IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 166

Methyl Bromide

UNEP

under the joint sponsorship of the United Nations Environment Programme, International Labour Organisation, and the World Health Organization

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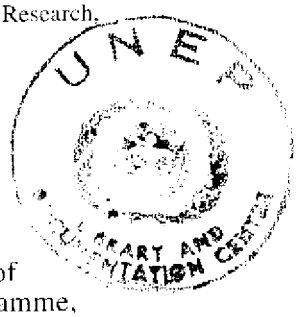
Environmental Health Criteria 166

METHYL BROMIDE

First draft prepared by Dr R.F. Hertel and Dr T. Kielhorn, Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany



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Geneva, 1995

The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria monographs, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

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ENVIRONMENTAL HEALTH CRITERIA FOR METHYL BROMIDE

A WHO Task Group on Environmental Health Criteria for Methyl Bromide met at the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany, from 9 to 13 August 1993. Dr E.M. Smith, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director of the IPCS, and the three IPCS cooperating organizations (UNEP/ILO/WHO). The Group reviewed and revised the draft and made an evaluation of the risks for human health and the environment from exposure to methyl bromide.

The first draft of the EHC on methyl bromide was prepared by Dr R. F. Hertel and Dr J. Kielhorn at the Fraunhofer Institute of Toxicology and Aerosol Research in Hanover, Germany. Dr J. Kielhorn assisted the IPCS Central Unit in the preparation of the second draft, incorporating comments received following circulation of the first draft to the IPCS contact points for Environmental Health Criteria monographs.

Dr E.M. Smith of the IPCS Central Unit was responsible for the scientific content of the monograph and Mrs M.O. Head, Oxford, England, for the editing.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

1. SUMMARY

1.1 Physical and chemical properties, and analytical methods

Methyl bromide is a colourless gas at room temperature and standard pressure with a boiling point of about 4 °C. It is heavier than air and easily liquefied below its critical points. It is odourless, except at high concentrations, when it has a chloroform-like smell. It is non-flammable in air, except in the concentration range of 10-16%, but burns in oxygen. Methyl bromide is slightly soluble in water but freely soluble in other common solvents. It can penetrate through many substances, such as concrete, leather, rubber, and certain plastics.

Methyl bromide hydrolyses to methanol and hydrobromic acid in aqueous solution, the rate of hydrolysis depending on pH. It is an effective methylating agent that reacts with amines and sulfur-containing compounds. Most metals are inert to pure, dry methyl bromide, but surface reactions take place on zinc, tin, aluminium, and magnesium in the presence of impurities or moisture. Explosive reactions with aluminium and with dimethyl sulfoxide have been reported.

Methyl bromide is commercially available as a liquefied gas. Formulations for soil fumigation contain chloropicrin (2%) or amyl acetate (0.3%) as warning agents. Other formulations include up to 70% chloropicrin or other fumigants or hydrocarbons as inert diluents. For commodity fumigation, 100% methyl bromide is used.

Analytical methods are described for the determination of methyl bromide in air, water, soil, food, and animal feed. Direct methods for determining methyl bromide in air, under field conditions, include thermal conductivity gas analysers, colorimetric detector tubes, infra-red analysers, and photo-ionization detectors. Gas chromatography (GC) with electron capture detection (ECD) is recommended for routine measurements with occasional mass spectrometric (MS) confirmation in the laboratory.

Purge and trap techniques as well as headspace sampling are used for the GC determination of methyl bromide in water. Extraction using acetone/water followed by headspace capillary gas

chromatography with ECD is recommended for the routine determination of methyl bromide in foods. As some of the methyl bromide is converted to bromide in soil, foods, and biological materials, methods of bromide determination are also discussed. Colorimetric methods, X-ray spectroscopy, potentiometry, neutron activation analysis, gas chromatography, and high-performance liquid chromatography (HPLC) are some of the methods used for bromide determination in various matrices.

1.2 Sources of human and environmental exposure

Oceans are believed to be the major source of methyl bromide. The main anthropogenic source of methyl bromide is the fumigation of soils and indoor spaces. A small amount of methyl bromide is emitted from motor vehicles using leaded petrol.

The world consumption of methyl bromide was over 67 million kg in 1990, an increase of 46% over 1984. It is commonly produced by the interaction of methanol and hydrobromic acid, and, in some processes, it is a coproduct together with tetrabromobisphenol A. Methyl bromide is usually stored and transported as a liquefied gas, under pressure, in steel containers.

About 77% of the methyl bromide produced is used for soil fumigation, 12% for quarantine and commodity fumigation, 5% for structural fumigation, and 6% for chemical intermediates.

The gas is used as a soil fumigant in either fields or greenhouses for the control of pests. Methyl bromide is applied as a liquid prior to planting, either by injection into the soil, or by using evaporating jars under sheeting and allowing it to vaporize *in situ* (cold method) or by heating (hot method). The methods permitted in various countries differ. The type of plastic sheeting is also important.

Doses of methyl bromide to be applied depend on the legal standards of different countries, the plant parasite to be controlled (type, extent of infestation), the following crop, type of soil, and the plastic cover used (covering time and plastic type). Methyl bromide is usually applied to soil at dosages of between 50 and 100 g/m^2.

In space fumigation, methyl bromide is used for agricultural commodity fumigation (e.g., foods, grains, nuts, etc.), termite control, and rodent control. Dosages of 16-30 g methyl bromide/m^3

are used for most goods stored in sealed rooms and silos and under gas-proof sheets. A period of aeration must follow fumigation. Fumigation is also important for fresh vegetables and fruits where quarantine regulations have to be adhered to.

The industrial uses of methyl bromide include organic synthesis, usually as a methylating agent, and as a low-boiling solvent, e.g., for extracting oils from nuts, seeds, and flowers. The uses of methyl bromide as a refrigerant and as a general fire extinguishing agent are now only of historical importance.

1.3 Environmental transport, distribution, and transformation

Methyl bromide is present naturally in the atmosphere. Anthropogenic sources add to this. Although a small amount of methyl bromide reacts with the hydroxyl radical in the troposphere, some methyl bromide is transferred to the stratosphere by upward diffusion. Here photolysis of methyl bromide becomes of increasing importance, it being the most dominant loss mechanism in the lower stratosphere. Active bromine species react with ozone in the stratosphere and are thought to be partly responsible for the destruction of the ozone layer.

In soil, methyl bromide is partially hydrolysed to bromide ion. After fumigation using methyl bromide, soil can be leached with water to prevent the bromide ions formed being taken up by plants subsequently planted on the sterilized soil. This increase in bromide levels may cause problems when surface water is used for leaching. Methyl bromide may diffuse through polyethylene drinking-water pipes, if the surrounding soil has been fumigated with methyl bromide.

In the soil, methyl bromide can diffuse to a depth of 0.8 m, depending on the soil type, dosage, method of application, and length of fumigation, the highest content of methyl bromide remaining in the upper soil. The transport of the gas is caused by mass flow and molecular diffusion, but it is also influenced by simultaneously occurring sink processes, such as sorption and dissolution, and irreversible sink processes, such as hydrolysis. The amount of methyl bromide converted to bromide depends mainly on the organic matter content of the soil. The bromide produced is largely water

soluble and can be taken up by plants or removed to lower soil levels by leaching with water.

In plants, the amount of bromide accumulated depends on various factors, such as dosage, exposure time, aeration rate, the physical and chemical properties of the soil, the climatic trend (temperature and rainfall), the plant species, and the type of plant tissue. Especially leafy vegetables, such as lettuce and spinach, can take up relatively large amounts of bromide ion without phytotoxic symptoms. In contrast, other crops, such as carnations, citrus seedlings, cotton, celery, peppers, and onions, are particularly sensitive to methyl bromide fumigation.

Methyl bromide and its reaction products, of which only bromide has been considered up to now, can enter the food chain in two ways; through consumption of food grown in greenhouses or fields fumigated before planting, or through eating food fumigated with methyl bromide during storage. At certain levels, bromide may be hazardous for health and tolerance levels are given for bromide in foodstuffs. Levels of other reaction products have not been investigated.

Methyl bromide is degraded in soil by hydrolysis and microbial degradation. The rate constant for hydrolysis varies with temperature and pH and is enhanced by light.

The octanol/water partition coefficient (log P_{ow}) of methyl bromide is 1.19, suggesting a low bioaccumulation.

The methyl bromide that is not degraded during fumigation finds its way into the troposphere and by upward diffusion into the stratosphere. There does not seem to be a significant vertical gradient for methyl bromide in the troposphere, but levels decrease rapidly in the lower stratosphere where photolysis takes place.

1.4 Environmental levels and human exposure

Methyl bromide concentrations, measured in the air in unpopulated areas, range from 40 to 100 ng/m^3 (10 to 26 pptv), readings in the Northern hemisphere being higher than those in the Southern hemisphere. Most readings are in the range of 9-15 pptv. Seasonal differences have been found in some studies. In urban and industrial areas, the levels are much higher, with average values of

up to 800 ng/m^3 and with some readings as high as 4 μg methyl bromide/m^3. In the proximity of fields and greenhouses, during fumigation and aeration, the concentrations of methyl bromide are considerably higher, values of 1-4 mg/m^3 being measured in one study at distances of up to 20 m from a greenhouse, a few hours after injection; a tenth of this value was found 4 days later.

The methyl bromide concentration in a sample of surface seawater has been given as 140 ng/litre. The average value of bromide ion concentrations in samples of coastal water near the North Sea was 18.4 mg/litre; the level of bromide ion in inland rivers was much lower, except in regions where fumigation with methyl bromide was practised, or, in areas of industrial pollution. In drainage water from a Netherlands greenhouse, levels of 9.3 mg methyl bromide/litre and 72 mg bromide ion/litre were reported. In water discharged from a Belgian greenhouse, a value of 280 mg bromide/litre was recorded after fumigation.

The natural bromide content of soil depends on the soil type, but is usually less than 10 mg/kg. The residue of bromide in fumigated soil depends on treatment, dosage, type of soil, amount of rain or leaching water, and temperature.

Levels of methyl bromide or bromide may be elevated in foods that have either grown on soil previously treated with methyl bromide or have been fumigated post-harvest.

On rare occasions, bromide levels in fresh vegetables, grown on soils previously fumigated with methyl bromide, have been observed to exceed the permitted residue level. In some countries, it is not permitted to grow vegetables on treated soils.

Methyl bromide is widely used for fumigating post-harvest commodities, such as wheat and cereals, spices, nuts, dried and fresh fruits, and tobacco. Methyl bromide concentrations usually decrease rapidly after aeration and residues are not detectable after some weeks. Some foods, such as nuts, seeds, and fatty foods like cheese, tend to retain methyl bromide and inorganic bromide.

Individuals may be exposed to the fumigant and residues of bromide ion. There could also be a risk of methyl bromide or increased bromide contents in water in shallow wells near methyl bromide fumigation operations.

People living in close proximity to fields, greenhouses, or stores fumigated with methyl bromide, could be at risk of exposure to the gas. Individuals can also be endangered if they accidentally, or deliberately, enter private houses that have been fumigated to eradicate pests before it is declared safe to do so.

Occupational exposure to methyl bromide is the most probable hazard for operators during production, filling processes, and fumigation operations. Because of strictly applied safety measures in production facilities, only fumigators are now considered a high-risk group. Fumigators engaged in structural fumigation may encounter exposure much higher than the TLV after 24 h aeration (80-2000 mg/m^3). However, properly trained operators will use appropriate protective equipment. Field workers during soil fumigation may be exposed for longer periods of time to transient doses of methyl bromide. Because of the nature of greenhouse fumigation, operators may also encounter higher concentrations (100-1200 mg/m^3). However, risk management developed for various aspects of fumigation requires strict safety procedures and the use of protective equipment. Despite this, individual cases of accidental overexposure still occur.

1.5 Kinetics and metabolism

Inhalation studies on rats, beagles, and humans have shown that methyl bromide is rapidly absorbed through the lungs. It is also rapidly absorbed in rats following oral administration.

After absorption, methyl bromide or metabolites are rapidly distributed to many tissues including the lung, adrenal gland, kidney, liver, nasal turbinates, brain, testis, and adipose tissue. In an inhalation study on rats, the methyl bromide concentration in tissues reached a maximum 1 h after exposure, but decreased rapidly, with no traces 48 h later. The metabolism of inhaled methyl bromide has not yet been elucidated, though glutathione may play a role.

Methylation of proteins and lipids has been observed in the tissues of several species, including humans, exposed via inhalation. Methylated DNA adducts have also been detected following the *in vivo* and *in vitro* exposure of rodents or rodent cells.

In inhalation studies using [^{14}C] labelled methyl bromide, the exhalation of $^{14}CO_2$ was the major route of elimination of ^{14}C. A

lesser amount of ^{14}C was excreted in the urine. Following oral administration of methyl bromide, urinary excretion was the major route of elimination of ^{14}C.

The central nervous system is an important target for methyl bromide. Changes in monoamine, amino acid contents and, possibly, catecholamine contents may be factors involved in methyl bromide-induced neurotoxicity.

1.6 Effects on organisms in the environment

Methyl bromide is used commercially to control nematodes, weeds, and soil-borne fungi that cause diseases, such as damping off, crown rot, root rot, and wilt.

There are few studies on the effects of methyl bromide on aquatic organisms, as methyl bromide itself is only slightly soluble in water. Values for LC_{50} range from a 4-h value of 17 mg/litre for *Cyprinus carpio* L. to a 48-h value of 1.2 mg/litre for *Poecilia reticulata*. At lethal concentrations, damage to the gills and oral epithelia was the probable cause of death.

Bromide ion is formed from methyl bromide after fumigation and is found in water after leaching. Bromide ions showed acute toxicity in various freshwater organisms at concentrations ranging from 44 to 5800 mg Br^-/litre; the no-observed-effect concentration (NOEC) in long-term tests varied from 7.8 to 250 mg Br^-/litre. Bromide ions markedly impaired reproduction in both crustaceans and fish.

As a fumigant, methyl bromide can be applied directly to plant seeds, plant cuttings, or harvested plant products, for disinfestation during transportation and storage. Delay in germination or loss of germinative capacity can occur if the moisture level or temperature is too high.

Some crops, particularly leafy vegetables, are sensitive to methyl bromide fumigation because of excess bromide in the soil, or, indirectly because of effects on soil microflora. Sometimes, methyl bromide has a positive effect on plants, increasing growth and crop yields.

Methyl bromide fumigation eradicates not only target organisms but also part of the soil flora, gastropods, arachnids, and protozoans.

Methyl bromide is often used in preference to other insecticides because of its ability to penetrate quickly and deeply into bulk materials and soils. Dosages for methyl bromide as a storage fumigant range mainly from 16 to 100 g/m^3 for 2-3 days, the dosage depending on temperature. A higher dosage is required to kill eggs and pupae than adult insects. There is a variation in tolerance between different insect species and stages and between different strains of the same insect.

There are no data on the direct effects of methyl bromide on birds and wild mammals.

1.7 Effects on experimental animals

Inhalation studies conducted on various mammalian species have shown that there are clear species-related and sex-related differences in susceptibility to methyl bromide. There was a steep dose-mortality response in all animal species tested.

Neurological manifestations were the major clinical signs of toxicity in rats and mice and, at higher concentrations, irritation of the mucosal membranes was also observed.

Neurological manifestations included twitching and paralysis. At lower dosages, changes in locomotor activity, dysfunction of the peripheral nerve changes in circadian rhythm, and conditioned taste aversion, have been reported by various authors.

Histopathological changes have been described in the brain, kidney, nasal mucosa, heart, adrenal gland, liver, and testis of rats and mice exposed to various levels of methyl bromide.

Olfactory sustentacular and mature sensory cells are damaged by short-term exposure to methyl bromide, but there is rapid repair and recovery.

Long-term inhalation studies (up to 2 years) on rats showed lesions in the nasal mucosa and myocardium. In a similar long-term study on mice, the primary toxic effects were observed in the brain, heart, and nasal mucosa. Evidence of carcinogenicity was not observed in either species.

Oral administration of 50 mg methyl bromide/kg body weight to rats for up to 25 weeks produced inflammation and severe

hyperplasia of the forestomach epithelium. Following a post-exposure recovery period, fibrosis of the forestomach was the principle lesion observed. An early carcinoma of the forestomach was observed in the rat treated daily for 25 weeks.

B6C3F mice and F344 rats exposed to up to 467 mg methyl bromide/m^3 for 13 weeks showed slight changes in sperm morphology while the length of the estrous cycle was not affected.

Inhalation exposure to up to 350 mg methyl bromide/m^3 did not induce any noteworthy effects on the growth, reproductive processes, and offspring of two consecutive generations of CD Sprague-Dawley rats. The male and female fertility indices were reduced at the two highest dose levels in the F_1 generation F_{2B} litter.

In studies on developmental toxicology with New Zealand White rabbits, exposure to 311 mg methyl bromide/m^3 (6 h/day; days 7-19 of gestation) showed moderate to severe maternal toxicity. Developmental effects, observed at the maternal toxic dose, consisted of decreased fetal weights, an increase in the incidence of a minor skeletal variation, and malformations (mostly missing gallbladder or missing caudal lobe of the lung). However, at 272 mg/m^3, maternal toxicity was less marked and there were no embryotoxic effects.

No adverse maternal, embryonal, or fetal effects were observed in rabbits exposed to 78 or 156 mg methyl bromide/m^3. A no-observed-effect level (NOEL) of 156 mg methyl bromide/m^3 was given for maternal and development toxicity in New Zealand White rabbits.

Methyl bromide has been found to be mutagenic in several *in vitro* and *in vivo* test systems. It induces sex-linked recessive lethal mutations in *Drosophila melanogaster* and mutations in cultured mammalian cells. It does not induce unscheduled DNA synthesis or cell transformation in cultured mammalian cells. DNA methylation of the liver and spleen was observed in mice administered methyl bromide by various routes. Micronuclei were induced in bone-marrow and peripheral blood cells of rats and mice.

The mechanism of methyl bromide toxicity is not known.

1.8 Effects on humans

Human exposure to methyl bromide may occur through inhalation of the gas or contact with the liquid. Exposure through ingestion of drinking-water contaminated with leaching water can also occur.

A controlled human study showed that uptake following inhalation exposure was about 50% of the administered dose.

Methyl bromide is damaging to the nervous system, lung, nasal mucosa, kidney, eye, and skin. Effects on the central nervous system include blurred vision, mental confusion, numbness, tremor, and speech defects. Topical exposure can cause skin irritation and burns, and eye injury.

Exposure to high levels of methyl bromide causes pulmonary oedema. Central nervous system depression with respiratory paralysis and/or circulatory failure are often the immediate cause of death, which is preceded by convulsions and coma.

Several different neuropsychiatric signs and symptoms have been observed during acute and long-term methyl bromide poisonings. Low-level short-term exposures to the vapour have produced a syndrome of polyneuropathy without overt central manifestations.

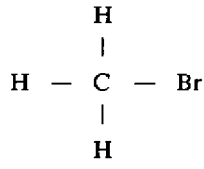
Late sequelae include bronchopneumonia after severe pulmonary lesions, and renal failure with anuria and severe weakness with, or without, evidence of paralysis. Generally, these symptoms tend to subside over a period of a few weeks or months. However, deficits without recovery usually characterized by sensory disturbances, weakness, disturbances of gait and blurred vision, have been observed.

Exposure to methyl bromide is accompanied by an increase in the bromide level in the blood. In fumigators, there is a relationship between the number of gas applications and the average plasma bromide level.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

2.1 Identity

2.1.1 Primary constituent

Chemical formula:	CH_3Br
Chemical structure:	
Relative molecular mass:	94.94
Common name:	methyl bromide; bromomethane
CAS name:	bromomethane
CAS registry number:	74-83-9
EEC No.	602-002-00-2
EINECS No.	200-813-2
Synonym:	monobromomethane

2.1.2 Technical product

Methyl bromide is typically available as a liquefied gas (Matheson Gas Data Book, 1980).

Purity:	> 99.5%
Max. water content:	0.015%
Max. acidity (as HBr):	0.0010% (Matheson Gas Data Book, 1980)
Impurities:	traces of chloromethane (Atochem, 1988)

Formulations include mixtures with other fumigants, most frequently with chloropicrin or hydrocarbons, as inert diluents (Stenger, 1978). Chloropicrin (2%) or amyl acetate (0.3%) are added to methyl bromide to serve as a warning agent. Chloropicrin is a toxic chemical with lacrimatory and irritating effects. However, it is sensed at the 9 mg/m^3 (1.3 ppm) level and a methyl bromide concentration could be well above regulatory exposure limits by the time the presence of chloropicrin is noticed.

Chemical, environmental, and toxicological data concerning chloropicrin have been reviewed by Sassaman et al. (1986). For commodity fumigation, 100 % methyl bromide should be used (Ethyl Corporation, 1990).

Methyl bromide is marketed under several different trade names, with formulations containing 30-100 % of the compound, e.g., Brom-o-gas, Desbrom, Haltox, MBR-2, Metabrom, Methybrom, Methyl Bromide, Methyl-o-gas, Sobrom 9B, Terr-o-gas 100 (all 98-100% methyl bromide); Bromopic, Sobrom 67, Terr-o-gas (80-30%, with decreasing methyl bromide and increasing chloropicrin content).

