodynamics

Mechansisms of toxicity	Neurological toxicity, lung injury: edema and hemorrhagic lesions, renal toxicity, irritation of the eyes and skin
Classifications for carcinogenicity	Group 3, IARC [8]
Classifications for reprotoxicity	Exposure of femal rats to dose levels up to 30 mg/kg/day and female rabbits to dose levels up to 10 mg/kg/day, during gestation days 6 to 15, were not fetotoxic or teratogenic to rat and rabbit fetuses. At these levels, maternal toxicity was evident [9]. From a two-generation study in rats it was concluded that total bromine residues in the diet at levels of up to 500 ppm do not affect reproductive performance including viability of offspring in rats [10]. In male animals, effects on the testes (delayed formation of spermatozoa, tubular degeneration, atrophy) have been observed in rats and mice exposed to 160-405 ppm for 1-6 weeks or 120 ppm for 13 weeks, cited in ATSDR [6]
Classifications for sensitizing properties	Not classified

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Biological monitoring

Biomarkers	**S-Methylcysteine adduct in hemoglobin**	**S-methylcysteine albumin adducts**	**Bromide in whole blood**	**Bromide in plasma**	**Bromide in serum**	**Bromide in urine**
Molecular weight	135.18	135.18	79.904	79.904	79.904	79.904
Involved enzymatic metabolism	Glutathion-S-transferase, transpeptidases [7]	Glutathion-S-transferase, transpeptidases [7]	Nucleophilic displacement of the bromide ion [6]	Nucleophilic displacement of the bromide ion [6]	Nucleophilic displacement of the bromide ion [6]	Nucleophilic displacement of the bromide ion [6]
Biological material	Blood	Blood	Blood	Blood	Blood	Urine
Type of sample	Blood	Blood	Blood	Blood	Blood	Morning spot urine
Sampling strategy	Adducts are stable during the lifespan of globin (126 days)	< 1 month	< 1 month	< 1 month	< 1 month	< 1 month
Excretion pattern	Globin adducts are stable during the lifespan of globin, approximately 120 days. [11]	Biological half-life of albumin is 20 days [11]	Half-life of 12 days in healthy people, cited in ATSDR [6].	Biological half-life bromide in humans: 10-12 days [14, 15]	Biological half-life of the bromide-ion is 10 – 12 days [16]	Slow first order process with a half-life ranging from 10.5 to 14 days [17].
Materials	Vacutainer tubes, containing coagulant (e.g. heparin, EDTA)	Vacutainer tubes, containing coagulant (e.g. heparin, EDTA)	Blood collection tube with anticoagulant, e.g EDTA	Blood collection tube with lithium heparin	Hard plastic or glass collection tube without any anticoagulant	nitric acid rinsed high density polyethylene bottles [18]
Transportation	-20°C	-20°C	-20°C	-20°C [19]	-20°C	Cooled (chilled in with gel ice) [18]
Storage	-20°C	-20°C	-20°C [20]	-20°C	-20°C [21]	-30°C [22]
Stability	Not reported	Not reported	Not reported	7 days at -20°C (bromate) [19]	Not reported	Not reported
Pretreatment	Isolation of hemoglobin and Edman degradation	Isolation of albumin		Plasma was treated with acetonitrile to precipitate bulk proteins and lipids. The resulting	1:10 dilution with 2 mmol/L potassium thiocyanate as an internal standard and directly injected [21]; oxidation of bromide to bromine and reaction with phenolsulfon-	Methylation of bromide ion to methyl bromide [18, 22]

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				actetonitrile extract was further concentrated using nitrogen and then diluted in water [19]	phthalein followed by a photometric determination [23]; filter the sample through an 30 000 cut-off membrane ultrafilter-paper [24]; ultra filtration cartridge to remove substances with > 10000 Dalton and centrifuged at 3000 rpm for 5 min [25]	
Measurement principle	HPLC with precolumn fluorescent derivatization [11]; LC/ESMS/SIM [26]	HPLC with precolumn fluorescent derivatization[11]	GC-MS [27]	IC-ICP-MS [19]	Photometric method absorption was measured at 589 nm [23]; capillary electropherograph P/ACE-MDQ with a diode array detector [21]; Ion-chroma-tography (IC) [24] HPLC [25]	ECD-GC [22] ICP-MS [18]
Aliquot for 1 analysis	9 mL [11] 2 mL [26]	9 mL [11]	1 mL	1 mL [19] – 10 mL	400 µL [23]; ≥ 30 µL [21]; 0.5 mL [24]; 150 µL [25]	0.25 mL [28] 1 mL [18]
Limit of quantification	LOD: 200 fmol (HPLC with precolumn fluorescent derivatization) [11] LOD: 2 nmol/ g globin (HPLC-MS-MS) [29]	LOD: 200 fmol [11]	LOD: 1000 µg/L (GC-MS) [27] LOQ: 2000 µg/L (GC-MS) [27]	5 µg/L (method reporting limit) [19] 1 µg/L (instrument detection limit) [19]	LOD: 1000 µg/L (photometry) [23]; 4000 µg/L (capillary electropherograph P/ACE-MDQ) [21]; 20 µg/L (IC) [24]; 5000 µg/L (HPLC) [25] LOQ: 8000 µg/L (capillary electropherograph P/ACE-MDQ) [21]	LOD: 10 µg/ L (ECD-GC) [28] LOD: 100 µg / L (ICP-MS) [18]
Recommended adjustments	Adjustment for globin	Adjustment for globin	n/a	n/a	n/a	Adjustment for specific gravity [22]
Preferred units for expression of results	ng/g globin	ng/g globin	mg/L	µg/L [19]	mmol/L	nmol / mol creatinine
Conversion factor	n/a	n/a	1 µg / L = 1.25 *10^{-2} µmol /L	1 µg / L = 1.25 *10^{-2} µmol /L	1 µg / L = 1.25 *10^{-2} µmol /L	1 µg / L = 1.25 *10^{-2} µmol /L
Biological exposure value US	n/a	n/a	n/a	n/a	n/a	n/a
Biological	n/a	n/a	n/a	n/a	n/a	n/a

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exposure value Germany [30]						
Background level	16.4 nmol / g globin [31]	3.9 +/- 1.9 µmol/l (range 1.4--6.5 µmol/l) [32]	5.3 ± 1.4 mg/L (mean ± SD) (range: 2.5 to 11.7 mg/L) [33]	5 -7 mg/L [19]	4.13 ± 1.05 mg/L (mean serum bromide level ± SD) (Germany, base don a group of 64 healthy and non-occupationally exposed volunteers) [23]	3.9 ± 1.1 mg / g creatinine (average ± SD) (USA, based on 7 controls) [18]
Possible confounders	Occupational exposure to methyl bromide or other industrial products such as 1-bromopropane, 2-bromopropane and ethyl bromide. Fruit and vegetables are sometimes fumigated with methyl bromide.					
Remarks	1. Not specific for methyl bromide exposure: bromide is also formed after exposure to among others 1-bromopropane, 2-bromopropane and ethyl bromide [22]. 2. Half-life of bromide ion in rats is dependent on the chloride status of the rat (Bromide half-lives varied from 2.5 days at high-chloride intake, via 3.5 days at normal dietary chloride intake, to 25 days at low-chloride intake) 3. About 25% of the population in Western countries are so-called “non-conjugators”, i.e., possess little or none of this enzyme which catalyzes the reaction between methyl bromide and glutathione [1]					

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