2.2.1 Physical properties

Methyl bromide is a colourless gas at normal temperature and pressure. Under increased pressure or below about 3 °C it is a clear, colourless to straw-coloured liquid. It is odourless except in relatively high concentrations, when it has a chloroform-like smell (Matheson Gas Data Book, 1980). Individual odour thresholds range between 80 mg/m^3 and 4000 mg/m^3 (Ruth, 1986).

The gas can penetrate many substances, including concrete, leather, and rubber (Bond, 1984) as well as brick and wooden walls (BBA, 1989). Methyl bromide did not permeate through certain plastics (Herzel & Schmidt, 1984) or through metal or polyvinyl-chloride (PVC) pipes, but permeation through low-density polyethylene (LDPE) occurred. Permeation through LDPE pipes resulted in a concentration of 6% in the contained water after one week. This was independent of the actual concentration outside the pipes. The methyl bromide seemed to concentrate within the polymer. Permeation through high density polyethylene (HDPE) was 5-8 times lower than through LDPE (Veenendahl & Dibbets, 1981).

Liquid methyl bromide has a solvent action on many plastics and organic materials. Natural rubber is attacked and acquires a strong unpleasant smell (Thompson, 1966).

The physical properties of methyl bromide are summarized in Table 1.

Table 1. Physical properties of methyl bromide

Freezing point (1 atm):	-93 °C[a,b]
Boiling point (1 atm):	3.56 °C[a,b]
Flash point:	194 °C, burns with difficulty[c]
Flammability:	13.5-14.5 % (by volume; flammable limits in air)[a] 10-16%[d]
Critical temperature	194 °C[c]
Autoignition temperature:	536.7 °C[a]
Vapour pressure (20 °C):	1893 kPa (1420 mmHg)[b,e]
Density (20 °C): (kg/m^3) (0 °C):	3.974[b] 1730[a,b,c]
Vapour density: (rel.; air = 1) (20 °C)	3.27[c]
Solubility in water: (g/litre; 20 °C)	18.5[f] (15.4 at 25 °C)[f] 18.00[g] 16[h] forms a voluminous crystalline hydrate ($CH_3Br.2OH_2O$) below 4 °C[b]
Solubility in other solvents:	freely soluble in alcohol, chloroform, ether, carbondisulfide, carbon tetrachloride, and benzene[b]
log *n*-octanol/water partition coefficient (log P_{ow}):	1.19[i,j]
Henry's law constant: (kPa m^3/mol)	0.533 (calculated using atmospheric pressure)[b]
UV absorption:	max. 202 nm[k,l,m]

[a] = Matheson Gas Data Book (1980); [b] = Windholz (1983);
[c] = Hommel (1984); [d] = NFPA (1984); [e] = Stenger (1978);
[f] = Wilhelm et al. (1977), [g] = Mackay & Shiu (1981); [h] = Atochem (1987);
[i] = Hansch & Leo (1979); [j] = Sangster (1989); [k] = Robbins (1976b);
[l] = Molina et al.(1982); [m] = Gillotay et al. (1989).

There are discrepancies in values for the solubility of methyl bromide in water, some values in the literature being substantially lower than those given in Table 1.

Methyl bromide is practically non-flammable in air, a narrow range of 13.5-14.5 % by volume being quoted in the Matheson Gas Data Book (1980), whereas a range of 16-20% is given in NFPA (1984). It burns in oxygen (Windholz, 1983).

2.2.2 Chemical properties

Methyl bromide hydrolyses to methanol and hydrobromic acid. It is a methylating agent reacting with amines, particularly the more basic ones, to form methylammonium bromide derivatives. Methyl bromide also reacts with sulfur compounds under alkaline conditions to give mercaptans, thioethers, and disulfides. Most metals, other than aluminium, are inert to pure, dry methyl bromide, but surface reactions take place on zinc, tin, and magnesium, in the presence of ethanol or moisture (Stenger, 1978). Explosions upon contact with aluminium, as well as with dimethyl sulfoxide, have been reported (NFPA, 1984). The liquid is corrosive to aluminium, magnesium and zinc metals and their alloys.

Methyl bromide is not considered to be flammable. However, it will burn in air in the presence of a high-energy source of ignition and when within a narrow flammability range (see section 2.2.1). Methyl bromide has no flash point. Thermal decomposition in a glass vessel begins above 400 °C (Stenger, 1978). The products include HBr, bromine, carbon oxybromide, as well as carbon dioxide and carbon monoxide (von Oettingen, 1964).

2.3 Conversion factors

1 ppm = 3.89 mg/m^3 at 25 °C, 1013 hPa
or 3.95 mg/m^3 at 20 °C, 1013 hPa

1 mg/m^3 = 0.257 ppm

1% methyl bromide = 10 000 ppm = 39.52 g/m^3 at 20 °C and 101.3 kPa

2.4 Analytical methods

Methyl bromide residues have been determined indirectly as total inorganic bromide. Methods are now available for the direct determination of methyl bromide.

2.4.1 Methyl bromide in air

A summary of methods for the detection of methyl bromide in air is given in Table 2.

The detection of methyl bromide in air is important at three levels: control readings for warning fumigation workers; working place (e.g. production/packing and sealing/transport) measurements; and the measuring of levels of methyl bromide in the atmosphere.

In the first case, exposed fumigation workers must be warned immediately of the presence of methyl bromide, as it is a toxic gas. Many formulations, particularly those for commodity fumigation, do not contain chloropicrin as a sensory warning.

Halide lamps cannot detect methyl bromide around occupational exposure thresholds of 20 mg/m^3 whereas electronic gas detectors, though not specific for methyl bromide, are extremely sensitive. Currently available gas detector tubes are also not specific for methyl bromide but can be used to provide a reasonably precise indication of methyl bromide level in a fumigation area before entry.

Direct reading colorimetric indicators are available (Saltzman, 1983; Leichnitz, 1985). However, Guillemin et al. (1990) noted that several batches of these tubes produced unreliable results.

There is a direct-reading infrared analyser (MIRAN) that monitors from 10 mg/m^3 (2.3 ppm) methyl bromide (Foxboro, 1989). As this instrument can measure methyl bromide below the threshold value, it has been used to determine whether buildings are safe for occupation after fumigation. However, Guillemin et al. (1990) reported that the portable systems were mechanically and electrically unstable under field conditions, and showed poor sensitivity and selectivity for methyl bromide.

Table 2. Methods for the analysis of methyl bromide in air[a]

Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Gas collected by pump and pressurized	GC (30 m capillary column) *a*) isothermal runs *b*) temperature programmed freeze-out technique	ECD	40 ng/m^3 2 ng/m^3	used for ambient air determinations	Harsch & Rasmussen (1977)
Injection of 5 ml sample	GC (3 m steel column)	ECD (scandium tritide)	2 μg/m^3 (upper limit 1 mg/m^3)	no common pollutants interfere with estimation	Pellizzari et al. (1978)
Adsorb on charcoal; desorb (heat, purge with helium); dry (calcium sulfate); readsorb (Tenax GC); desorb as before; trap liquid nitrogen cooled; vaporize onto GC	100 m glass capillary column	MS	14 ng/m^3 (21 °C)		Pellizari et al. (1978)
Adsorb (polymeric beads); desorb (heat, purge with helium); trap directly on GC column		ECD	500 ng/m^3		Krost et al. (1982)
Gas collected by pump	GC (2 m steel column)	ECD	40 μg/m^3		Angerer (1982)

Table 2 (continued)

Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Adsorb on charcoal; desorb (carbon disulfide inject aliquot	GC	FID	1 mg/m^3		Eller (1985), Peers (1985)
Not given	GC	FID	2 ng	for fumigation control	Dumas & Bond (1985)
Not given	GC	PID	10 pg	for ambient air sampling	Dumas & Bond (1985)
Direct capillary trapping with pump	GC	ECD	50 ng/m^3	methyl bromide and chloropicrin detected	Kallio & Shibamoto (1988)
Charcoal air sampling tube/headspace sampler	GC	ECD	50 ng	designed to handle large numbers of samples (45 samples in 24 h); not specific for methyl bromide	Woodrow et al. (1988)
HBr-treated activated charcoal tubes/solvent desorption	GC	FID ECD	1 mg/m^3- 1 g/m^3	personal monitoring method	Lefevre et al. (1989)

[a]Abbreviations:
ECD = electron capture detector;
FID = flame ionization detector;
GC = gas chromatography;
HECD = Hall electroconductivity detector;
MS = mass spectrometry;
PID = photoionization detector.

Portable gas chromatographs measuring down to 0.04 mg/m^3 (0.01 ppm) are also available for field work (Bond, 1984). Guillemin et al. (1990) recommended for field conditions a photo-ionization detector using a 10.2 eV source previously calibrated in the laboratory for methyl bromide. The limitations were that readings were not specific for methyl bromide and that sensitivity decreased with time.

Linenberg et al. (1991) used a portable GC with an argon ionization detector (AID) to identify methyl bromide (0.12 mg/m^3; 31 ppb) in the presence of other halohydrocarbon compounds for on-site analysis.

In situ measurement of methyl bromide in indoor air using long path Fourier transform infrared (FTIR) spectroscopy has been described (Green et al., 1991). Quantitative determinations were made by comparison with reference spectra of known concentration. Detection limits were given as 0.14 mg/m^3 (35 ppb), but conditions could be optimized to obtain more sensitivity.

Methyl bromide is present in the atmosphere and its degradation products may react with the ozone layer (see section 5.1.1).

Air samples can be collected using the following methods:

- cryogenesis using liquid nitrogen or helium,
- adsorption on (activated) charcoal,
- pumping into special containers,
- entry into already evacuated containers (BUA, 1987).

Plastic tubing or containers must not be used as they absorb methyl bromide (Herzel & Schmidt, 1984).

Methods using electron capture detectors (ECD) are suitable for routine measurements. GC/MS may be used for confirmation purposes.

In the monitoring of methyl bromide in air, stainless steel canisters are recommended for collection with analysis using automated cryogenic preconcentration followed by gas chromatography with a selective detector - flame ionization (FID) and electron capture detectors (ECD) connected in parallel (Jayanty, 1989).

2.4.2 Methyl bromide in water

Methods of determination of methyl bromide in water are summarized in Table 3.

Purge and trap techniques, as well as headspace sampling, have been used for the GC determination of methyl bromide in water. Details of the collection, preservation, and handling of the water sample to be analysed for methyl bromide are given in most references mentioned in this section.

The headspace sampling technique can be used for analysis of virtually any matrix.

Wylie (1988) compared headspace with purge and trap techniques for the analysis of volatile priority pollutants. The headspace method is more easily automated running 24 samples against only up to 10 with a purge and trap unit with autosample. There is also less chance of contamination from foaming or from high concentrations of a previous analyte with headspace. Virtually any matrix can be used with headspace, and glassware is disposable, which minimizes contamination. Under some conditions, purge and trap is more sensitive than headspace. US EPA recommended the purge and trap method for the analysis of volatiles (EPA; 1984a).

An evaluation of methods for testing groundwater recommended in US EPA Methods 8010 (GC/ECD) and 8240 (GC/MS) gave practical quantification limits of 20 and 10 μg/litre, respectively, for methyl bromide (Garman et al., 1987).

US EPA Methods 601 (GC/ECD), 602 (GC/MS) (Driscoll et al., 1987; Duffy et al., 1988) and 624 (GC/MS) (Lopez-Avila et al., 1987) have been updated for use with capillary column GC, to provide greater sensitivity.

A sensitive headspace method for the gas-chromatographic determination of methyl bromide in surface and drinking-waters was reported by Cirilli & Borgioli (1986). This method is based on the conversion of methyl bromide into methyl iodide by reaction with sodium iodide.

Table 3. Determination of methyl bromide in water[a]

Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Headspace	GC	ECD	1 µg/litre		Wegman et al. (1981)
Purge and trap	GC	ECD	(n.d.)[a]		US EPA (1982a) (Method 8010)
Purge and trap	GC	MS	5 µg/litre		US EPA (1982b) (Method 8240)
Purge and trap	GC (packed column)	MS	(n.d.)[a]		US EPA (1984a) (Method 624)
Purge and trap desorb as vapour (heat to 180 °C, backflush with inert gas) on to GC column	GC	ECD	1.18 µg/ litre		US EPA (1984b) (Method 601)
Add internal standard (isotope labelled methyl bromide); purge, trap and desorb as above	GC	MS	50 µg/litre		US EPA (1984c) (Method 1624)
Purge (80 °C, nitrogen); trap (Ambersorb or Porapak N); desorb (flash-heat) and trap in "mini-trap" (Ambersorb or Porapak N, - 30°C); desorb (flash-heat) on to GC column	GC	ECD MS	0.05 µg/ litre 0.05 µg/ litre		Piet et al. (1985)

Table 3 (continued)

Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Headspace	capillary GC	ECD	5×10^{-3} µg/litre	methyl bromide converted quantitatively to methyl iodide, which is then determined	Cirilli & Borgioli (1986)
Purge and trap	capillary GC	ECD PID		optimization of methods 601, 602 to capillary column	Driscoll et al. (1987) Duffy et al. (1988)
Purge and trap	capillary GC	MS		updating of methods; no separation of bromomethane from chloromethane	Lopez-Avila et al. (1987)
Headspace sampling	capillary GC	MS	20 µg/litre		Gryder-Boutet & Kennish (1988)
Samples purged for 45 seconds directly to a cryogenically cooled, capillary column	capillary GC	FID	1 µg/litre		Cochran (1988)
Purge and trap	capillary GC	ECD	1.1 µg/litre		Ho (1989)

[a] For other abbreviations see Table 2.
n.d. = methyl bromide was not detected in the earlier determinations.

Singh et al. (1983) described the analysis of methyl bromide in seawater samples. A 50-ml volume of seawater and an equal volume of ultra-pure air were enclosed in all-glass syringes of 100-ml volume. Once in the syringe, the equilibrium was allowed to reach completion (enhanced by repeated shaking) in 15-30 min. This also allowed the water to reach room temperature, which was carefully recorded. The air in equilibrium with the 50-ml seawater was analysed for methyl bromide using gas chromatography with ECD; the corresponding equilibrium concentration of methyl bromide in seawater was determined from solubility data at the measured room temperature, and the two were added to obtain the methyl bromide concentrations in seawater. The partition coefficient data and their temperature dependence for methyl bromide were taken from Wilhelm et al. (1977) for pure water. The salting-out coefficient of 1.2 was determined on the basis of available data on the measured solubility of moderately soluble gases in pure water and seawater.

2.4.3 Determination of methyl bromide in soil

Equipment and methods for sampling and analysing deep field soil atmospheres have been described (Kolbezen & Abu-El-Haj, 1972). Soil atmosphere samples were obtained from a vertical and horizontal grid of sampling points placed into the soil before it was treated with methyl bromide. The samples were withdrawn through fine stainless steel tubing into syringes that could be transported to the laboratory and directly applied to the gas chromatograph. A flame ionisation detector (FID) was used (detection limit 40 mg/m^3).

US EPA Methods 8010 and 8240 (Table 3) can also been used for the determination of methyl bromide in solid waste and soils (US EPA, 1982a,b) with a detection limit of 1 μg/g. Extraction of non-aqueous samples is carried out using methanol or polyethylene glycol.

2.4.4 Methyl bromide in cereal grains and other foods

Analytical methods are summarized in Table 4.

Table 4. Determination of methyl bromide in plant material and foods[a]

Medium	Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Flour, unground wheat, sultanas, peanuts, maize, ground-nuts	cold solvent extraction, extraction time increasing with food particle size	GC	FID	0.3 mg/kg	95% recovery	Heuser & Scudamore (1968; 1970), Scudamore (1987)
Whole wheat, flour, ground-nut, rapeseed, dried milk powder, cocoa beans	extracted methyl bromide is reacted to form methyl iodide	GC	ECD	0.01 mg/kg		Fairall & Scudamore (1980)
Grain	acetone/water extraction; headspace analysis	GC (Carbowax-20 M)	ECD	0.05 mg/kg		Greve & Hogendoorn (1979)
Wheat	flasks containing wheat flushed with nitrogen and trap at -78.5 °C	GC (2 m Tenax)	FID	0.3 µg/kg	determination of methyl bromide in wheat after fumigation	Dumas (1982)
Grapefruit	blended with water and vial sealed, 5 ml headspace gas removed with syringe and injected	GC	ECD	0.1 mg/kg 2 µg/kg		King et al. (1981)

Table 4 (continued)

Medium	Sampling method	Analytical	Detector method	Detection limit	Comment	Reference
Wheat, flour, cocoa, peanuts	water added, equilibration at 30 °C headspace	GC	ECD	0.4 µg/kg		De Vries et al. (1985)
Cereal grains and other foods	extract with acetone: water; add sodium chloride; separate layers; dry acetone solution over anhydrous calcium chloride; inject aliquot	GC	ECD	150 µg/kg		Scudamore (1985a)
	extract with acetone: water, inject aliquot of headspace vapour	GC	ECD	10 µg/kg		Scudamore (1985b)
Cherries	headspace; adapted from King et al. (1981)	GC	ECD	0.5 mg/kg	determination of the rate of desorption from fumigated cherries	Sell et al. (1988)
Apples	headspace; adapted from King et al. (1981)	GC	ECD	0.01 mg/kg		Sell & Moffitt (1990)

Table 4 (continued)

Medium	Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Food	extraction with 83% acetone (grains), 20% acetone (softer foods); residues partitioned into isooctane by shaking; fatty food passed through micro-Florisil columns	GC (packed column)	ECD, HECD	55 µg/kg 20 µg/kg	poor recovery and high coefficient of variation	Daft (1987; 1988; 1989)
Nuts, food	comminuted food sample with sodium sulfate; aliquot to head-space; cryogenic focusing at -60°C and then elution by temperature programming	GC (capillary)	ECD	dependent on lipid content of food 0.15-0.65 µg/kg		Page & Avon (1989)
Nuts	extraction with sodium sulfate at 80 °C; purge overnight	GC (capillary)	ECD, HECD		suitable for screening nut samples at ng/g levels; 40% recovery; 29% coefficient of variation	Daft (1992)
Fish	homogenization purge and trap	GC	MS	200 µg/kg		Easley et al. (1981)

[a] For abbreviations see Table 2.

Although bromide levels in food have been measured and documented for several decades, the methods for the determination of methyl bromide in foods are still being refined. The cold extraction or soaking procedure was developed and optimum extraction times determined for several foods, the extraction time increasing with food particle size (Heuser & Scudamore, 1968, 1970). With several foods, there was evidence of methyl bromide loss through reaction with food components. The following extraction times for methyl bromide were reported: flour (1 h), unground wheat (8 h), sultanas (8 h), peanuts (8 h), maize (24 h), groundnuts (24 h), and cocoa beans (48 h). When the procedure was reevaluated, it was found that the longer extraction time required for unground grain, compared with flour, probably reflected the migration of methyl bromide into the interior of the grain (Scudamore, 1987).

An acetone/water extraction of grain followed by headspace analysis was described by Greve & Hogendoorn (1979). The headspace method has also been developed for sampling other selected foods, e.g., grapefruit (King et al., 1981), flour, cocoa, unground wheat, and peanuts (DeVries et al., 1985), cherries and apples (Sell et al., 1988; Sell & Moffitt, 1990).

Headspace capillary gas chromatography with electron capture detection was described by Page & Avon (1989). The difference between this and other headspace procedures is the particle size reduction by the blending or homogenization of the cold or frozen sample with ice and cold water with only minimal loss of methyl bromide, resulting in a rapid 1-h equilibrium in the headspace vial. An advantage of headspace is that nonvolatile material is not introduced into the chromatographic column or injector body, thus shortening the run. The method is sensitive with detection limits of 0.15-0.65 μg/kg. These different detection limits are due to an inverse relationship of methyl bromide headspace response and food lipid content. Duplicate samples from the same vial are not possible, and, for quantification, a separate calibration curve is necessary for each food item.

Combining the methods of Page & Avon (1989) and Daft (1987, 1988, 1989), an improved method for the detection of methyl bromide in nuts was developed using extraction with sodium sulfate solution at 80 °C and purging overnight (Daft, 1992). A Hall

electrolytic conductivity detector, used in the determinative step, has been found to be about 3 times more sensitive to methyl bromide than ECD. Additionally, the Hall detector is said to eliminate endogenous interference from the nut samples. The recovery was 40% (coefficient of variation, 29%) and the method can be used to screen assorted nut samples for ng/g levels of incurred residues.

Siegwart (1987) suggested using the headspace method for screening, but that with positive findings, the methyl bromide concentration should be confirmed using mass spectography. In addition, methyl bromide should then be converted to methyl iodide and determined again. A detection limit of under 10 μg/kg, is given.

US EPA Method 624 (GC/MS) has been adapted for the determination of methyl bromide in fish (Easley et al., 1981).

2.4.5 *Methyl bromide in serum, plasma and blood, and post-mortem tissue*

Marraccini et al. (1983) used a purge and trap method followed by mass spectroscopy to determine methyl bromide levels in post-mortem tissues. Tissue levels lower than 1 mg/kg (1 ppm) were detectable.

Honma et al. (1985) detected methyl bromide in rat tissues using GC/ECD. The tissues were extracted with toluene. The presence of methyl bromide was confirmed by GC/MS. No detection limit was given but the lowest values reported were 1 ng/g.

Headspace gas chromatography with split flame-ionization, electron-capture detection has been used to detect volatile substances including methyl bromide in biological fluids. The method offered economy of time with a sensitivity equivalent to a packed column (Streete et al., 1992).

2.4.6 *Determination of inorganic bromide in air*

Analytical methods for the determination of inorganic bromide in air are not described here as the concentration of bromide is not specifically related to the amount of methyl bromide in the atmosphere.

2.4.7 Determination of inorganic bromide in water

Vanachter et al. (1981) carried out bromide determinations in leaching water using the colorimetric method described by Malkomes (1970), in which the sample is first heated to dryness, then phenol red and chloramine-T (sodium *p*-toluenesulfochloramine) solution added. After 5 min, the reaction is stopped with sodium thiosulfate. The resulting blue colour is read on a spectrophotometer at 590 mμ. The detection limit is 0.1 mg/litre (0.1 ppm).

In another method, water samples were evaporated to dryness at 90 °C. Sulfuric acid, ethylene oxide in diisopropylether, and acetonitrile were added and the sample shaken. After 30 min, an aliquot was removed and solid ammonium sulfate added and shaken. After separation, the upper layer was removed and anhydrous sodium sulfate added. An aliquot of the dried sample was analysed using GC/ECD (detection limit 0.01 mg/litre) (Wegman et al., 1981, 1983).

2.4.8 Determination of inorganic bromide in soils

The colorimetric method of Malkomes (1970) (section 2.4.7) can also be used for soil. The sample is first sieved, dry-ashed, boiled in distilled water, and filtered. The filtrate is then analysed.

Brown et al. (1979) determined bromide in soil by extracting with calcium nitrate solution (0.1 mol/litre) and using a bromide-specific electrode for detection in the extract. No detection limit was given.

2.4.9 Determination of inorganic bromide in plant material/food

Various methods, such as X-ray spectroscopy, potentiometry, thiosulfate titration, gas/liquid chromatography, and high-performance liquid chromatography, have been used to determine bromide content (section 5.1.4). A summary of methods is given in Table 5.

Table 5. Inorganic bromide in plant material/food[a]

Medium	Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Grain	grind samples, add acetonitrile, ethylene oxide, and sulfuric acid (4 h, 20 °C); separate supernatant with ammonium sulfate; extract with anhydrous sulfate; supernatant analysed	GLC	ECD	0.07 mg/kg	not suitable for fresh vegetables	Heuser & Scudamore (1970)
Salad/ vegetables	dry samples at 110 °C; grind; add NaOH, ethanol; evaporate to dryness; add to sulfuric acid solution/slurry acetonitrile and ethylene oxide; analyse 2-bromoethanol	GLC	ECD	0.1 mg/kg (fresh mass)		Roughan et al. (1983)
Vegetables	extract sample with aqueous ethanol; ash aliquot of extract in the presence of NaOH; treat extract with ethylene oxide	GC	ECD	0.5 mg/kg (fresh mass)	interlaboratory study	Greve & Grevenstuk (1979)
Cereals, dried fruit, dried vegetables	extraction of inorganic bromide and conversion to 2-bromoethanol by suspension in aqueous ethylene oxide and acidification by sulfuric acid; 2-bromoethanol partitioned into ethyl acetate and analysed	GC	ECD	1 mg/kg (fresh mass) 5 mg/kg (dried mass)		Thier & Zeumer (1987)
Vegetables	dried for 3 days and comminuted aliquots soaked in alcoholic KOH and mineralized overnight at 600 °C; ash homogenized with diluted $NaNO_3$; supernatant analysed	specific ion electrode		lowest value given 0.1 mg/kg		Basile & Lamberti (1981)
	grind sample, shake with water (6 h); centrifuge extract (50 ml) + $NaNO_3$; evaporate residue, dissolve in water	potentiometric measurement with specific electrode	ECD	0.1 mg/kg		Cova et al. (1986)

Table 5 (continued)

Medium	Sampling method	Analytical method	Detector	Detection limit	Comment	Reference
Peaches	peaches blended with $NaNO_3$ crystals and water; centrifugation supernatant	bromide-selective electrode		0.2 mg/litre (wet mass)		Austin & Phillips (1985)
Cereals, nuts, spices, fruit	ground/minced; dried 100 °C (18 h), ground powdered sample with boric acid-sodium sulfate	X-ray fluorescence spectroscopy		5 mg/kg		Love et al. (1979)
Grain	macerated grain refluxed in ethanol-ethanolamine; alkali digested; ashed (600 °C); water extraction; oxidized with sodium hypochlorite	thiosulfate titration		lowest value given 4.5 mg/kg		Urga (1983)
Vegetables	fresh sample homogenized and macerated with water then homogenate centrifuged; supernatant filtered and the filtrate used for analysis	HPLC	UV (205 nm)	4 mg/kg	pH of the mobile phase must be adjusted to 5.0 (at higher pH, e.g., 6.0-6.5, an overlap between Br peak and sample interferences may occur)	Van Wees et al. (1984)

[a] For abbreviations see Table 2.

In the method described by Heuser & Scudamore (1970), bromide ion is converted into 2-bromoethanol by reaction with ethylene oxide in acetonitrile-diisopropyl ether, under acidic conditions. The 2-bromoethanol is then determined by gas-liquid chromatography with an electron-capture detector (ECD). This procedure is suitable for wheat and maize but is not ideal for salad crops (because of cleaning procedures) where problems arise, such as severe tailing, lack of resolution, and poor recovery (Roughan et al., 1983). These authors varied some conditions, such as preparing the ethylene oxide in acetonitrile and using Carbowax 20M TPA to prepare the GC column. The samples (e.g., lettuce) were hydrolysed with alcoholic sodium hydroxide overnight, ashed for 2 h at 500 °C (600 °C for oily substances), and ground, prior to digestion with 0.6 N sulfuric acid (Greve & Grevenstuk, 1976; 1979). Recoveries of 97 % were achieved and the method was used to determine bromide down to 0.1 mg/kg of substrate fresh mass (Roughan et al., 1983). A wide range of vegetables and other crops have been analysed using this method (section 5.1.4).

A similar procedure for cereals, dried fruit, and vegetables has been described using GC/ECD (Thier & Zeumer, 1987). The finely ground sample is suspended in an aqueous solution of ethylene oxide acidified with sulfuric acid. The inorganic bromide is extracted simultaneously and converted to 2-bromoethanol. This derivative is partitioned into ethyl acetate and determined, without further clean up, by electron capture gas chromatography.

Bromide concentration in plant material has also been determined by X-ray fluoroscopy with a detection limit of around 5 mg/kg (Brown et al., 1979; Love et al., 1979).

A specific ion electrode can be used for inorganic bromide determination using a standard calibration curve with a detection limit of around 0.1 mg/kg (Basile & Lamberti, 1981; Cova et al., 1986). Austin & Phillips (1985) used a bromide-selective electrode to detect levels of bromide ion in peaches; the detection limit for peach extract was 0.2 mg/litre.

Urga (1983) used a thiosulfate titration method: the macerated grain was refluxed in ethanol-ethanolamine mixture, and then ashed (600 °C). The bromide ion was extracted with water and determined by oxidizing with sodium hypochlorite solution. This was titrated

with sodium thiosulfate, using starch solution as indicator. The lowest level measured was 4.5 mg/kg.

A quick screening method for inorganic bromide in vegetables, using high-performance liquid chromatography (HPLC) with a detection limit of around 4 mg/kg, was described by Van Wees et al. (1984).

2.4.10 Determination of inorganic bromide in urine, blood/serum/plasma

Various methods for the determination of bromide in biological fluids have been described: colorimetry (Kisser, 1967), X-ray fluoroscopy (Rapaport et al., 1982; Shenberg et al., 1988), neutron activation analysis (Heurtebise & Ross, 1971; Ohmori & Hirata, 1982), ion-sensitive electrode (Angerer, 1977, 1980); and headspace GC with FID (Yamano et al., 1987). Koga et al. (1991) compared headspace GC and an ion chromatography coupled with a conductivity detector to evaluate levels of bromide ion in urine. GC was more sensitive with a detection limit of 0.04 mg/litre. Honma et al. (1985) used an GC/ECD method for their studies on rats (section 6.2). A summary of methods is given in Table 6.

In forensic science studies (overdose of bromide-containing sleeping tablets as well as suspected methyl bromide poisoning), colorimetric methods, such as that of Kisser (1967), have been routinely used (Weller, 1982). For routine occupational studies, other methods are more suitable.

Table 6. Determination of bromide in biological fluids and tissues[a]

Medium	Sampling method	Analytical method	Detection limit	Comment	Reference
Urine/ blood	add soda solution; evaporate and ash (550°C); ash + water →filter filtrate→bromide	+ chloramine T-solution, sodium thiosulfate	-	-	Kisser (1967)
Urine	alkali ashing (Kisser, 1967); with $KMnO_4$, bromide→bromine; bromine + sulfide soln→bromide	ion-sensitive electrode	1 mg/litre	suitable for occupational exposure studies	Angerer (1977, 1980)
Urine	headspace; methylation with dimethylsulfate	GC	0.4 mg/litre	2.7% standard deviation	Koga et al. (1991)
Urine		ion chromatography	1.0 mg/litre	8.7% standard deviation	Koga et al. (1991)
Serum		X-ray fluorescence	0.05 μg		Rapaport et al., (1982); Shenberg et al. (1988)
Urine, saliva, serum, plasma		neutron activation analysis	not given		Heurtebise & Ross (1971)
Serum/hair		neutron activation analysis	120 μg/g; 4 μg/g (estimated)	occupational studies	Ohmori & Hirata (1982)
Plasma	head space plasma + water + dimethylsulfate (Br^-→ methyl bromide)	GC/FID	0.5 mg/litre		Yamano et al. (1987)

[a] For abbreviations see Table 2.

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural sources

The atmospheric levels of methyl bromide are controlled by the amounts from natural and anthropogenic (man-made) sources and by the atmospheric and surface removal processes. Observational data (UNEP, 1992) indicate that the current best estimate for the globally averaged abundance of methyl bromide in the troposphere is between 9 and 13 pptv, which is equivalent to a total atmospheric loading of 150-220 million kg. If the atmospheric lifetime of methyl bromide is two years, i.e., only tropospheric removal by reaction with OH^- is significant, then a total emission of about 75-110 million kg per year is required to maintain the observed atmospheric level. However, if the atmospheric lifetime is only one year (assuming surface removal comparable in magnitude to the atmospheric removal), a global emission of 150-220 million kg per year is required to maintain the atmospheric methyl bromide at the same level (UNEP, 1992).

Khalil et al. (1993) have used similar input data (global abundance of 10 pptv, lifetime of two years) to calculate a global source of about 100 million kg/year. On the basis of their measurements of ocean abundance and supersaturation (which differ considerably from those of Singh et al. (1983)), they estimated an ocean source of 35 ± 5 million kg/year. They proposed that the anthropogenic sources must be about 30 million kg/year, assuming that the differences in calculated emissions for the northern and southern hemispheres are solely due to man-made sources. This leaves about 35 million kg/year of emissions that cannot be categorized but are believed to originate from the tropics.

From the surface water and air observations of methyl bromide concentrations off the Pacific coasts of North and South America, Singh et al. (1983) estimated the total natural emissions of methyl bromide from the oceans to be 300 million kg/year. The total oceanic emission quantified from the extrapolation of the limited data may not be entirely justifiable. Using the currently accepted global atmospheric loading of 150-220 million kg, a tropospheric lifetime of 6-9 months can be expected, meaning surface removal processes

are even more important than reaction with OH. It would also mean that fumigation sources of methyl bromide are less than 10% of the total global emission.

It is likely that the calibration standards of Singh et al. (1983) were in error, leading to overestimation of methyl bromide concentrations by a factor of about two. Corrections for this factor would resolve part of the discrepancy between the estimates of Khalil and Singh of the oceanic source. However, an unresolved difference in supersaturation measurements (140% and 180% from two Khalil voyages and 250% from Singh) leaves a conflict of about a factor of three that cannot be resolved without more measurements.

In any event, the natural/anthropogenic balance of methyl bromide emissions is very uncertain.

The major natural sources of methyl bromide are considered to be oceanic biological processes (mainly algal), but the mechanism for the production of methyl bromide in the marine environment, and its oceanic distribution, are not well understood (Rogozen et al., 1987; WMO, 1992).

Methyl bromide occurs naturally in coastal waters together with methyl chloride and methyl iodide (Lovelock, 1975). This author suggested that methyl iodide produced by large kelp, such as *Laminaria*, reacts with the chloride and bromide ions in sea water to produce methyl chloride and methyl bromide, respectively.

Harper (1985) reported the formation of methyl bromide from cultures of a common wood-rotting fungus (*Phellinus pomaceus*) in the presence of sodium bromide solution, with cellulose as the substrate.

3.2 Anthropogenic sources

Anthropogenic sources, primarily soil fumigation, add to the amount of methyl bromide in the atmosphere. The amount released depends greatly on the regulations, methods used, dosage, type of plastic cover, length of covering, and precautions taken by the fumigators. The portion released is a question of dispute. Daelemans (1978) calculated that 70-90% of the applied amount of methyl bromide (50-100 g/m^2) disappeared into the atmosphere. Using a common application method (15-25 cm injection with a

2-day cover), analysis predicted emissions ranging from 45 to 53% (UNEP; 1992). In contrast, Rolston & Glauz (1982) estimated that 70% of the applied methyl bromide escaped into the atmosphere after fumigation using injection chisels.

During structural fumigation, up to 90% of the applied methyl bromide was estimated to escape into the environment (Reichmuth & Noack, 1983). During storage fumigation, an estimated 30% of the methyl bromide may escape from the fumigation chamber and enter the environment, while the rest decomposes to organic bromine and methylated derivatives of organic compounds (National Academy of Science, 1978). Other estimates give an 80% loss of methyl bromide used on perishable products (UNEP, 1992).

On the basis of the inventory of use and emissions coupled with the analyses of Singh & Prather (UNEP, 1992), the current best estimate for total anthropogenic emissions of methyl bromide is about 30 thousand tonnes per year, representing $25 \pm 10\%$ of the total emissions.

Methyl bromide is also emitted from motor vehicles using leaded petrol (section 3.2.3).

Methyl bromide is listed as a controlled substance in the "Montreal Protocol on Substances that Deplete the Ozone Layer".

3.2.1 Production levels and processes

3.2.1.1 Producers and world production figures

The total annual methyl bromide sales for the years 1984-90, tabulated according to region, are shown in Table 7; production figures for this period were almost identical. In Table 8, methyl bromide sales are tabulated according to use. These figures were provided by companies reporting to the Methyl Bromide Industry Panel, Chemical Manufacturers Association in February, 1992.

Table 7. Methyl bromide sales (tonnes) according to region for 1984-90[a,b]

Year	North America	South America	Europe	North Africa	Africa	Asia	Australia	Total sales
1984	19 659	1 389	11 364	183	1 595	10 678	704	45 572
1985	20 062	1 503	14 414	45	1 975	9 743	531	48 273
1986	20 410	1 775	13 870	380	2 205	11 278	538	50 445
1987	23 004	1 820	15 359	385	1 751	12 816	555	55 690
1988	24 848	2 058	17 478	277	1 582	13 555	812	60 610
1989	26 083	1 701	16 952	618	2 075	14 386	755	62 570
1990	28 101	1 621	19 119	432	1 838	14 605	928	66 641
Total	162 167	11 866	108 556	2 320	13 021	87 061	4 823	389 814

[a]Compiled by the Methyl Bromide Industry Panel, Chemical Manufacturers Association (unpublished report, February 1992).
[b]The 1990 production figures from other producing countries (e.g., India, China, former USSR) is estimated to be about 2500 metric tonnes.

Table 8. Methyl bromide sales (tonnes) according to use category for 1984-90[a]

Year	Pre-plant	Post harvest	Structural	Residential/ commercial	Chemical intermediates	Total sales
1984	30 408	9 001	1 285	881	3 997	45 572
1985	33 976	7 533	1 274	983	4 507	48 273
1986	36 090	8 332	1 030	999	4 004	50 455
1987	41 349	8 708	1 763	1 160	2 710	55 690
1988	45 131	8 028	1 910	1 737	3 804	60 610
1989	47 542	8 919	2 083	1 530	2 496	62 570
1990	51 306	8 411	1 740	1 494	3 693	66 644
Total	285 802	58 932	11 085	8 784	25 211	389 814

[a]Compiled by the Methyl Bromide Industry Panel, Chemical Manufacturers Association (unpublished report, February 1992).

The following is a list of the companies, including any related subsidiaries and/or joint ventures, that reported production and release data:

1. Association of Methyl Bromide Industry Japan (Japan)
   (*a*) Sanko Kagaku Kogyo Co. Ltd
   (*b*) Teijin Chemicals Ltd
   (*c*) Nippon Chemicals Co. Ltd
   (*d*) Dohkal Chemicals Co. Ltd
   (*e*) Nippon Kayaku Co. Ltd
   (*f*) Ichikawa Gohsei Chemical Co. Ltd
2. Atochem S.A. (France)
   (*a*) Derivados Del Etilo, S.A. (Spain)
3. Dead Sea Bromine Group
   (*a*) Dead Sea Bromine (US)
   (*b*) Eurobrom B.V. (The Netherlands)
4. Ethyl Corporation (US)
   (*a*) Ethyl S.A. (Belgium)
5. Great Lakes Chemical Company (US)
   (*a*) Great Lakes Chemical (Europe) Ltd (UK)
6. Societa Azionaria Industria Bromo Italiano (Italy)

According to Eurobrom B.V. (personal communication), Atochem is the sole producer of methyl bromide in Europe. Methyl bromide is also imported into Europe from the USA and Israel (Ethyl Corporation and Dead Sea Bromine Group).

The average rate of increase in total world sales between 1984 and 1990 was about 6% per year, more than 90% of these sales being in the Northern Hemisphere. Of the 51.3 thousand tonnes used as a pre-planting fumigant in 1990, about 80% was used in Europe and North America.

3.2.1.2 Production processes

Methyl bromide is commonly produced by the interaction of methanol (CH_3OH) and hydrogen bromide (HBr). The hydrogen bromide can be generated *in situ* from bromine and a reducing agent, such as sulfur or hydrogen sulfide (Dagani et al., 1985). Methyl

bromide is distilled from the reactant mixture and the crude product purified by further low-temperature fractional distillation (National Academy of Science, 1978). Another method is to add sulfuric acid to a concentrated sodium bromide and methanol solution (National Academy of Sciences, 1978; Stenger, 1978).

Ethyl Corporation and Great Lakes Chemical Co. both use a coproduction process that produces methyl bromide as a coproduct with the production of tetrabromobisphenol A (TBBPA). In this process, bisphenol A (BPA) is dissolved in methanol and then reacted with bromine to yield TBBPA and hydrobromic acid. The hydrobromic acid reacts with the methanol to yield methyl bromide (Ethyl Corporation, Personal communication to the IPCS, 1990).

In the manufacturing process of a Japanese plant, bromine is first mixed with methyl alcohol and heated at 60-80 °C in a boiler. The methyl bromide produced is cooled, purified, and condensed. These processes are mainly conducted in a closed system (Kishi et al., 1991).

3.2.1.3 *Losses to the environment during normal production*

In 1973, the emission of methyl bromide from manufacturing processes in the USA was estimated to be 100 000 kg compared with 11.3 million kg emitted when used as a fumigant (National Academy of Science, 1978).

However, in 1990, in the USA, the total reported emission of methyl bromide from industry was 1000 kg (US EPA Toxic Release Index, 1990). In general, because processes are enclosed, the amount of methyl bromide lost during manufacture is negligible compared with the amount released to the atmosphere when it is used as a fumigant.

3.2.1.4 *Methods of transport*

Methyl bromide is easily liquefied and is shipped in steel cylinders as a liquefied gas under its own vapour pressure (Matheson Gas Data Book, 1980). This may be augmented with nitrogen or carbon dioxide before shipment to permit rapid ejection at low temperatures (Stenger, 1978). Methyl bromide is also transported in cans and tanks.

An industrial code of practice for the handling and transportation of methyl bromide in Europe has been recommended (EMBA, 1988).

3.2.1.5 Accidental release or exposure

Incidents of methyl bromide poisoning occur through accidental exposure to the compound, particularly during soil or structural/space fumigation and also during manufacture (section 9).

3.2.2 Uses

Methyl bromide is used as follows: soil (pre-planting) fumigation (77%), quarantine and commodity fumigation (12%), structural fumigation (5%), and chemical intermediates (6%) (UNEP, 1992) (Table 8).

The general use of methyl bromide in fire extinguishers has been abandoned as it was the cause of a number of fatal accidents (see section 9). However, it is still used for special-purpose fire extinguishers (Matheson Gas Data Book, 1980).

Since 1960, methyl bromide has been used as a fumigant for a wide range of stored, dry foodstuffs and other products, such as tobacco, fresh fruit, and vegetables, in particular to comply with quarantine regulations (Bond, 1984). It is used pre-harvest in glasshouses and in the open as well as post-harvest in mills and warehouses. It is also used to fumigate buildings, furniture, books, and archived material (Alexeeff & Kilgore, 1983).

The techniques used for the different types of methyl bromide fumigation are given in Table 9.

3.2.2.1 Soil fumigation

The gas is a soil fumigant for the control of weeds, weed seeds, nematodes, insects, and soil-borne diseases (Meister, 1985). Methyl bromide can be applied to soil under sheeting in a vaporized form using either evaporating jars (cold method) or heating (hot method), or injected as a liquid and allowed to vaporize *in situ* (Table 9).

Table 9. Outline of methyl bromide fumigation techniques[a]

Type	Examples of application	Fumigation dosage	Fumigation period	Application technique	Ventilation of methyl bromide residues
1. Space fumigation	Buildings (mills, factories, museums)	0.5-1% in air (20-40 g/m^3)	2-3 days	Sealing of all openings except one door with plastic foil and adhesive tape; placement of methyl bromide cylinders at selected locations inside building; opening of cylinders by team of operators working backwards towards escape door; sealing of escape door	Natural ventilation (opening of doors, windows) assisted by mechanical exhaust ventilation if available
2. Chamber fumigation	Dried food products, wood	0.8-1% chamber volume (32-40 g/m^3)	< 1 day	Permanently installed delivery systems, operated from outside of chamber	Mechanical ventilation: continuous dilution with fresh air in atm. pressure chambers, batch dilution cycles in "vacuum" chambers
3. Fumigation with movable delivery system	Ducts, bins; stacked goods, pieces of machinery	1-2% in air (40-80 g/m^3)	1-3 days	Sealing of goods/machines under plastic foil or tarpaulins; methyl bromide injection through ports via flexible tubing, using (*a*) hot vapour systems (methyl bromide passed through heat exchanger in a water boiler), or (*b*) cold vapour systems (pressurized cylinders on trolleys)	Removal of sheeting, natural ventilation
4. Surface fumigation	Soil, compost	50-100 g/m^2	2-5 days	(*a*) Hot vapour application using perforated tubing prepared under plastic sheeting; (*b*) liquid methyl bromide injection, truck/trailer with cylinders connected to injection nozzles and reel unfolding plastic sheeting behind truck; (*c*) methyl bromide cans place in puncturing cups underneath sheeting, punched open by operator walking on the sheeting	Removal of sheeting, latency period and/or watering before tillage

[a]From Guillemin et al. (1990).

The methods practised in various countries differ. In the USA, methyl bromide is mainly applied by chisel application (injection). Methods of soil disinfestation used in Belgium, for example, are given in Table 10. In Israel, both soil fumigation in strips and blanket (large area) fumigation are widely used (Klein, 1989). The methods used are the hot gas method and injection method. Strip fumigation is not as effective as blanket fumigation but, in some circumstances, is more economical.

Table 10. Soil disinfestation methods and products used in Belgium and their relative importance[a]

Physical methods:	
- steaming : - sheet steaming/steaming via drain pipes	7%
- vacuum steaming of rockwool substrates	2%
- solarization	0%
- microwave radiation	0%
- ozone	0%
Chemical methods:	
- methyl bromide (MB) : fumigation (greenhouse/outdoor) + injection (outdoor)	50%
- chloropicrin (CP) : injection (greenhouse/outdoor)	10%
- MB + CP : injection (outdoor)	10 %
- metham-sodium : injection (greenhouse/outdoor)	8%
- dazomet : soil mixing (greenhouse/outdoor)	3%
- dichloropropene : injection (greenhouse/outdoor)	8%
- others	2%

[a] From: Pauwels (1989).

Not only the method of application but also the type of plastic sheeting used for covering is important for optimal fumigation conditions as well as for the safety of the fumigators and reduction of environmental pollution. Munnecke et al. (1978) showed that using gas-tight films very high concentrations of methyl bromide reached the soil, whereas, under low density polyethylene (LDPE) covers, these concentrations rapidly dissipated. In the Netherlands where extensive horticulture plays an important economic role,

Wegman et al. (1981) reported that 2 million kg of methyl bromide were being used in glasshouses each year. De Heer et al. (1983) compared different plastic films in trials in the main glasshouse district of the Netherlands. They confirmed that the dose of methyl bromide could be substantially reduced, without affecting the concentration-time product in the soil, if gas-tight films were used instead of LDPE. They emphasized that the reduction of methyl bromide losses depends greatly on how the films are laid down and wetted and on how the methyl bromide is distributed under the films. The use of methyl bromide for soil fumigation was banned in the Netherlands in 1991. Prior to this date, the use of LDPE sheeting was prohibited, the mandatory cover time of the soil was extended to 10 days, and the dose reduced to 20 g/m^2 (De Heer et al., 1983). In 1983, this dose was increased to 40 g/m^2 but, in practice, doses of 60-80 g/m^2 were used up to the phase-out in 1991, because applying the protective sheeting in a careful manner proved to be too time-consuming. In a comparison of methyl bromide diffusion through different plastic films 40 μm thick, some showed excellent barrier properties to the gas whereas 75% of the methyl bromide applied was lost through LDPE and another type of plastic within 5 h (Van Wambeke et al., 1988).

Doses of methyl bromide to be applied depend on:

- the legal standards (regulations differing for each country) and methods used;
- the pest to be controlled (type/degree of infestation/ infection);
- temperature;
- soil type;
- the plastic soil cover (covering time and type of plastic).

Methyl bromide is particularly used in intensive horticulture, where, because of specialization, only a few selected crops are grown with a resulting increase in pests, microorganisms, and weeds that could decrease the quality and quantity of the crop.

Table 11 gives examples of the use of methyl bromide as a soil fumigant and the recommended dosage. Common rates of application of methyl bromide to soil vary between 50 and 125 g/m^2

Table 11. Pest controlling dose rates of a 98% methyl bromide formulation in g/m² according to soil type (in United Kingdom)[a,b]

Crops	Dosage in g/m² [b]		Aeration	Remarks	
	to control nematodes, annual and perennial weeds[c] and broomrape	to control damping-off fungi, e.g. *Rhizoctonia, Pythium spp., Thielaviopsis basicola, Phytophtora spp.*	to control fungi causing rots[d] and wilts, e.g., *Scleroctiun rolfsii, Pythium spp., Verticillium spp., Fusarium spp., Pyrenochaeta spp.*	(days)[e]	
Plant nurseries: vegetables, flowers	35-50	50		7-14	do not fumigate heavy soils to be used for celery nurseries
Vegetables: cucurbits, tomatoes, eggplants, peppers, onions, radishes	35-50	75	75-100	7-14	for beta-alpha-type cucumbers, soil leaching is obligatory
Leafy vegetables: celery, chicory, cabbage, lettuce, spinach	35-50	75	75	7-21	
Strawberries (nursery and field)	35-50	75	75	7	

Table 11 (continued)

flowers: annual, perennial cut flowers, ornamentals	35-50	75	75-100	7-14	even light soils must be leached before planting carnations
Bulbs and corms (on light soils only)	35	50	75	7	
Citrus replanting			50	14	
Deciduous replanting			75-100	14	

[a] From: Bromine & Chemicals Ltd. (1990).
[b] When a dose range is given, the smaller dose relates to light soil, the larger to medium and heavy soils.
[c] Purple nutsedge (nut grass) corms and seeds of horseweed, Erigeron (*Conyza*), mallow (*Malva*), and legumes are not efficiently controlled.
[d] The dose rate to control *Fusarium* on all soil types is 100 g/m^2.
[e] For light soils and/or high temperatures, the shorter aeration period is sufficient; for medium and heavy soils, and all soil types at low temperatures, the longer aeration period is required; the long aeration period is also desirable for direct seeded crops; if rain is expected during the aeration period, do not remove the plastic sheets entirely, but allow for aeration while protecting the soil from direct rain.

(FAO, 1980). Industry recommends that the dosage should not exceed 100 g/m^3.

In some cases, it is recommended that, after fumigation, the ground should be thoroughly leached to remove the bromide salts that are formed in the soil. Fumigation of peat soils before planting leafy vegetables is not recommended, because of the resulting high bromide residues. There are different national regulations concerning the crops permitted to be grown after soil fumigation. In some countries, the use of methyl bromide is severely restricted or prohibited.

3.2.2.2 *Quarantine and non-quarantine commodity treatments*

Methyl bromide is currently used for quarantine and non-quarantine commodity treatment, because it is rapidly effective (often less than 24 h) and can be used for pests on a wide range of commodities at fumigation temperatures exceeding 4 °C. Imports of products subject to infestation are often only permitted if the product is fumigated in the country of origin or at the ports of destination (UNEP, 1992).

Commodities fumigated with methyl bromide include durable food commodities (such as cocoa and coffee beans, grains, dried fruit, nuts), perishable food commodities (mainly fruits and vegetables), and non-food commodities (forestry products, cut flowers, cotton, tobacco, packaging, animal feed stuffs, artifacts, and other commodities). Suggested dose rates for storage fumigation are given in Table 12 and Table 13.

In special extermination problems, such as that of the khapra-beetle (*Trogoderma granarium* Ev.) larvae in the transport of bulk-loaded expeller (pressed remains from oil and fat seeds that are used for making cattle feed), methyl bromide is used in combination with hydrogen phosphide (Wohlgemuth et al., 1976).

Fumigation is followed by an aeration period when fresh air is passed through the fumigation chamber to remove methyl bromide from the air space. At least 2 h of aeration is required for fresh fruit fumigated with methyl bromide. In addition, the aeration must continue until the concentration of methyl bromide in the air vented

Table 12. Dosage rates and exposure times for space fumigation with methyl bromide

Commodity	Vacuum chamber fumigation		Fumigation at atmospheric pressure[a]		Notes
	Dosage rates (g/m^3)[b]	Exposure time (h)	Dosage rates (g/m^3)[b]	Exposure time (h)	
Foods:					
coffee	32-55	3	16-40	16-24	
cocoa beans	32-55	3	16-40	16-24	
grains	-	-	20-38	24	Maximum moisture content of 12%; lower doses for upright storage and higher doses for flat storage; do not fumigate seed grain; values are for 21-25 °C; between 10-15 °C multiply dosage by 1.5; between 16-20 °C multiply by 1.25
spices	40	3	16-24	16-24	At 20 °C and above only
cigarette tobacco	54-80	4	20-32	45-72	

Table 12 (continued)

Commodity	Vacuum chamber fumigation		Fumigation at atmospheric pressure[a]		Notes
	Dosage rates (g/m^3)[b]	Exposure time (h)	Dosage rates (g/m^3)[b]	Exposure time (h)	
Packing materials:	40-58	3-4	24-48	16-24	Compressed bales should be fumigated under vacuum at 55 g/m^3, for 48 h at 15 °C and above
Factories and storage premises	-	-	16-40	24	Use lower doses of range for spaces over 14 000 m^3
Transport vessels, freight containers	-	-	16-40	10-12	Multiply dose by 6 against Khapra beetle

[a] Including stacks under gas-proof sheets.

[b] Where a range is given, the fumigation dosage depends on temperature: the dosage rates are for a temperature range of 4-32 °C; at lower temperatures higher doses and longer times should be used.

Table 13. Use of methyl bromide as a storage fumigant in Germany[a]

Area of use	Dosage (g/m^3)	Length of fumigation (h)
Stored goods		
- mills	16-30	24-48
- silos (elevators)	16-30	24-48
Expeller		
- in barges, inland and coastal motor boats		
a) in sacks	56-96	24
b) as bulk material[b]	56-96	72
- in railway carriages		
in sacks[b]	56-96	72
Stored goods (apart from grain, expellers, tobacco)		
- in vacuum chambers with gas circulating apparatus	50	2
- in small silos with gas circulating apparatus	70	16
- packed in gastight sheeting	16-30	24
- in sufficiently gastight rooms	16-30	24

[a] Adapted from: BUA (1987) and BBA (1989).
[b] Together with hydrogen phosphide.

from the chamber is below an exposure limit value of 20 mg/m^3 (usually within 4-12 h). This is to protect workers entering the fumigation chamber immediately after the aeration period (Sell et al., 1988).

The development of acceptable alternatives to methyl bromide for certain commodities is complex (UNEP, 1992).

3.2.2.3 *Structural fumigation*

Methyl bromide is used extensively as a structural fumigant, and this application currently accounts for about 5% of production. The current use of methyl bromide as a structural fumigant is widespread because of its efficacy, applicability for a wide variety of sites and

pests, suitability for use on accessible and inaccessible pests, short fumigation period (about 1 day), lack of insect resistance, cost effectiveness, and because it does not damage food, structures, or equipment when used correctly. However, methyl bromide is toxic, must be applied by skilled operators, and, in some instances, requires multi-day aeration periods to reduce methyl bromide exposure to levels safe for humans (UNEP, 1992).

In California and Florida, where homes are fumigated to eradicate insect pests, poisoning incidents have occurred through unauthorized access to buildings under fumigation (section 9.2.1.2). Fumigating food in houses is mentioned in section 5.2.1.

3.2.2.4 Industrial uses

Methyl bromide is used in organic synthesis, principally as a methylating agent (Torkelson & Rowe, 1981) and as a low-boiling solvent, for example, for extracting oils from nuts, seeds, and flowers (Windholz, 1983). Because of the toxicity of methyl bromide (section 9), its use as a refrigerant and as a general fire extinguishing agent is now of historical interest (likewise its use as an anaesthetic in the 19th century). Methyl bromide may still be used in fire extinguishers in special situations (Matheson Gas Data Book, 1980).

3.2.3 Methyl bromide emission from motor car exhausts

Harsch & Rasmussen (1977) reported the presence of methyl bromide at sub-part per-billion concentration levels in urban areas (section 5.1.1). The major source of methyl bromide in urban areas is believed to be automobile exhaust.

Engines operating on "leaded" petrol, containing ethylene dibromide (EDB) as an additive, contribute a much larger amount of methyl bromide to urban atmospheres than engines with catalytic converters burning "unleaded" fuel. On the basis of an estimated consumption of 12 million tonnes of leaded petrol per year, Bell (1998) calculated that about 45 tonnes of methyl bromide is produced from car exhaust in the United Kingdom annually. Methyl bromide concentrations in the range of 90-190 $\mu g/m^3$ have been measured in the exhaust emissions of motor vehicles using leaded petrol with EDB (Baumann & Heumann, 1987). According to these authors, the

portion of organobromine compounds is 22-44% of the total bromine that is emitted in the exhaust gases, the concentration decreasing with increasing engine temperature. Furthermore, the methyl bromide content of these organic components varies between 64 and 82% (Baumann & Heumann, 1987). On the basis of an estimated global consumption of 50 000 tonnes of 1,2-dibromoethane as a petrol additive (Roskill, 1992), and, from the above figures, and assuming that the bromide from the EDB is emitted in full from the exhaust gases, it can be estimated that between 7000 and 18 000 tonnes of methyl bromide could be emitted annually from car exhaust. The increasing use of unleaded fuel should result in a decrease in these levels.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Transport and distribution between media

4.1.1 Transport in air

In view of the destructive effects thatbromine compounds have on the ozone layer, the release of methyl bromide into the atmosphere may pose an environmental problem. Models indicate that inorganic bromine can significantly affect ozone levels in the stratosphere (Wofsy et al., 1975; Prather et al., 1984; Prather & Watson, 1990; UNEP, 1992).

The atmospheric budget of methyl bromide is controlled by the magnitude of natural and anthropogenic sources (sections 3.1, 3.2, and 5.1.1) and by the atmospheric and surface removal processes.

The major natural source is oceanic and the major anthropogenic source is the release into the atmosphere of methyl bromide during its use as a fumigant and, to a lesser extent, from industrial and motor vehicle emissions. As far as is known, removal processes are mainly atmospheric. However, ocean and terrestrial surface removal could be significant, but this remains to be quantified (UNEP, 1992).

There are three possible removal mechanisms for methyl bromide within the atmosphere: (*a*) reaction with the hydroxyl radical and other chemical species in the troposphere; (*b*) precipitation in the troposphere; and (*c*) transport and subsequent photolytic and chemical removal in the stratosphere (section 4.2.2). Removal by precipitation is thought to be unimportant (UNEP, 1992). According to the report, the most significant removal process is that of the reaction of methyl bromide with the hydroxyl radical in the troposphere (estimated removal time of 2 ± 0.5 years). A minor removal process is transport to the stratosphere followed by reaction with the hydroxyl radical and photodissociation with an estimated lifetime of about 30-40 years.

Between 20 and 25 km above sea level, photodissociation is of equal importance to loss by diffusion and reaction with the hydroxyl radical. Above this, photolysis plays the most important role (Robbins, 1976a).

From the sparse data available (section 5.1.1), it appears that methyl bromide has no significant vertical gradient in the troposphere, but decreases rapidly in the high-latitude lower stratosphere by at least a factor of 3-5 within 10 km of the tropopause (UNEP, 1992). Further details are discussed in sections 4.2.2, 4.4, and 5.1.1.

4.1.2 Transport in water

The solubility of methyl bromide in water is between 16 and 18 g/litre at 20 °C (Table 1). In soil, it is partially hydrolysed to bromide ion. After fumigation using methyl bromide, the soil may be leached with water to prevent the uptake by plants, subsequently planted on the sterilized soil, of the bromide ions formed. Between 300 and 600 mm of irrigation water is necessary to remove the bromide ions effectively from the root zone of plants (Wegman et al., 1981). In the Netherlands, this leaching caused problems because the water was mostly withdrawn from surface waters and the drainage water after leaching was discharged again into the surface waters; thus the bromide ion concentration accumulated during leaching periods.

Vanachter et al. (1981) found a linearity in the inorganic bromide amounts in the leaching water up to 200 mm. Between 200 and 400 mm, a decreased concentration was seen in two types of soil tested, a sandy soil containing 2.15% organic matter and a loamy soil containing 7.22 % organic matter. There was a direct correlation between the initial bromide ion concentrations and the bromide ion concentrations in the first fractions of leaching water. The average half-life for methyl bromide in surface water, under field conditions, was calculated to be 6.6 h at a water temperature of about 11 °C, the decline being attributed to degradation and volatilization processes (Wegman et al., 1981).

It has been found that methyl bromide is able to diffuse through, and is adsorbed by, certain plastics, e.g., polyethylene. Drinking-water pipes that are either free or in earth can thus be contaminated within a few days, if surrounded by methyl bromide that is being used for fumigation (Herzel & Schmidt, 1984).

4.1.3 Transport in soil

Methyl bromide is nearly four times heavier than air, and much of that used as a soil fumigant diffuses throughout the surface to depths of 60-240 cm, some of it being hydrolysed to bromide ion or decomposed by microorganisms, the remainder (45-90%) (section 4.1.1) eventually being dissipated into the atmosphere (Brown et al., 1979). Daelemans (1978) found the rate of degradation of methyl bromide in soil was about 6-14% per day at 20 °C.

Lepschy et al. (1979) carried out short- and long-term studies on the effects of fumigation with methyl bromide on various soil types. They found that methyl bromide could be detected up to 3 weeks after fumigation in different soil types, the highest content being found in the upper soil layers (0-40 cm). Traces of methyl bromide could be measured down to a depth of 80 cm. The bromide derived from methyl bromide was largely water soluble, the water solubility and total bromide content reducing with time. Bromide levels were back to normal after 1 year of cultivation.

During fumigation, the transport of methyl bromide gas through soil (pores) is caused by mass flow and molecular diffusion, but its transport is also influenced by simultaneously occurring sink processes, such as sorption and dissolution, and irreversible sink processes, such as hydrolysis (Brown & Rolston, 1980). Earlier experiments by Chisholm & Koblitsky (1943) showed that the reversible and irreversible methyl bromide sink capacities depended on soil moisture content and decreased in the sequence peat, clay, sand. A review of the mechanisms of breakdown of methyl bromide by Moje (1960) indicated that unimolecular nucleophilic substitution should be the major mechanism for the hydrolysis of methyl bromide in water. Maw & Kempton (1973) suggested that the reactions of dissolved methyl bromide with the soil organic matter involved the transference of the methyl group to the carboxy groups and N- and S-containing groups of the amino acids and proteins of soil organic matter. The reactions are expected to be first order because of the excess of organic matter and the production of bromide ion. Following fumigation by methyl bromide, methylation is expected to be highly dependent upon the amount of organic matter present.

Laboratory experiments by Brown & Rolston (1980) confirmed this earlier work to a great extent, showing that rates of bromide

production were significantly influenced by soil type, being greatest with muck, intermediate with loam, and least with sand. A first-order kinetic model for the reversible sink term described effluent curves more adequately than a linear, equilibrium model, though it appeared that both models were inadequate in completely describing the adsorption-desorption process. Irreversible sink processes had a negligible effect on bromide ion production.

Methyl bromide is changed by the methylation of the organic matter and to a smaller extent by hydrolysis to form bromide ion. In contrast to naturally occurring bromide, the bromide formed from methyl bromide is at first only slightly bound to soil particles and is therefore free to move in the soil. Thus, it can be taken up by plants or can be washed out by leaching the soil. It can be completely leached out of sandy soils, but this is very difficult in clay soils (CEC, 1985).

Arvieu & Cuany (1985) also described the dependence of the adsorption and degradation of methyl bromide on the organic matter content of the soil. Adsorption on to organic matter reduces the available methyl bromide concentration in the aqueous and gaseous phases of the soil. Irreversibly adsorbed molecules no longer have biological activity and may persist as bound residues, if not hydrolysed. Organic matter is also a main factor involved in the degradation of methyl bromide in the soil. The reaction rate depends on its nature, composition, and stage of decomposition.

Laboratory experiments carried out by Herzel & Schmidt (1984) confirmed that the degradation of methyl bromide in soil depends almost entirely, if not completely, on the organic composition of the soil. In soil with much humus, the "half-life" of methyl bromide was 10 days, while, in a lighter soil, it was 30 days, and, in sand, about 100 days. The authors concluded that although methyl bromide is degraded in shallow top soils, the fumigant is relatively persistent in the underlying strata, where its diffusion into the atmosphere is no longer possible. If there are unsuitable conditions, such as a high water table, low temperatures, and a low density of the underlying strata, then contamination of groundwater with methyl bromide after fumigation cannot be ruled out.

Rolston & Glauz (1982) described a simulation model for the transport of methyl bromide gas from injection chisels within the field. The injected methyl bromide is assumed to form cylindrical,

parallel sources at the depth of injection. Transport of methyl bromide is described by radial diffusion from the injection cylinders.

A theoretical model has been developed giving profiles of the concentration of methyl bromide in the soil in both liquid and gas phases, making it possible to judge the extent of the soil zone treated and to forecast the behaviour of the substance (Mignard & Benet, 1989).

4.1.4 Vegetation and wildlife

Bromide accumulation in plants depends on various factors, such as the physical and chemical properties of the soil, the climatic conditions (temperature and rainfall), the plant species, and the type of plant tissue (Basile & Lamberti, 1981).

Wheat and soil/bromide dynamics have been studied in methyl bromide-fumigated plots. The total crop bromine concentration was 0.5 g/m^2 (only aerial parts) (Fransi et al., 1987). The bromine concentration in the different parts of spring wheat decreased throughout its development, indicating that the largest rates of bromide uptake were in the first stages of growth. When the grain filling started, there was an increase in bromide concentration, except for the dried leaves fraction, coinciding with an increase in ambient temperature. This increase was more marked in the senescent leaves, which remained in the plant top and were subject to a higher transpiration rate. Afterwards, throughout the grain-filling period, the bromide concentration in all parts decreased sharply. The bromide concentration in the ears was low, especially in the grains. There was no scorching of plants. In another study, Brown & Jenkinson (1971) reported scorching of wheat grown on soil fumigated with methyl bromide by injection; the scorched plants contained up to 6.1% bromide.

Leafy vegetables, such as lettuce and spinach, can take up relatively large amounts of bromide ion without phytotoxic symptoms (Wegman et al., 1981; see also section 5.1.4). In contrast, other crops, such as carnations, citrus seedlings, cotton, celery, pepper, and onions, are particularly sensitive to methyl bromide fumigation (Bromine & Chemicals Ltd., 1990).

There are no data for accumulation in wildlife (see also section 4.2.3).

4.1.5 Entry into the food chain

The two main uses of methyl bromide connected with soil and food fumigation, i.e., "sterilization" of soil prior to planting and fumigation of foods after harvesting, must be considered in relation to entry into the food chain. In the former case, the level of bromide ion must be considered. In post-harvest fumigation, it is possible that methyl bromide itself, as well as bromide and other possible reaction products, may be found in food.

Most attention has been paid to bromide residues in foodstuffs, as methyl bromide seems to be only transient (sections 5.1.4 and 6.3). Possible methylation products are methionine sulfonium methyl bromide, 1-methyl histidine, *S*-methyl cysteine, *S*-methyl-glutathione, and other minor methylated compounds. The composition and amount of each residue depends on the type of foodstuff fumigated (Starratt & Bond, 1990a,b). These residues are also found in foodstuffs that have not been fumigated.

4.2 Transformation

4.2.1 Biodegradation

4.2.1.1 Soil

Methyl bromide is degraded by three species of nitrifying bacteria, the soil nitrifiers *Nitrosomonas europaea* and *Nitrosolobus multiformis*, and the marine nitrifier *Nitrococcus oceanus* (Rasche et al., 1990). Ammonia monooxygenase is thought to be the enzyme that catalyses the degradation. Oxidation results in dehalogenation with the release of bromide ions (Hyman & Wood, 1984).

4.2.1.2 Stored product fumigation

During stored product fumigation, most of the methyl bromide is converted to inorganic bromide and other residues (section 6.3), probably by reaction with amino or sulfhydryl groups in the products.

4.2.2 Abiotic degradation

4.2.2.1 Hydrolysis

Methyl bromide hydrolyses at neutral pH in laboratory light to methanol, bromide, and hydrogen ion:

$$CH_3Br + H_2O \rightarrow CH_3OH + H^+ + Br^-.$$

The rate constant of 3.0×10^{-7} s^{-1}, at 25 °C, reported by Moelwyn-Hughes (1938) has been confirmed by Castro & Belser (1981).

The influence of temperature (18 °C and 30 °C) on the hydrolysis rate of methyl bromide was investigated using distilled water buffered at pH 3, 5, 7, and 8 (Gentile et al., 1989). The results are given in Table 14. The authors suggest two types of reaction. The dominant mechanism in pH region 3-8 (where the OH^- concentration is low) is of the S_N1 type. However, at higher pH values (>8), the faster S_N2 type reaction is dominant.

$$CH_3Br \xrightarrow{H_2O} CH_3^+ + Br^- \rightarrow CH_3OH + H^+ \quad (S_N1)$$

$$OH^- + CH_3Br \rightarrow [HO...CH_3...Br]^- \rightarrow CH_3OH + Br^- \quad (S_N2)$$

Table 14. Hydrolysis constant (K) and half-life of methyl bromide in distilled water at different pH and at two different temperatures[a]

pH	18 °C K($10^{-7}s^{-1}$) (±SD)	Half-life (days)	30 °C K($10^{-7}s^{-1}$) (±SD)	Half-life (days)
3.0	2.70(±0.11)	29.0	2.84(±0.19)	28.00
5.0	4.08(±0.10)	19.0	4.51(±0.22)	18.00
7.0	6.63(±0.34)	12.0	7.80(±0.25)	10.00
8.0	8.60(±0.44)	9.0	10.32(±0.15)	8.00

[a] From: Gentile et al. (1989). Distilled water was buffered at the given pH 3, 5, 7 and 8 using 0.2 mol/litre phosphate-citrate buffer. Methyl bromide was added to obtain a final concentration of 50.5 μmol/litre.

The hydrolysis rate of methyl bromide in water taken from four different wells was also measured at 18 °C and 30 °C (Table 15). The authors could not explain the discrepancy between the results of the two sets of experiments. The results from well water are comparable with those given in Table 16 from other authors.

No significant variation in pH occurred with time in well water after the addition, or during the hydrolysis, of methyl bromide (Gentile et al., 1989). The authors explained these results for natural waters by the low amounts of HBr produced by complete hydrolysis of the fumigant and by the presence of natural buffering systems, such as calcium bicarbonate.

Experiments by Herzel & Schmidt (1984) on the persistence of methyl bromide in water confirmed the earlier work by Moelwyn-Hughes (1938), which showed that hydrolysis depends mainly on temperature. Whereas, at 40 °C, there was rapid degradation, at 22 °C, it took several days before there was a rapid decrease in methyl bromide concentrations. At 10 °C, there was an even slower rate of reaction. Fig. 1 shows graphically the rate of hydrolysis of methyl bromide in tap water at these three different temperatures.

The rate constant for methyl bromide hydrolysis in tap water varies with temperature, not according to an equation of the Arrhenius type, but according to the following formula:

$$\log_{10}k = 112.656 - 10236/T - 34.259 \log_{10}T$$

where T is the absolute temperature.

This formula agrees with experimental observations by Moelwyn-Hughes (1938) carried out at temperatures of up to 100 °C. Table 16 shows the dependence of the rate constant and half-life on temperature.

Addition of soil to water greatly enhanced the degradation of methyl bromide (Gentile et al., 1989).

Degradation by hydrolysis is the primary route of degradation of methyl bromide in soils with a very low organic matter content. The adsorption isotherms in these soils were found to be linear but slopes were greatly reduced as moisture content increased (Arvieu, 1983). In soils containing organic matter, two different reactions occurred, adsorption and conversion through reaction with organic matter.

Table 15. Hydrolysis constant (K) and half-life of methyl bromide in well-water at 18 °C and 30 °C[a]

Site or well no.	pH	18 °C K($10^{-7}s^{-1}$) (± SD)	Half-life (days)	30 °C K($10^{-7}s^{-1}$) (± SD)	Half-life (days)
1	7.4	2.20 (±0.33)	36.0	5.28 (±0.24)	15.0
2	7.7	2.01 (±0.08)	40.0	4.62 (±0.34)	17.0
3	7.7	1.81 (±0.28)	43.0	4.27 (±0.34)	18.0
4	7.8	1.58 (±0.14)	50.0	3.95 (±0.53)	19.0

[a] From Gentile et al. (1989). Methyl bromide was added to well water to obtain a concentration of 50,5 µmol/litre.

Table 16. Hydrolysis rate constant (k) and half-life of methyl bromide in water at different temperatures

Temperature (°C)	Observed rate constant (sec^{-1})	Half-life
17	[a] 1.07×10^{-7}	75 days
25	[b] 4.09×10^{-7}	20 days[b]
25	[a] 3.57×10^{-7}	21.3 days
35.7	[a] 1.65×10^{-6}	117 h
46.3	[a] 6.71×10^{-6}	28.6 h
100	[a] 1.28×10^{-3}	0.6 h

[a] Values from Moelwyn & Hughes (1938) using distilled water.
[b] Values from Mabey & Mill (1978) using freshwater, pH 7.

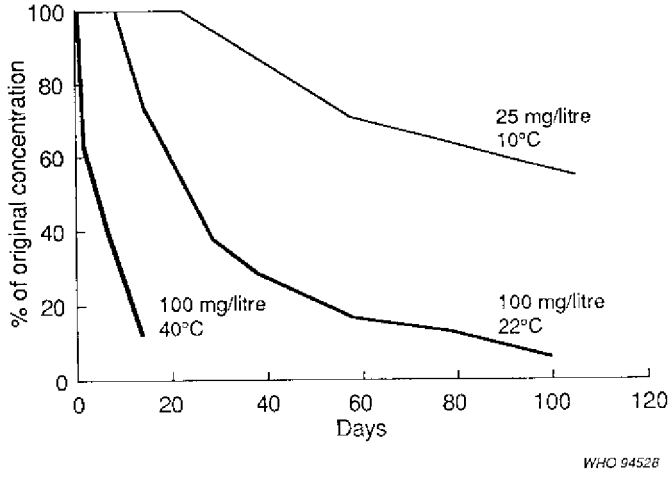


Fig. 1. Hydrolysis of methyl bromide in tapwater at 10, 22, and 40°C. From Herzel & Schmidt (1984).

Degradation occurred by the methylation of carboxylic groups on moist H-substituted peat. In soils containing other groups that can be methylated, the mechanism and factors of methyl bromide degradation are more complex.

Adsorption on to organic matter reduced the available concentration of methyl bromide in the aqueous and gaseous phases of soil. Organic matter was also the main factor involved in the degradation of methyl bromide in the soil (Arvieu & Cuany, 1985).

4.2.2.2 *Light-assisted hydrolysis in water*

The UV-absorption cross sections for methyl bromide (174-262 nm) have been confirmed by several authors (Robbins 1976b; Uthman et al., 1978; Molina et al., 1982; Gillotay et al., 1989). The UV absorption spectrum has a maximum of 202 nm with a steep decrease at longer wavelengths reaching 0.2% of the maximum at 260 nm (Table 17). This is much shorter than 290 nm, which is the shortest wavelength radiation reaching the earth's surface from the sun.

It should be noted that the photoactivation of methyl bromide, as well as its hydrolysis products in water or on soil surfaces, will differ from the gas phase activities of these processes. The hydrolysis products are in solution and differ energetically. Since the species energy levels are changed from those of the isolated molecule, critical absorption wavelengths would be shifted.

The influence of sunlight versus dark using natural waters in a laboratory test showed little effect on the hydrolysis of methyl bromide (Gentile et al., 1989, 1992).

Irradiation with a "pen-ray" low-pressure mercury lamp at 254 nm gave a 6.6-fold increase in the rate constant. However, photolysis does not alter the stoichiometry of the hydrolysis (Castro & Belser, 1981). The authors concluded that the almost exclusive path of decay (>99.6 %) was the direct hydrolysis of photoactivated methyl bromide with the formation of methanol, bromide ion, protons, and a trace of methane (<0.4%).

Table 17. Absorption cross sections of methyl bromide[a]

λ (nm)	$10^{20}\,\sigma$ (cm^2)	λ (nm)	$10^{20}\,\sigma$ (cm^2)
190	44	230	15
192	53	232	12
194	62	234	9.9
196	69	236	7.6
198	76	238	5.9
200	79	240	4.5
202	80	242	3.3
204	79	244	2.5
206	77	246	1.8
208	73	248	1.3
210	67	250	0.96
212	61	252	0.69
214	56	254	0.49
216	49	256	0.34
218	44	258	0.23
220	38	260	0.16
222	32		
224	28		
226	23		
228	19		

[a] Values recommended by NASA (1992) and taken from Gillotay et al. (1989). These authors measured the cross sections down to 210 K; for <210 nm, the temperature effect is negligible.

4.2.2.3 *Reaction with the hydroxyl radical*

Reaction of methyl bromide with the hydroxyl radical is believed to be the primary mechanism for the removal of methyl bromide from the lower troposphere (Singh et al., 1981).

Methyl bromide reacts slowly with the hydroxyl radical:

$$CH_3Br + OH^- \rightarrow CH_2Br^- + H_2O$$

with a reaction rate constant of about 3×10^{-14} cm^3/molecule per second at 298 °K (NASA, 1992).

Table 18 shows values for hydroxyl radical rate constants.

Table 18. Atmospheric reactions of methyl bromide

Reaction	Rate constant	Height above sea level (km)	Reference
$CH_3Br + h\nu$	1×10^{-11}/s	16	Robbins (1976a)
	1×10^{-9}/s	20	
	1×10^{-6}/s	30	
	5×10^{-5}/sec	50	
$CH_3Br + OH^-$	3×10^{-14} cm^3/s (298 °K)		NASA (1992)[a]
	$k(T) = 3.6 \times 10^{-12} \exp[-(1430 \pm 150) K/T]$ cm^3/s		

[a] Profiles of OH^- and temperature of the stratosphere are given in NASA (1992).

Recent laboratory data for the rate coefficient of the reaction of methyl bromide (Mellouki et al., 1992a,b) with the hydroxyl radical together with the estimated distribution of the hydroxyl radical (WMO, 1992), gave an estimated OH^--removal lifetime for methyl bromide of 2 ± 0.5 years (UNEP, 1992).

4.2.2.4 Photolysis in the atmosphere

In the upper stratosphere, above 25 km, the photodissociation of methyl bromide is the most dominant loss mechanism. Below this, as less UV radiation is able to penetrate through the atmosphere, the role of photolysis decreases. Between 20 and 25 km above sea level, photodissociation is equally as important as loss by diffusion and reaction with OH^-. Below 20 km, down to the troposphere, photodissociation becomes negligible and losses by diffusion and reaction with OH^- are of approximately equal importance (Robbins, 1976a) (Table 18).

The end-products of photodissociation of methyl bromide and reactions with hydroxyl radicals in the atmosphere are probably carbon dioxide, carbon monoxide, and bromide species (BUA, 1987).

4.2.3 Bioaccumulation

There are no experimental data on bioaccumulation potential. The octanol/water partition coefficient (log P_{ow}) of methyl bromide

has been given as 1.19 (Hansch & Leo, 1979; Sangster, 1989), so it probably does not have any significant tendency to bioaccumulate (see also section 4.1.5).

4.3 Interaction with other physical, chemical, or biological factors

It has been found that methyl bromide is able to diffuse through certain plastics (Herzel & Schmidt, 1984).

A reaction is possible between methyl bromide and the following materials (Bond, 1984):

- iodized salt, stabilized with sodium hyposulfite;
- certain baking sodas, salt blocks used for cattle licks, or foods containing reactive sulfur compounds;
- full fat soy flour;
- sponge rubber;
- foam rubber as used in rug padding, pillows, cushions, and mattresses;
- rubber stamps and similar forms of reclaimed rubber;
- furs, horsehair, and pillows (especially feather pillows);
- leather goods tanned using a sulfur process;
- woollens, especially angora; some adverse effects have been noted on woollen socks, sweaters, and yarn;
- viscose rayons, made by a process that uses carbon disulfide;
- cinder blocks or mixtures of mortar; mixed concrete occasionally picks up odours;
- charcoal, which not only becomes contaminated but absorbs great amounts of methyl bromide and, thus, reduces effective fumigant concentrations;
- paper that has been cured by a sulfide process and silver polishing papers;
- photographic chemicals, not including films;

- rug padding, vinyl, cellophane;
- any other materials that may contain reactive sulfur compounds.

4.4 Ultimate fate following use

4.4.1 Methyl bromide and the ozone layer

Methyl bromide from natural and anthropogenic sources is released into the atmosphere. Once organic bromine compounds, such as methyl bromide and the halons (section 5.1.1), enter the stratosphere, they decompose to release bromine atoms. Fig. 2 depicts the key bromine-containing species in the stratosphere and shows the interconversion between reactive ($Br^{\cdot}$ and $BrO^{\cdot}$) and reservoir (HBr, HOBr, BrCl, and $BrONO_2$) species (UNEP, 1992).

Yung et al. (1980) proposed the following reactions for ozone loss due to bromine:

$$Br^{\cdot} + O_3 \rightarrow BrO^{\cdot} + O_2$$

$$Cl^{\cdot} + O_3 \rightarrow ClO^{\cdot} + O_2$$

$$BrO^{\cdot} + ClO^{\cdot} \rightarrow Br^{\cdot} + Cl^{\cdot} + O_2$$

$$\text{Net } 2O_3 \rightarrow 3O_2$$

Ozone removal by bromine is far more efficient on a per molecule basis than that by chlorine. This bromine-catalysed ozone removal in the lower stratosphere is thought to occur via the reaction between $BrO^{\cdot}$ and $ClO^{\cdot}$ (WMO, 1992) whereby the efficiency of bromine-induced ozone loss increases with increasing abundance of stratospheric chlorine. Bromine catalysis is most efficient in the lower stratosphere where the ozone concentration is largest.

Reactive bromine has been detected directly in the stratosphere in the polar regions, as well as $OClO^{\cdot}$, for which the only known source is the reaction of $BrO^{\cdot}$ with $ClO^{\cdot}$. Analyses of these measurements indicate that the $BrO^{\cdot}$ + $ClO^{\cdot}$ catalytic cycle is responsible for roughly 25% of the observed total ozone loss in the appearance of the Antarctic ozone hole (an event mainly restricted to

Antarctica and to the months of September-November, involving heterogenous reactions on polar stratospheric clouds) (WMO, 1992).

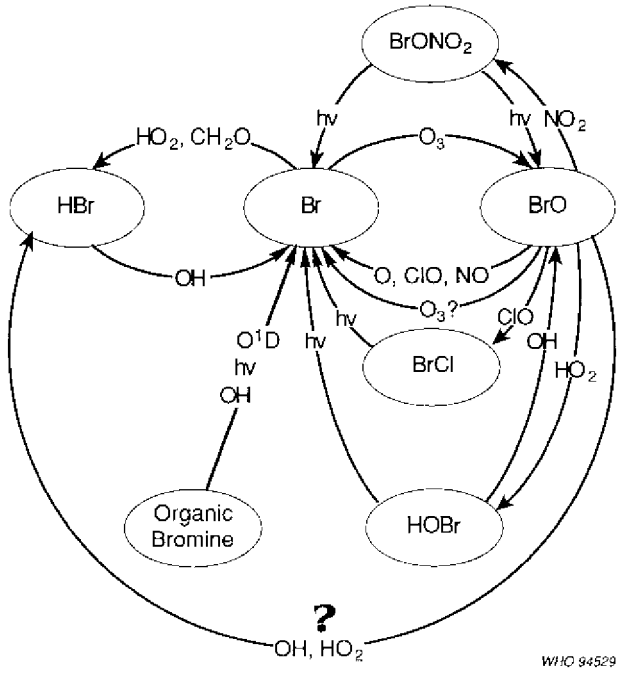


Fig. 2. Gas phase bromine cycle[a]

[a]Adapted from UNEP (1992).

Note that methyl bromide constitutes 55% of the atmospheric organic bromine (Schauffler et al., in press).

O^1D denotes electronically excited oxygen atom. A profile of O^1D can be found in NASA (1992).

Another possible catalytic cycle is that between BrO^- and HO_2 (Poulet et al., 1992).

The Ozone Depletion Potential (ODP) represents the amount of ozone destroyed by the emission of one kg of a chosen gas over a

particular time scale, compared with 1 kg of a reference molecule, usually CFC-11 (Table 19). The amount of ozone depletion from methyl bromide, and the ODP of the gas are dependent upon the atmospheric abundance of chlorine. On the basis of current understanding, the higher the abundance of chlorine, the higher the ODP of methyl bromide and the amount of ozone depletion it causes.

Table 19. Lifetime and time-dependent depletion potential (ODP) for methyl bromide (CH_3Br) in comparison with chlorofluorcarbons[a]

Species[c]	Total atmospheric lifetime (year)	Stratospheric lifetime (year)	Steady-state empirical polar ODP[b]
CFC-11 ($CFCl_3$)	55	55	1,0
CFC-113 ($CFC1_2CF_2Cl$	110	110	1,10
CH_3Br	2,0	35	0,7

[a] Values are relative to CFC-11 as the reference gas.
[b] ODP = ozone depletion potential.
[c] CFC = chlorofluorocarbon.

The key factors influencing the ODP of methyl bromide include: (*a*) the atmospheric lifetime of the compound (relative to CFC-11); (*b*) the release of reactive bromine from methyl bromide (relative to CFC-11); and (*c*) the relative efficiency of reactive bromine for ozone destruction compared with that of reactive chlorine (alpha factor).

(*a*) Atmospheric lifetimes for methyl bromide have been estimated at 1.6 years (WMO, 1992) and 2.0 years (UNEP, 1992). However, oceanic and terrestrial surface removal processes have not been taken into account.

(*b*) As methyl bromide is a relatively short-lived molecule within the stratosphere, it is expected that its release of reactive bromine is faster than that of chlorine from CFC-11.

(*c*) The current best estimate of alpha in the lower polar stratosphere is about 40 (UNEP, 1992).

The current best estimate of the steady-state ODP for methyl bromide from the semi-empirical approach and models including both gas-phase and heterogeneous chemistry is 0.7 (UNEP, 1992). This assumes its lifetime is solely determined by reaction with OH^- in the troposphere.

The anthropogenic contribution to the current atmospheric abundance of methyl bromide is estimated to be about 3 pptv (UNEP, 1992). If anthropogenic methyl bromide is about 13-14% of total atmospheric bromine (calculated by taking 25% of 11 pptv total methyl bromide (UNEP, 1992) = 2.75% of total atmospheric bromine from anthropogenic sources; and 55% of 20.8 pptv total organic bromine as methyl bromide (Schauffler et al., in press) = 11%), the global ozone loss due to anthropogenic methyl bromide is approximately 3%.

4.4.2 *Containment, recovery, recycling, and disposal options for methyl bromide*

At present, after soil, commodity, and structural fumigation, there is no special effort at containment of methyl bromide (see section 3.2 for estimated emission rates from various fumigation processes).

The methyl bromide industry is currently investigating practical methods of recovering the gas by adsorption (using activated charcoal), condensation, and scrubbing techniques. Most of these methods are still in the research and development stage (UNEP, 1992). When methyl bromide cylinders are refilled, instead of the present practice of venting, it may be possible to recondense and recover the gas. In this way, 1-2% of the total methyl bromide used could be saved.

Methyl bromide is a toxic gas and the recommended waste disposal method for large quantities is incineration by specialists. However, incineration may be difficult to arrange safely unless an efficient method of feeding the gas into the incinerator can be arranged. Incineration requires dilution with additional fuel. If a suitably designed combustion chamber is not available, return

labelled containers to supplier. Any release into the atmosphere should take place in well-ventilated outdoor locations only.

All national and local regulations should be observed when disposing of methyl bromide.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 Air

5.1.1.1 Global abundance

The current best estimate for the global abundance of methyl bromide in the troposphere is between 9 and 13 pptv (section 3.1 and Tables 20 and 21) giving a total global burden of 150-220 million kg (UNEP, 1992). From observations taken from the surface waters of the Pacific, off North and South America, Singh et al. (1983) had previously estimated the total natural emission of methyl bromide from the oceans at 300 million kg/year with a residence time of 1.2 years. This estimate is probably too high because of the difficulties with absolute calibration.

The most abundant bromine source gas is methyl bromide, which arises from both natural and anthropogenic sources (WMO, 1992; also sections 3.1 and 3.2). The main natural sources of methyl bromide are oceanic biological processes (mainly algal) where it is formed together with bromoform ($CHBr_3$), methylene bromide (CH_2Br_2), CH_2BrCl, and $CHBrCl_2$ (WMO, 1992). Apart from methyl bromide, other anthropogenic sources are the halons, $CBrF_3$ (CFC-13B1; Halon 1301), $CBrClF_2$ (CFC-12B1; Halon 1211), and $C_2Br_2F_4$ (Halon 2402), which are used as special purpose fire extinguishers (Singh et al., 1988; Schauffler et al., in press).

The atmospheric abundance of methyl bromide appears to be 1.3 ± 0.15 greater in the Northern than in the Southern hemisphere (Tables 20, 21) indicating an excess source in the Northern hemisphere. The major source of methyl chloride is also thought to be oceanic, but the atmospheric abundance of this gas appears to be comparable in both hemispheres (UNEP, 1992). Some atmospheric models compute the interhemispheric OH^- concentration ratio (OH_N^-/OH_S^-) to be about 0.8 (Tie et al., 1992). Assuming reaction with OH^- is the major tropospheric destructive process for methyl bromide, this southern excess of OH^- could largely explain the lower southern atmospheric concentration of methyl bromide. In contrast,

Spivakovsky et al. (1990), using a model based on different assumptions, calculated a higher OH^- concentration in the northern than in the southern hemisphere.

Ozone loss, catalysed by bromine, occurs mainly in the lower stratosphere.The primary cause of the Antarctic ozone hole is most certainly halogen chemistry (WMO, 1992). Bromine is now believed to have a greater potential per molecule to destroy stratospheric ozone than chlorine (section 4.4).

The upward mass transfer of air from the troposphere to the stratosphere occurs mainly in the tropical latitudes between 30 °S and 30 °N (WMO, 1992). Schauffler et al. (in press) give the mixing ratios of brominated compounds and total organic bromine from 12 samples collected at the tropical tropopause (altitude about 16 km) from January to March, 1992. The mean mixing ratio of total organic bromine was 20.8 ± 0.8 pptv. Methyl bromide was found to contribute 55% of the total organic bromine, CH_2Br_2, about 7%, and the remaining 38% was nearly evenly distributed between Halon 1302, Halon 1211, and Halon 2402.

It is against this background of the role of bromine in the ozone depletion in the stratosphere that there has been recent concern about levels of methyl bromide in the atmosphere and the potential effect of the continuing use of this fumigant (see also sections 3.1, 3.2, 4.4).

5.1.1.2 Measured oceanic and coastal air levels of methyl bromide

Table 20 shows levels of methyl bromide in oceanic areas, measured by ground-based, aircraft, and balloon techniques. The differences between the individual readings do not seem to be due to trends in abundance over the last decade or to seasonal variation, but more likely to variations in calibration (UNEP, 1992). An abundance of methyl bromide in the atmosphere of 9-13 pptv is equivalent to a total global burden of 150-220 million kg.

Table 20. Atmospheric abundance of methyl bromide at, or near, ground level (pptv)[a]

Source	Time period	Northern hemisphere	Southern hemisphere	N/S ratio	Observational platform	Reference
Singh	1981	26	20	1.3	Ship	Singh et al. (1983)
Penkett	1982-83	15	11	1.4	Ship	Penkett et al. (1985)
Rasmussen	1983-92	11	8	1.3	Coastal land	MBSW (1992)
Cicerone	1985-87	12	10	1.2	Coastal land	Cicerone, et al. (1988)
Rowland	1991	10	8	1.2	Coastal land	MBSW (1992)
Heidt	1991	14	-	-	Aircraft	MBSW (1992)

[a] From: UNEP (1992).
[b] MBSW = Methyl Bromide Science Workshop (1992).

Although there are differences in the values reported for the absolute magnitudes of the observed methyl bromide abundances, ranging from 10-26 pptv in the Northern hemisphere and 8-20 pptv in the Southern hemisphere, the N/S ratio is almost constant at 1.3 (Table 20). The greater abundance of methyl bromide in the Northern than the Southern hemisphere has been confirmed by all studies published up to now. This is possible evidence for the anthropogenic addition of methyl bromide to the atmosphere from its use as a fumigant (see also sections 3.1, 3.2, and 4.4) as well as from motor vehicle exhaust.

Methyl bromide concentrations in the atmosphere are summarized in Table 21, comparing oceanic and continental values with those in urban areas.

Measurements by Singh et al. (1983) of air and seawater concentrations of methyl halides in, and over, the Eastern Pacific (40° N-32° S) gave average concentrations of 90 ng/m^3 (23 pptv) in air. However, there was a considerable difference between the readings in the northern (101 ng/m^3 [26 pptv]) compared with the southern (74 ng/m^3 [19 pptv]) hemisphere. Because of the large scattering of values, a seasonal trend was not identifiable. As mentioned in section 3.1, it is possible that calibration standards were in error, which would explain the higher values compared with those of other authors.

Rasmussen & Khalil (1984) found that the highest concentrations of methyl bromide in Arctic and Arctic haze were found in the summer (average - 48.2 ng/m^3 (12.4 pptv)) compared with the autumn and winter (average - 39.7 ng/m^3 (10.2 pptv)), and, that methyl bromide did not show the same seasonal patterns as other bromine-containing trace gases.

Penkett et al. (1985) measured four different bromine compounds, including methyl bromide, over a large latitudinal range (40° N to 75° S). They found that there was a clear reduction in concentrations between the two hemispheres, the average concentration of methyl bromide in the Northern Hemisphere being 60 ± 7 ng/m^3 (15.4 ± 1.9 pptv) compared with 41.2 ± 3.5 ng/m^3 (10.6 ± 0.9 pptv) in the Southern Hemisphere.

Table 21. Measured ambient concentrations of methyl bromide

Location	Concentration pptv (ng/m^3)[a]		Reference
	mean or range	max	
Oceanic and coastal air levels			
Eastern Pacific	40°N	26 (101)	Singh et al. (1983)
Ocean	32°S	19 (74)	
Arctic	72°N	11.3 (44)	Rasmussen & Khalil (1984); Berg et al. (1984)
	90°S	7.5	Khalil & Rasmussen (1985)
Atlantic Ocean	40°N	15.4 (60)	Penkett et al. (1985)
Southern Ocean	75°S	10.6 (41)	
Alaska	71°N	11.16 (43)	Cicerone et al. (1988)
Hawaii	20°N	10.75 (42)	
Samoa	14°S	10.23 (40)	
Tasmania	44°S	9.58 (37)	
Alaska	71°N	14.1	Khalil et al. (1993)[c]
Oregon	45°N	12.6	
Hawaii	19°N	11.4	
Samoa	14°S	8.5	
Tasmania	42°S	7.5	
Antarctic	64.5°S	9.0	
Continental air levels			
USA			
Pullman, Washington	< 10-220 (< 40-870)		Harsch & Rasmussen (1977)
Los Angeles	244 (950)	894 (3480)	Singh et al. (1981)
Oakland	55 (214)	108 (420)	
Phoenix	67 (261)	190 (740)	
Badger Pass	5 (19)	8 (31)	Brodzinsky & Singh (1983)
Denver	120 (467)	190 (740)	
Houston	100 (390)	170 (660)	
Jetmore	5 (19)	5 (19)	
Los Angeles[b]	150 (584)	580 (2256)	
Menlo Park	16 (62)	16 (62)	
Mill Valley	25 (97)	25 (97)	
Oakland[b]	55 (214)	78 (303)	
Palm Springs	24 (93)	24 (93)	

Table 21 (continued)

Location	Concentration pptv (ng/m^3)[a] mean or range	max	Reference
Continental air levels (*continued*)			
USA (*continued*)			
Phoenix[b]	67 (261)	120 (467)	Brodzinsky & Singh (1983)
Point Arena	17 (66)	20 (78)	
Point Reyes	93 (362)	93 (362)	
Reese River	5 (19)	5 (19)	
Riverside	250 (973)	560 (2180)	
San Jose	31 (120)	31 (120)	
St. Louis	81 (315)	100 (390)	
San Jose (California, USA)			Singh et al. (1992)
[4-16 April 1985]	400 (44-4661)		
[12-24 August 1985]	121 (5-1067)		
[13-21 December 1985]	2869 (239-15 424)		
Downey, California, USA [8-27 February 1984]	212 (18-815)		
Houston, Texas, USA [9-17 March 1984]	23 (11-48)		
Denver, CO, USA [24 March-1 April 1984]	22 (13-64)		
The Netherlands			
Delft, Vlaardingen and Terscheilling[d]	50-200 (195-780)	100-900 (390-3500)	Guicherit & Schulting (1985)
Japan			
urban and suburban	15-31 (59-122)		JEA (1981)

[a] The converted values in brackets ( ) are only approximate.
[b] Includes substantial overlap with data reported in Singh et al. (1981).
[c] Values given from spring 1991. Fig. 3 gives averages over the last decade.
[d] About 350 samples per site during 1989.

Approximately 750 air samples from five surface sampling sites in Alaska, Hawaii (2), Samoa, and New Zealand were analysed by Cicerone et al. (1988) for methyl bromide between January 1985 and October 1987 (using GC/MS). Methyl bromide concentrations were typically 40-44 ng/m^3 (10-11 pptv).

Khalil et al. (1993) presented a series of 1700 measurements showing the latitudinal distribution of atmospheric methyl bromide from 1983 to 1992 (Table 21 and Fig. 3). The levels of atmospheric methyl bromide measured between 1988 and 1992 seemed to be higher than those measured between 1983 and 1988.

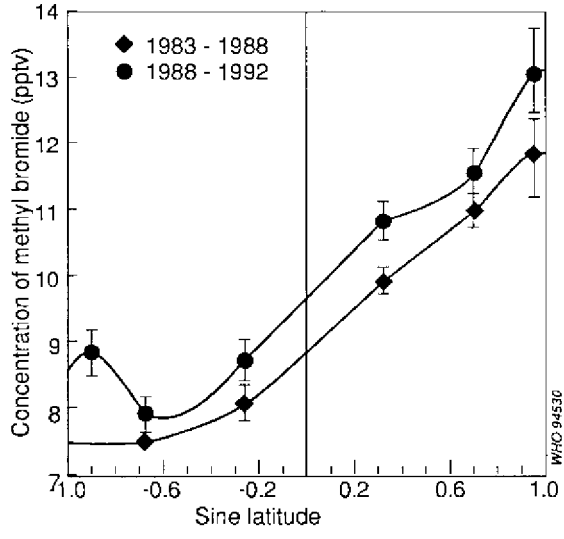


Fig. 3. Latitudinal distribution of atmospheric methyl bromide between 1983 and 1992[a]

[a] From Khalil et al. (1993). Measurements taken at points in Alaska (71° N), Oregon (45° N), Hawaii (19° N), Samoa (14° S), Tasmania (42° S), Antarctic (64.5° S).

5.1.1.3 Measured continental and urban levels of methyl bromide

Data from seven cities in the USA showed significant elevations of methyl bromide levels in urban areas with average concentrations of 159-1004 ng/m^3 (41-259 pptv) (Singh et al., 1982). Concentrations as high as 4000 ng/m^3 were also reported. A further study of methyl bromide levels at 16 sites in the USA confirmed these findings, showing that the larger the city the higher the methyl bromide level (Brodzinsky & Singh, 1983). Methyl bromide is emitted from motor vehicles using leaded petrol. Since many of these urban studies were made, unleaded petrol has been introduced, which could mean that current urban levels of methyl bromide would be lower. Some background levels of 20 ng/m^3 (5 pptv) appear to be lower than oceanic values (Singh et al., 1981).

The high values reported for 1984/85 by Singh (1992) in California (Table 21) may have been influenced by nearby soil fumigation.

In a 1980 environmental survey of methyl bromide levels in Japanese urban and suburban areas, the gas was detected in 5 out of 27 samples with levels ranging from 59 to 122 ng/m^3 (15 to 31 pptv) (JEA, 1981). In the Netherlands, a study of the concentrations of methyl bromide in ambient air was carried out by Guicherit & Schulting (1985). Between 1979 and 1981, air samples were measured in three locations: at the island of Terschelling in the north (little pollution); at Delft, a small city in the densely populated western part of The Netherlands, and in Vlaardingen, in a heavily industrialized area near Rotterdam. The study gave an average of 195-778 ng/m^3 (50-200 pptv) and a maximum 1-h concentration of 390-3500 ng/m^3 (100-900 pptv). The estimated daily (10.0 μg) and yearly (4.5 μg) average exposure values given were based on a total respiratory volume of 20 m^3 per day.

5.1.1.4 Vertical profiles of methyl bromide in the atmosphere

Data on vertical levels of methyl bromide lead to a better understanding of the ultimate fate of methyl bromide in the atmosphere and its role in ozone reduction in the lower stratosphere (section 4.4). Rasmussen & Khalil (1984) and Berg et al. (1984) showed no significant decrease in methyl bromide levels up to 7 km. Penkett et al. (1985) detected a methyl bromide level of 40 ng/m^3

(10 pptv) in the upper troposphere. As shown in Fig. 4, Fabian et al. (1981) measured 1.2 pptv at 14.4 km, but could not detect any methyl bromide at an altitude of 20 km. It has been suggested (UNEP, 1992) that there is no significant vertical gradient in the troposphere, but that the level of methyl bromide decreases rapidly in the lower stratosphere (by at least a factor of 3-5 within 10 km above the tropopause). It is here that ozone loss occurs. Schauffler et al. (in press) gave methyl bromide levels in the mid to low troposphere of 13.6±1.4 pptv (37-45° N; 69° W) and 12.7±1.1 (22-26° N; 94-97° W). In the tropical tropopause (altitude 15.3-16.76 km; 24° N, 68-85° W), levels of 11.4±0.5 pptv (mean of 12 samples) were measured.

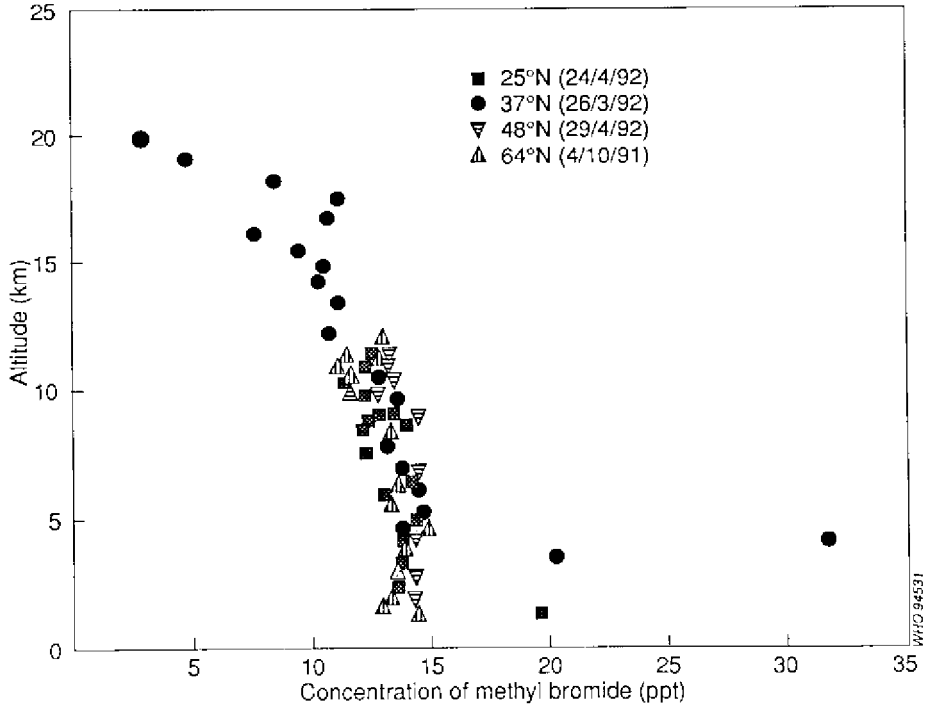


Fig. 4. Vertical profile of methyl bromide in the atmosphere (with permission from Dr E.L. Atlas).

Fig. 4 shows the vertical profile for methyl bromide (Schauffler et al., in press). Fig. 5 shows the vertical profile of methyl bromide together with other atmospheric source gases in the middle Northern hemisphere from air samples taken from the troposphere and stratosphere (Fabian, 1984).

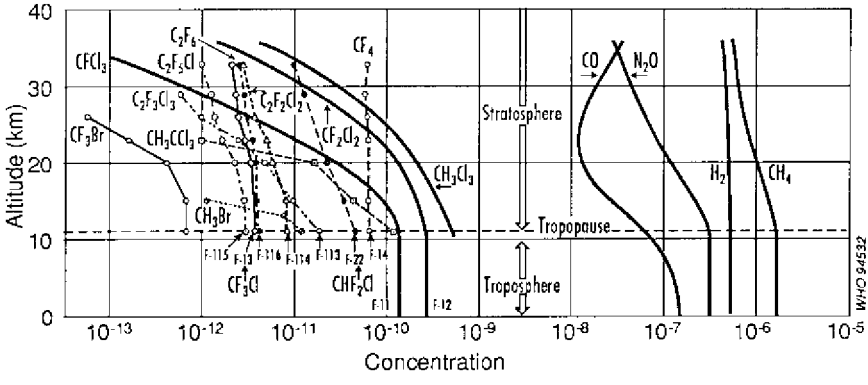


Fig. 5. Vertical profile of some atmospheric source gases in the middle northern hemisphere from air samples taken from the troposphere and stratosphere.[a] Natural source gases, CH_4, H_2, N_2O, CO and CH_3Cl, as well as anthropogenic halogenated compounds are depicted.

[a] Modified from: Fabian (1984).

5.1.1.5 Release of methyl bromide to the outside air from greenhouses

During 1986, 400 000 kg methyl bromide were emitted into the air in the Westland area of the Netherlands (Van Doorn et al., 1989). Although soil disinfection is only allowed when the diluting capacity of the atmosphere (wind force) is sufficient, this is very difficult or

impossible to control. Investigations by Netherlands Institutes (TNO and RIVM) showed that the hourly average concentrations within a 20-m distance from the green-houses in 1981 (after the introduction of gas-tight film) during the first hours was 5.9 mg/m^3 after fumigation with methyl bromide at a dose of 700 kg/ha. In 1982 and 1983, a few hours after injection and at a probable dosage of 400 kg/ha, concentrations measured ranged between 1 and 4 mg/m^3 at distances of 20 m. After the first few hours, the concentration of methyl bromide decreased rapidly and, after 4 days, also at 20 m, hourly averages of 0.2 mg/m^3 were measured. Ten days after fumigation, the covering foil was removed, after which the hourly average concentration increased to a maximum of 0.4 mg/m^3 (Van Doorn et al., 1989).

5.1.2 Water

5.1.2.1 Seawater

In 1975, samples of seawater from near the shore at Dorset, England were analysed for halomethanes and methyl bromide was detected at levels ranging from 2.0 to 3.9×10^{-9} ml gas/ml water [~ 10 ng/litre] (Lovelock, 1975).

Average concentrations of 1.2 ng methyl bromide/litre were measured in surface seawater in the Eastern Pacific Ocean (Singh et al., 1983). The authors estimated that the oceans are supersaturated with methyl bromide to 250%.

Khalil et al. (1993) measured methyl bromide concentrations in ocean water in two open-ocean surveys, one covering latitudes from 45° N to about 30° S, the other from 67° N to 50° S. On the first survey, they found supersaturation of methyl bromide at 180% and, on the second, 140%.

5.1.2.2 Inland waters

In 1988, the California Department of Food and Agriculture (CDFA) reported the results of analyses of 43 056 well water samples taken from 2977 wells in various Californian counties. Residues of 10 chemicals were detected. Methyl bromide detection was undertaken in 32 counties, but in all the wells tested only one sample showed the presence of methyl bromide (CDFA, 1988).

5.1.2.3 *Waters around greenhouses*

In the Netherlands, where intensive horticulture in greenhouses is practised, the soil level is lower than sea level in some areas, with the result that water transport is very slow and the static water volume is very high. There is a high density of greenhouses and all holdings have to use the water from ditches as leaching water, thus, this water is successively loaded with bromide. However, it should be noted that, in 1992, methyl bromide was banned in the Netherlands for soil fumigation purposes.

The concentrations of methyl bromide and bromide-ion were measured in irrigation water, drainage water, and surface water during the leaching periods in two Netherlands glasshouse soils after fumigation with methyl bromide (Wegman et al., 1981). Maximum concentrations in drainage water, determined within 24 h of the start of leaching, were 9.3 mg/litre (methyl bromide) and 72 mg/litre (Br^-).

Further studies of bromide ion concentrations in precipitation, surface water, and ground water in the polder district in the Netherlands (a main horticultural area) in 1979-80 gave maximum values of 0.98, 41, and 17 mg/litre respectively, the highest concentrations being found during the main fumigation/leaching time in September-October 1979 (Wegman et al., 1983). During these few weeks, an estimated 1.78 million kg methyl bromide (about 1.5 million kg bromide ion) were used for soil fumigation. From their measurements, Wegman et al. (1983) calculated that 14% of the applied methyl bromide was converted to bromide ion. This is in agreement with Daelemans (1978), whose studies showed that 10-30% of methyl bromide is converted to Br^-. The fumigation method used was the "hot gas method", whereby the fumigant was discharged under thin low-density polyethylene (LDPE) sheeting. Subsequently, in June 1981, the use of LDPE for this purpose was forbidden.

In 1985, bromide concentrations of 10-35 mg/litre were observed in Westland (the Netherlands) surface water with maximum concentrations in the Poel and Bosch polders of 38.7 and 31.7 mg/litre, respectively (Van Doorn et al., 1989). Private water supplies from shallow pumps in the Netherlands near methyl bromide soil operations were expected to have increased bromide contents (Van Doorn

et al., 1989). In 1986, in the Westland, 260 000 kg bromide ended up in surface water, at an average dosage of 700 kg/ha.

Similar investigations were carried out by Vanachter et al. (1981) in the glasshouse crop growing region of Malines - Antwerp (Belgium) into bromide concentrations in surface water in periods of intense soil fumigation and leaching (August-September) compared with periods before and after this, when soil fumigation and leaching were less frequent. Sampling was also carried out during leaching, near the greenhouses, as well as in the ditches and draining water. For comparison, samples of natural Br^- concentrations in surface water were taken from a region where methyl bromide fumigation was not carried out.

The results showed that during the leaching period, concentrations of Br^- in the surface water in the greenhouse crop growing area were significantly higher (maximum 9.6 mg/litre) but, five weeks later, were either not detectable (< 0.1 mg/litre) or very low (1.59 mg/litre) in little brooks. The bromide concentration in rivers was less than 0.8 mg/litre, except for one site, where either sea water or the effluents from a local photographic plant resulted in concentrations of up to 4.5 mg/litre. In the direct drainage area of the glass houses, transient concentrations of up to 33 mg/litre were measured, decreasing rapidly within a few days.

Guns (1989) measured groundwater levels in four greenhouses in Belgium from September 1986 to August 1988. The bromide content of groundwater depended, not only on the length of leaching, but also on the type of soil. When the deeper soil layers contained more clay, the concentration of the bromide ion in the groundwater, after fumigation and leaching, was still relatively high (48 mg/litre before and 280 mg/litre after fumigation in one study).

5.1.3 Soil

The natural bromide present in unfumigated soil depends on the soil type. Van Wambeke et al. (1974) gave values of 3.3 mg/litre for fresh sandy loam soil and 2.5 mg/litre for peat soil. Hoffman & Malkomes (1974) stated that the natural concentration of bromide in the soil was less than 10 mg/kg, depending on the type of soil and geographical situation.

Fallico & Ferrante (1991) measured bromide concentrations in greenhouse soil before, and after, the application of methyl bromide (80 g/m^2). Before fumigation, bromide levels were about 5 mg/kg. Two months after treatment, bromide levels of over 30 mg/kg were measured. After a further 3 months, levels had decreased to less than 10 mg/kg.

Bromide ion concentrations following greenhouse and soil fumigation depend on the dosage, exposure time, aeration period, temperature, the type of soil, the amount of rain or leaching water, and the type of covering (sealing conditions). A year after fumigation with 70-80 g methyl bromide/m^3, bromide values of 0.2-11.5 mg/kg were recorded in the upper 30 cm of soil (Basile et al., 1987).

The bromide remaining in the soil after fumigation can affect soil fertility (Rovira & Ridge, 1979). As wheat particularly tends to concentrate bromine, soil and wheat dynamics were studied (1981-83) in methyl bromide-fumigated plots in a Mediterranean climate (Italy). Bromide residues ranged between 5 and 10 mg/kg in the fumigated soil to a depth of 50-60 cm. The total amount of bromide in the soil was 5.8 g/m^2 up to a depth of 1 m and remained almost constant during the wheat-growing period (Fransi et al., 1987). The amount of bromide residues was about 8 % of that applied (900 kg/ha) five months previously, compared with the 20 % found by Van Wambeke et al. (1974) in similar soils.

5.1.4 Food

When considering the published levels of methyl bromide and inorganic bromide in various foods, the method of analysis is important (section 2.4.9). Originally, bromide content only was measured and there is very little information on the methyl bromide content. Measurements of both entities are important as well as other residual products.

5.1.4.1 After soil fumigation

Bromide accumulation in plants depends on various factors, such as the physical and chemical properties of the soil, the climatic condition, the plant species and particular tissues, and the cultural

practices (Basile & Lamberti, 1981). Moreover, it depends on dosage, exposure time, and aeration.

A study was carried out in 1980 in Metaponto, in southern Italy, where methyl bromide was used to control nematodes and other plant pathogens in the soil (Basile & Lamberti, 1981). Bromide ion levels were 20-51 mg/kg (tomatoes), 8-44 mg/kg (string beans), 25-149 mg/kg (radishes), 18-60 mg/kg (aubergines), 6-165 mg/kg (cucumbers), 13-46 mg/kg (courgettes), and 3-27 mg/kg (peppers) on a fresh weight basis. In experimental plot conditions, the methyl bromide concentration was 60 g/m^2 under a plastic cover with the soil temperature 14-17 °C at 10 cm depth. The covering was removed after 2 days and the plot rotavated at a depth of 20 cm to eliminate residual gases.

Roughan & Roughan (1984a,b) carried out surveys of bromide ion residues in lettuces, cucumbers, tomatoes, and self-blanching celery grown in soil fumigated with methyl bromide, and compared these values with those in a range of home-produced and imported fruit and vegetables. Lettuce grown on unfumigated soil contained less than 10 mg bromide ion /kg, while most lettuces harvested from methyl bromide fumigated soil were found to contain considerably more, 30 % containing over 500 mg/kg and 2 % even in excess of 2000 mg/kg (Roughan & Roughan, 1984a).

Studies on vegetables grown under protective covers on soil previously fumigated with methyl bromide showed levels ranging from 1 to 109 mg/kg (fresh weight) in 29 late-season cucumbers, 5 to 326 mg/kg in 242 tomato samples, and 2 to 521 mg/kg in 38 samples of celery (Roughan & Roughan, 1984b); 65 % of the late season cucumbers contained more than background of bromide levels up to 10 mg/kg. Crops of tomatoes (summer 1981) grown on sites where methyl bromide fumigation had taken place in 1980/1981, contained considerably higher levels than those grown on a site fumigated in 1979. In a survey from retail outlets (January-November 1979), tomatoes and cucumbers from the Canary Islands and Spain generally contained less than 10 mg/kg (fresh weight). Of those grown in the United Kingdom, levels exceeded 10 mg/kg in 35 %, and 100 mg/kg in 5 %, ranging up to 177 mg/kg. These higher levels of bromide ion could be attributed to the plants having been grown on soil fumigated with methyl bromide prior to planting (Roughan & Roughan, 1984b). The total bromide ion contents of

various crops obtained from retail outlets in the United Kingdom during the period June 1981 to July 1982 are summarized in Table 22. The survey indicated that vegetables, such as tomatoes, celery, cucumbers, lettuce, radishes, and aubergines, grown in United Kingdom and the Netherlands contained higher levels than elsewhere. Other crops had mean bromide levels of less than 10 mg/kg, similar to other figures published for background bromide ion content.

Table 22. Total bromide ion content of various crops obtained from retail outlets in United Kingdom during the period June 1981 to July 1982[a]

Crop	Country of origin	Total No. of samples	Bromide ion (mg/kg fresh weight)	
			Range	Mean
apple	France	5	0.1-0.3	0.2
aubergine	Netherlands	4	2-23	11
avocado pear	not known	1	1	
banana	Windward Islands	2	2	2
bean, broad	England	3	1-2	2
bean, french	Guernsey	1	1	
bean, runner	England	2	1	1
bean, sprouts	England	3	1	1
cabbage	England	3	1-2	2
calebrese (broccoli)	England	2	1	1
carrot	England	1	2	
cauliflower	England	3	0.3-1	1
Chinese leaves	England	3	1-2	1
celery	England	12	1-178	28
	Guernsey	1	9	
	Israel	4	7-14	10
	Spain	16	2-8	4
	USA	1	4	
courgette	England	3	1-3	2
cucumber	Canary Islands	15	0.3-10	3
	England	36	0.2-87	9
	Spain	3	0.2-10	4
	Netherlands	7	0.1-14	7
grapefruit segments	Cyprus/Israel, S. Africa	4	0.1-0.4	0.3
green pepper	Netherlands	7	0.4-5	2

Table 22 (continued)

Crop	Country of origin	Total No. of samples	Bromide ion (mg/kg fresh weight)	
			Mean	Range
lettuce	Belgium	1	5	
	Cyprus	5	1	1
	England	69	1-241	15
	France	9	0.2-19	4
	Israel	6	1-4	2
	Spain	11	0.4-4	2
	Netherlands	26	2-57	21
	USA	12	0.1-2	1
marrow	England	2	1-2	1
mushroom	England	62	0.2-24	1
onions	Israel, Netherlands	3	0.4-1	1
onion, spring	England	3	2-4	3
orange segments	S. Africa, Spain	6	<0.1-0.4	0.2
pea	England	4	1-3	2
potato	Cyprus, England	3	1-2	1
radish	England	18	0.2-3	1
	Israel	2	5	5
	Netherlands	12	0.1-48	13
	USA	1	1	
strawberry	England	1	0.3	
tomato	Canary Islands	8	1-5	4
	England	33	1-70	13
	Spain	15	1-7	3
	Netherlands	14	1-39	11

[a] From: Roughan & Roughan (1984b).

Brown et al. (1979) measured the bromide concentration in several plant species in unfumigated and methyl bromide-fumigated plots in California (Table 23). Many plants showed increased bromide concentrations. Strawberries and grapevines absorbed relatively little. As the interval increased between soil fumigation and planting, there was a general decline in bromide levels, though the interval could be as long as three years before the crops returned to a level of about 10 mg/kg (Brown et al., 1979; Roughan & Roughan, 1984a). Table 24 shows bromide concentrations in plant material 1, 2, 3, and 4 years after fumigation with methyl bromide.

Table 23. Bromide concentrations in several plant species in unfumigated and methyl bromide-fumigated plots[a,b]

Plant species and part	Treatment	Range of bromide concentrations (mg/kg dry weight)	Average bromide concentration (mg/kg dry weight)	S.E. of means
barley	control	4 to 575	106 (19)[c]	38
(whole top)	fumigated	120 to 5235	1788 (23)	373
bur clover	control	1 to 407	96 (11)	40
(whole top)	fumigated	196 to 2371	1334 (14)	155
filaree	control	4 to 546	135 (14)	47
(whole top)	fumigated	718 to 7380	2600 (10)	683
wild oats	control	9 to 876	196 (14)	66
(whole top)	fumigated	1233 to 5034	3364 (11)	441
spinach (leaves)	fumigated	1772 to 3195	2521 (4)	387
ryegrass	fumigated	1481 to 2790	2378 (4)	302
sweet potato (leaves)				
1st sampling	fumigated	640 to 923	753 (4)	69
4th sampling	fumigated	312 to 372	330 (4)	14
sweet potato (root)	fumigated	204 to 237	220 (2)	17
strawberry	control	14 to 129	63 (9)	16
(leaves)[d]	fumigated	3 to 372	88 (36)	13
grape (leaves)[e]	control	1 to 101	28 (90)	3
	fumigated	1 to 402	48 (278)	4

[a] From: Brown et al. (1979).
[b] These data represent samples collected the first year after fumigation with MeBr at rates of 34-68 g/m^2, except for grape leaves.
[c] Numbers in parentheses refer to the number of samples in the average.
[d] Strawberry leaves were collected after 1-6 annual fumigations with methyl bromide.
[e] Grape leaves were collected 2-4 years after fumigation with methyl bromide.

Fallico & Ferrante (1991) measured bromide levels in tomatoes in crops grown in soil that had been fumigated with methyl bromide ten days prior to planting. Bromide levels in tomatoes grown in the treated soil and harvested after 60 days were about double (55 mg/kg) those in tomatoes grown in untreated soil. The bromide levels decreased with each successive harvest, but were still higher than those in control plants after the fourth harvest.

Table 24. Bromide concentrations in plant material (mg/kg dry weight), 1, 2, 3, and 4 years after fumigation with methyl bromide[a]

County	Untreated controls	Years after fumigation			
		1	2	3	4
Sonoma	94(19)[b]	3018(16)	360(15)	516(8)	12(3)
Napa	163(21)	1476(15)	742(10)	430(2)	

[a] From: Brown et al. (1979).
[b] Numbers in parentheses = number of samples included in the average.

The results of a further survey (1988-89) in the United Kingdom of inorganic bromide levels in fruit and vegetables are summarized in Table 25. Fourteen samples of lettuce produced in the United Kingdom exceeded the Codex Alimentarius Commission maximum residue limit (CAC MRL) for inorganic bromide of 100 mg/kg (MAFF, 1990).

The effects of leaching following soil fumigation with methyl bromide up to 100 g/m^2 are shown in Table 26. At sites with low soil bromide residues, the resulting bromide residues in lettuce were nearly unaffected by leaching. At other sites, there was a positive, but diminishing, response to increasing rates of leaching, very high residues probably being due to high levels of organic matter (Smart, 1990).

Recent monitoring of samples of individual crops having a likelihood of being grown on soil fumigated with methyl bromide showed that only a small percentage contained residues above Codex Alimentarius Commission recommended limits. The high levels were mainly in lettuce. The report of Smart (1990) showed that the proportion of samples having high residues had declined since the late 1970s, when, in some countries, residues in lettuce were as high as 500-1000 mg/kg. Leaching of treated soils, attention to timing of application, and integrated pest control have all helped to reduce such residue levels.

Table 25. Inorganic bromide residues detected in samples of fruit and vegetables in UK (1988 to 1989)[a]

Commodity	Concentration range (mg/kg)[c]	Number of samples
Lettuces, produced in United Kingdom (proposed CAC MRL[b] = 100)	n.d.	0
	1-20	48
	21-100	15
	101-300	9
	301-529	5
Lettuces, imported	n.d.	0
	1-20	21
	21-45	3
Rice, imported [MRL = 50 (unprocessed rice)]	n.d.	59
	1-10	37
	11-20	16
	21-50	14
	50-100	10
	121 and 124	2
Nuts (no MRL)		
almonds	n.d.	4
	1-147	24
brazil nuts	n.d.	0
	3-140	22
cashew nuts	n.d.	16
	3-53	5
chestnuts	n.d.	5
	3-23	3
coconuts	n.d.	0
	2-6	5
hazel nuts	n.d.	7
	1-194	10
peanuts	n.d.	4
	2-109	18
pine nuts	n.d.	4
	46	1
pistachio nuts	n.d.	0
	3-104	4

Table 25 (continued)

Commodity	Concentration range (mg/kg)[c]	Number of samples
Nuts (continued)		
tiger nuts	n.d.	0
	17-20	4
walnuts	n.d.	3
	2-210	21
sesame seed	n.d.	5
	17-56	5
sunflower seed	n.d.	3
	2	6
	3	1
Dried fruits		
currants, imported (CAC MRL = 100)	n.d.	22
		1-3 9
		6-15 5
sultanas (CAC MRL = 100)	n.d.	20
	1-6	6
		6-12 7

[a] From: MAFF (1990).
[b] CAC = Codex Alimentarius Commission; MRL = maximum residue limit (mg/kg) legally permitted in, or on, food commodities or animal feed.
[c] n.d. = not detected.

Bromide level tolerances for a variety of methyl bromide fumigated raw agricultural commodities in the USA are shown in Table 27. However, according to the US EPA, because of its existing toxicological data base and its environmental ubiquity, inorganic bromide is not of toxicological concern. Requirements for residue data to support existing inorganic bromide tolerances were waived by the Agency (US EPA, 1989).

Table 26. Bromide residues in lettuce grown under protection of soil fumigated with bromomethane and leached with water before planting in the United Kingdom[a]

Site	Soil texture	Soil organic matter (%)	Number of applications in previous years	Interval between planting and harvest (weeks)	Bromide residues in lettuce (mg/kg fresh weight) for the water application rates (mm)				
					0[b]	100	200	300	400
A	fine sandy loam	4	2	16	81	102	92	150	142
B	sandy loam	12	1	12	62	70	232	93	114
C	sandy loam	13	2	13	307	215	98	157	117
D	sandy loam		1	24	765	427	392	284	250
E	sandy loam	8	4	21	676	335	328	164	134
F[c]	loamy peat	51	4	14	1958	1534	1001	-	-
Mean sites A-E					378	230	228	170	151

[a] Summarized from Food and Agriculture Organization (1985) by Smart (1990).
[b] Residue figures for crops grown in soils not having any leaching.
[c] At F, the leaching treatments were applied after planting the lettuce crop.

Table 27. USA tolerances[a]

Br in, or on, the following raw agricultural commodities, which have been fumigated with the antimicrobial agent and insecticide methyl bromide after harvest (with the exception of strawberries)	(mg/kg)
corn (pop)	240
almonds, brazil nuts, bush nuts, butternuts, cashews, chestnuts, cottonseed, filberts, hickory nuts, peanuts, pecans, pistachio nuts, soybeans, walnuts	200
asparagus, copra, cumin (seed), ginger (roots), pomegranates	100
avocados, coffee beans, potatoes, sweet potatoes	75
alfalfa (hay), barley, beans, beans (green), benas (lima), beans (snap), cabbage, cippolini (bulbs), cocoa beans, corn, corn (sweet), garlic, oats, peas, peas (blackeyed), rice, rye, sorghum (grain), timothy (hay), wheat	50
artichokes (Jerusalem), garden beets (roots), sugar beets (roots), carrots, citrus citron, cucumbers, grapefruit, horseradish, kumquats, lemons, limes, okra, oranges, parsnips (roots), peppers, pimentos, radishes, rutabagas, salsify (roots), squash (summer), tangerines, turnips (roots)	30
apricots, blueberries, cantaloupes, cherries, eggplant, grapes, honeydew melons, mangoes, muskmelons, nectarines, onions, papayas, peaches, pineapples, plums, pumpkins, squash (winter), squash (zucchini), tomatoes, watermelons	20
apples, pears, quinces	5

[a] From: US EPA (1988b; CFR 180.124).

5.1.4.2 *After post-harvest fumigation*

Methyl bromide is widely used as a post-harvest fumigant to kill, or prevent, pest infestation. In 1976, around 100 000 metric tonnes of food commodities were treated with methyl bromide in the United Kingdom (Fairall & Scudamore, 1980).

Fairall & Scudamore (1980) measured methyl bromide residues in dried milk, wheat, flour, rapeseed, and groundnut samples after store fumigation (see Table 28). Products such as groundnuts and rapeseed retained higher amounts of methyl bromide. No methyl bromide was detected in any commodity after storage for 1 month (detection limit 10 μg/kg).

DeVries et al. (1985) measured the rate of decrease of methyl bromide in wheat, flour, cocoa, and peanuts after fumigation with the gas. Samples were analysed immediately and then after various time intervals of exposure of the sample to air. The methyl bromide concentration decreased very rapidly in all cases, no residual methyl bromide being found in any of the samples after 2 weeks (detection limit, 0.4 μg/kg).

Table 28. Methyl bromide residue levels (mg kg^{-1}) during storage[a]

	Days							
Commodity	0	0.04	0.25	1	2	4	7	11
dried milk	0.5	0.15	0.03	0.006	-	-	-	-
wheat	0.8	0.42	0.33	0.08	0.04	n.d.[b]	-	-
flour	0.28	0.09	0.04	0.02	n.d.	-	-	-
rapeseed	4.2	3.0	1.5	-	0.95	0.5	0.10	0.08
groundnuts	7.7	4.5	3.2	2.6	1.6	0.38	0.38	0.03

[a] From: Fairall & Scudamore (1980).
[b] n.d. = none detected.

(a) Wheat and cereals

Pesticide residues in home-grown and imported wheat were measured in the United Kingdom by Osborne et al. (1989); 45 samples were analysed for methyl bromide (method: Fairall & Scudamore, 1980) and inorganic bromide. No methyl bromide was found in excess of the detection limit (0.01 mg/kg); all samples contained inorganic bromide, but at levels of 4 mg/kg or less, which is given as the level naturally present in wheat as a result of uptake from the soil (Heuser & Scudamore, 1970; Osborne et al., 1989).

Trials carried out on a commercial scale showed that CT (concentration×time) products for methyl bromide generally lay in the range of 50-2000 mg.h/litre (Scudamore, 1987). The higher values are usually found in pockets of grain at the bottom of silos or bins. Scudamore (1987) recommended careful monitoring, especially at increased temperature and moisture content, when treating more sorptive cereals, such as oats or maize, or those with which methyl bromide reacts more readily. In three samples of wheat from different parts of the United Kingdom, bromide levels increased between 2 and 3 times over a range of 11-16 % moisture content.

Table 29. Bromide ion and methyl bromide concentrations (mg/kg) in flours exposed to methyl bromide only in silos and in pastas obtained from these fumigated and unfumigated flours[a]

Material	Treatment	Number of samples	Bromide ion (mean ± S.D.)	Methyl bromide[b]
flours	unfumigated	3	1.26 ± 0.03	n.d.
	fumigated	3	1.60 ± 0.11	n.d.
pasta (macaroni)	from unfumigated flours	6	1.24 ± 0.13	n.d.
	from fumigated flours	6	1.91 ± 0.22	n.d.

[a] From: Cova et al. (1986).
[b] n.d. = not detected, i.e., lower than the detection limit of 0.01 mg/kg.

Stacks of bags containing stored grains and pulses (wheat, lentils, maize, barley, chick-peas, peas, and sorghum) were covered with PVC sheets and exposed to methyl bromide fumigation for 48 h (Urga, 1983). Following aeration, residues of less than 50 mg/kg bromide were measured, with the exception of 60 mg/kg after 24 h aeration and 59 mg/kg after 36 h aeration. Cova et al. (1986) investigated the effects of exposure to methyl bromide in flour, and pastas made from it. Flour was exposed to methyl bromide in silos (conditions: mean temperature - 18 °C, concentration - 24 g/m^3, duration of treatment - 68 h, duration of ventilation - 3 days). Table 29 shows levels of bromide ion before, and after, fumigation. Methyl bromide could not be detected. In a second experiment (summarized in Table 30) on pasta made from unfumigated flour, rice flour, and white flour, Cova et al. (1986) examined the influence

Table 30. Bromide ion and methyl bromide concentrations (mg/kg) in unfumigated and fumigated foodstuffs, treated in their retail packagings[a]

Material	Treatment	Number of samples	Bromide ion (mean ± S.D.)	Methyl bromide[b]
rice	unfumigated	3	0.72 ± 0.06	n.d.
	fumigated	3	10.63 ± 0.67	n.d.
flour	unfumigated	3	3.17 ± 0.09	n.d.
	fumigated	3	6.66 ± 0.01	n.d.
white flour	unfumigated	3	1.22 ± 0.15	n.d.
	fumigated	3	4.19 ± 0.82	n.d.
pasta (macaroni)	unfumigated	6	2.40 ± 0.26	n.d.
	fumigated	6	2.60 ± 0.27	n.d.
pasta (spaghetti)	unfumigated	6	1.92 ± 0.17	n.d.
	fumigated	6	2.03 ± 0.07	n.d.
pasta with eggs	unfumigated	6	4.13 ± 0.12	n.d.
	fumigated	6	46.23 ± 1.57	n.d.
pasta with eggs and spinach	unfumigated	6	4.62 ± 0.31	n.d.
	fumigated	6	39.00 ± 0.01	n.d.

[a] From: Cova et al. (1986).
[b] n.d. = not detected, i.e., lower than detection limit of 0.01 mg/kg.

of the type of packaging on the effects of fumigation. Every item was packed in two different ways, i.e., a cardboard box or a transparent envelope made of a double layer of polypropylene. The products were fumigated in a closed room under the conditions given above, and the mean bromide ion concentrations ranged between 2.03 mg/kg (pasta) and 46.23 mg/kg (egg pasta), while methyl bromide was not detected.

(*b*) *Spices, nuts, and dried fruits*

In the USA in 1980, two warehouses containing imported spices were fumigated to eradicate a khapra beetle infestation. Methyl bromide and inorganic bromide residues were determined in the 52 spices before, and after, fumigation (using GC-ECD). In addition, an ashing titration method for bromide ion residue was used, allowing a comparison of the two analytical methods (Reeves et al., 1985). Before fumigation, the highest methyl bromide residue was in parsley (14.9 mg/kg). Seventy-two hours after fumigation with 100 g/m^3 for 12 h, samples were collected and analysed. The highest methyl bromide residue was found in sage (65.8 mg/kg). Levels of inorganic bromide residues before fumigation (GC-ECD) were all lower than 200 mg/kg; after fumigation, only two samples contained higher levels.

In a Canadian study, a number of spices, seeds, nuts, and dried fruits and vegetables, including samples of celery, mustard, sesame, coriander, pumpkin and sunflower seeds, cloves, peppercorns, dates, figs, prunes, raisins, beans, minced onion, a vegetable mix, walnuts, and peanuts were analysed for methyl bromide residues (Page & Avon, 1989). Of the 30 samples, only a sample of pumpkin seeds was found to contain methyl bromide (3 μg/kg). Fifty-one chocolate and grain-based products were also analysed and found not to contain any methyl bromide.

In contrast, when samples of food known to have been treated with methyl bromide were analysed, of the 60 samples, 16 contained residues >1 ng/kg and 5 contained >100 ng/kg methyl bromide. These samples included dried currants (2.9 mg methyl bromide/kg), chocolate-covered nuts (0.66 and 0.19 mg/kg), and rice (2.3 mg/kg) and maize (0.21 mg/kg) flours. These findings were confirmed by mass spectrometry (Page & Avon, 1989).

Bromide residues after methyl bromide fumigation were determined in samples of dried fruits, cereals, nuts, and spices imported into New Zealand in 1977 and early 1978 (Love et al., 1979). About one-half of the nut and spice samples contained total bromide levels exceeding 50 mg/kg, and occasional high levels of bromide residues were found in cereals.

Fairall & Scudamore (1980) showed that rapeseed and groundnut samples retained higher amounts of methyl bromide than other foodstuffs after store fumigation (Table 28). A survey of retail nuts, seeds, and nut products in October 1984 (Table 31) showed that levels of methyl bromide in some of these products were higher than the Codex Alimentarius Commission guideline (MAFF, 1989).

Table 31. Residues of methyl bromide in samples of nuts, seeds, and nut products[a,b]

	Number of samples		Residue concentrations (mg/kg)	
	tested	containing residues	range[c]	mean
almonds	5	2	n.d. to 0.06	< 0.02
brazil nuts	4	0	n.d.	-
dried chestnuts	1	1	0.2	-
hazelnuts	4	0	n.d.	-
mixed nuts	3	0	n.d.	-
nuts and raisins	3	2	n.d. to 0.2	0.08
peanuts	12	9	n.d. to 0.3	0.06
walnuts	7	4	n.d. to 2.2	0.4
others[d]	6	0	n.d.	-

[a] From: MAFF (1989).
[b] 45 samples were obtained during October 1984.
and analysed for residues of methyl bromide. The CAC (1986) guideline level for methyl bromide in nuts is 0.01 mg/kg.
[c] n.d. = not detected (the limit of determination was 0.02 mg/kg).
[d] One sample each of cashews, pecans, pine kernels, pistachios, sunflower seeds, and tiger nuts.

(c) *Fresh fruit*

Methyl bromide residues determined in laboratory studies on fresh fruits are summarized in Table 32. Studying the effects of fumigation dose and length of the following aeration periods, Sell & Moffitt (1990) and Sell et al. (1988) found that desorption of methyl bromide from apples and cherries, respectively, followed pseudo-first-order decay curves, the first component resulting from removal of the pesticide from free air space in the chamber, and the second, from the desorption from the fruits. Singh et al. (1982) found that methyl bromide absorption in avocados depended on oil content rather than skin thickness or protein content.

(d) *Milk and cheese*

Bromides may be present naturally in cows' milk in amounts up to 8 mg/litre. When cows were fed on grain fumigated post-harvest with methyl bromide, higher levels of bromide were found in the milk, e.g., cows fed grain containing bromide at 220 mg/kg had bromide levels in their milk of 10-20 mg/litre (Lynn et al., 1963).

Cheese fumigated with methyl bromide showed high bromide residues (Laug, 1941).

5.1.5 Animal feed

Knight & Costner (1977) reported bromide residues of 6800-8400 mg/kg in hay that was harvested in the spring after the field had been injected with methyl bromide. The resulting toxic effects on animals fed with this hay are reported in section 7.3.7.

5.1.6 Other products

The chlorine and bromine contents in tobacco and tobacco smoke were investigated by Häsänen et al. (1990). Smoke per cigarette contained 1 μg bromine in the particulate phase and 5 μg bromine in the gaseous phase. In the gaseous phase, methyl bromide accounted for 80% of the total bromine. Methyl bromide is used widely as a fumigant in uncured tobacco storage and this can increase the bromine content in tobacco considerably.

Table 32. Methyl bromide residues in fresh fruits after fumigation

Fruit	Fumigation time and dose	Storage temperature (°C)	Time[a]	Residue (mg/kg)	Reference
grapefruit	2 h, 64 mg/litre	24	1 h 48 h	26.9[b] 0.52	King et al. (1981)
peaches	3.5 h, 32 g/m^3	2.5	1 day 7 days	11.0 4.0	Austin & Phillips (1985)
mango	N.D.[c], 64 g/m^3	N.D.	1 h	< 15.0	Stein & Wolfenbarger (1989)
grapefruit	2h, 48 g/m^3	15.6	5 days	< 5	King & Benschoter (1991)
oranges, mandarines, tongors	2h, 48 g/m^3	15.6	5 days	< 10	
avocado	2h, 32 g/m^3	20	1 day 2 days	up to 0.5[d] up to 0.1	Singh et al. (1982)

[a] Time of analysis after end of fumigation period.
[b] Aeration period: 15 min.
[c] N.D. = no data given.
[d] Aeration period: 30 min.

Methyl bromide has been used in growing tobacco seedlings (Ostrec & Korunic, 1989).

5.1.7 Terrestrial and aquatic organisms

No data are available.

5.2 General population exposure

5.2.1 Food

The general population may be exposed to residues of methyl bromide and inorganic bromide, and other possible metabolic products, which may be present in food marketed for consumption. Levels of methyl bromide and inorganic bromide in food are described in section 5.1.4.

Food commodities containing higher levels of oil and fat, such as groundnut and rapeseed (Table 28), retain higher amounts of methyl bromide residues after fumigation, which disappear after a storage period of about one month (Fairall & Scudamore, 1980; DeVries et al., 1985). However, higher levels of inorganic bromide residues may remain in food commodities marketed after fumigation (section 5.1.4.2).

Scheffrahn et al. (1992) investigated the effects of methyl bromide fumigation on foods in retail packages, in sealed and unsealed plastic containers, with a view to simulating conditions in which residues may be found in food products after fumigation of a residential house in the USA. Fatty commodities in unsealed packages contained higher residues (> 1 mg/kg) than other foods. The fumigant may have entered the containers by two routes, diffusion through the air-spaces around the lids (opened peanut butter jar) or in porous packaging (parmesan cheese in cardboard box), and by permeation into polyurethane bagged foods. Factory sealed, polyethylene terephthalate (PETE) containers gave better protection. Vacuum-packed foods in metal (soup, coffee) or glass (sauce) containers yielded no residues.

Bromide residues in foodstuffs were discussed by Van Leeuwen & Sangster (1987) in a review of the toxicity of the bromide ion. Total diet surveys in the United Kingdom in 1978 and 1979 gave a

daily intake of 8.4 mg bromide per person. These values are consistent with those of two Dutch surveys where average daily intakes of 9.4 and 7.7 mg bromide per person, respectively, were recorded, i.e., approximately 3 mg/kg diet (Van Leeuwen & Sangster, 1987).

The metabolites resulting from methyl bromide post-harvest fumigation of a number of crops have been analysed (Starratt & Bond, 1990a,b). Both physically- and chemically-bound residues were measured. In 7 out of the 9 commodities, over half of the total residue was chemically bound 1 h after fumigation. These chemically bound residues were stable for at least 6 months. Most reaction products were *O*-, *S*-, and *N*-methylated proteins (section 6.3). Methylation of purines and pyrimidines in the nucleic acids accounted for 0.1-6 % of the chemically-bound residue, with *N* being the only site of methylation. The methylation products identified in this study are also known to occur naturally.

5.2.2 *Drinking-water*

In 1988, in California, only one sample out of 43 056 taken from 2977 wells, showed any presence of methyl bromide (detection limit - 1 μg/litre) (CDFA, 1988).

In areas, such as in the Netherlands, where private water supplies are from shallow wells near methyl bromide soil operations, there could be increased bromide contents in the water (Van Doorn et al., 1989).

5.2.3 *Human breast milk*

There are no data available.

5.2.4 *Sub-populations at special risk*

People who live in close proximity to greenhouses or to fields or storehouses that are being fumigated have a higher risk of exposure to methyl bromide gas than the general population. Similarly, persons inadvertently, or intentionally, entering buildings following, in particular, structural fumigation, are at risk.

5.3 Occupational exposure during manufacture, formulation, or use

The number of incidents and fatalities (section 9) show that occupational exposure, especially during fumigation, is potentially hazardous.

5.3.1 During manufacture

In a methyl bromide plant in the USA, workplace air concentrations of 78-116 mg/m^3 (20-30 ppm) were recorded using direct measurement (Evans, 1979).

In a methyl bromide-producing factory in Japan, methyl bromide concentrations in the worker's breathing zone were usually under 4 mg/m^3, but sometimes exceeded 20 mg/m^3 (Kishi et al., 1988).

5.3.2 During fumigation

If safety procedures are not followed, workers may be exposed to methyl bromide accidentally during, or after, fumigation operations.

Methyl bromide in low concentrations is odourless so that a toxic atmosphere may not be apparent to the worker. Only at higher concentrations (100 × the actual TLV® of 20 mg/m^3 (5 ppm) does it have a sweet smell (Van Den Oever et al., 1982). An odour threshold of 65 mg/m^3 has been reported for methyl bromide (Worthing & Walker, 1983). Therefore, it is usually marketed in the form of 98% methyl bromide and 2% chloropicrin, as a lacrimatory agent. For post-harvest fumigation, 100% methyl bromide is used.

The various fumigation techniques used together with methyl bromide exposure values and methods of application are outlined in Table 33 (Guillemin et al., 1990).

5.3.2.1 Structural fumigation

In carrying out the general fumigation of a building, sufficient gas must be liberated into the free space to kill the insects and then the toxic level maintained for a defined period of time. After the

Table 33. Integrated samples of methyl bromide in air taken in a survey of methyl bromide fumigation in Switzerland[a]

Circumstances of sampling	Exposure category	Sample No.	Range of values	
			Minimum mg/m³(ppm)	Maximum mg/m³(ppm)
1. Space fumigation				
- during fumigation[b]	occupational	7	<0.8 (<0.2)	500 (128.4)
- during aeration[b]	occupational	7	2.3 (0.6)	646 (166.0)
- resuming operation	para-occupational	47	<0.8 (<0.2)	9 (2.3)
- during fumigation	environmental	12	<0.8 (<0.2)	79 (20.4)
- during aeration	environmental	12	<0.8 (<0.2)	105 (27.1)
2. Soil fumigation				
- during fumigation[b]	occupational	5	2 (0.5)	151 (39.0)
- removal of sheeting[b]	occupational	3	34 (8.8)	144 (36.9)
- inside greenhouse[c]	para-occupational	5	12 (0.3)	9 (2.2)
3. Chamber fumigation				
- outside chamber	para-occupational	3	35 (8.9)	293 (75.3)
- removing contents	para-occupational	4	5 (1.2)	17 (4.3)

[a] From: Guillemin et al. (1990).
[b] Fumigators generally wore respiratory protection during these operations.
[c] Greenhouse only partially fumigated; includes post-fumigation soil tillage.

treatment, the residual gas remaining in the building is dispersed to the outside atmosphere. However, there are basic differences in defining structures amongst various countries. In the USA, structural fumigations mainly involve residential houses whereas, in Europe, they generally refer to flour mills and food processing areas. The fumigation procedures and the safety aspects in these circumstances could be very different.

Methyl bromide exposure levels for structural fumigation workers in California were measured by Anger et al. (1986). They described the work involved. "Structural fumigation is conducted by a work crew of 2-4 men who cover the buildings to be fumigated with large vinyl tarpaulins and connect them by spring clamps. Cylindrical tubes filled with sand (sand snakes) are placed at the base of the structure to hold down the tarpaulins, thus sealing the building. After this one to two hour procedure, termed a closing, the fumigant is introduced into the unoccupied house via a tube or hose, and the fumigators leave the site. The fumigators wear self-contained breathing apparatus (SCBA). The next day the work crew removes the tarpaulins, opens the windows, and places fans in the house to clear the fumigant. It is in this 30- to 45-min process, termed the opening, that worker exposures may occur. Typically, each work crew, led by a State-licensed fumigator (the "licensee"), conducts three openings and/or closings each day".

Personal samples from fumigators taken when they entered houses 24 hours after fumigation with 23 000 to 31 000 mg methyl bromide/m^3, indicated that a house might contain 80-2000 mg methyl bromide/m^3 (Table 34). Personal samples taken on fumigators working outside the houses when they were opened again showed concentrations of between 0 and 8 mg/m^3 in the half-hour periods during the cover removal (Anger et al., 1986). Area samples taken within 3 and 6 m from the buildings during the same period ranged from 0 to 31 and 0 to 10 mg/m^3, respectively (Anger et al., 1986).

Concentrations of methyl bromide inside flour mills and in the atmosphere around the mills during, and after, fumigation were measured by Bond & Dumas (1987). Considerable variations in concentration were found in buildings of different structure and under varyious weather conditions. Concentrations ranging from trace amounts up to 90 mg/m^3 (23 ppm) were found in the air around the mills during the aeration period.

Table 34. Methyl bromide exposure concentrations (mg/m^3) in residential fumigation[a]

State licensed fumigator when inside house	Fumigators working outside house		Under covers	Within 3 m of house		3-6 m from house
1875.0	5.1	2.0	46.7	32.3	0	0
75.9	0	1.2		12.5	0	10.1
90.3	0	7.0		0	17.5	10.1
1042.1	3.9	3.1		0	0	0
204.2	8.6	0		0		0
Mean						
657.4	3.1		46.7	7.0		3.9

[a] Adapted from: Anger et al. (1986).

Guillemin et al. (1990) conducted a survey in Switzerland on exposure during space fumigation. The maximum exposure levels for 7 integrated samples was 646 mg/m^3 (166 ppm) during aeration (see Table 33). Fumigators wore respiratory protection during these operations. Samples of transient air taken around the buildings not from any specific spot (distance not given), showed methyl bromide levels in the range of 0-105 mg/m^3 (see Table 33).

5.3.2.2 *Soil fumigation*

The amount of methyl bromide released into the atmosphere during soil fumigation depends on the methods used (Table 9), the type and time of covering (section 3.2.2) and soil type.

(*a*) *Field fumigation*

A formulation of 75% methyl bromide was used to kill insects and nematodes in a strawberry crop, with 25% chloropicrin as a fungicide. The fumigant injected into the soil produced an equilibrium of 47 000-58 000 mg/m^3 which, under the covers, resulted in personal average exposures ranging from 0 to 24 mg/m^3 for the fumigators (Anger et al., 1986). Personal sample measurements of methyl bromide in farm workers when removing the film

ranged between 0 and 33 mg/m^3. Other data showed that the personal exposures of fumigators and farm workers, who covered the plastic film with earth were between 0 and 29 mg/m^3 and 0 and 17 mg/m^3, respectively. Exposure of soil fumigators, about 8 h a day, was relatively constant during most of the year, whereas farm workers received only occasional exposures when fields were fumigated. Spot (area) samples, taken before and after film removal, showed that the airborne concentration under the intact film was 8950 mg/m^3 before removal and 9.3 mg/m^3 an hour after removal.

(b) Greenhouse fumigation

Roosels et al. (1981) compared two methods of methyl bromide fumigation in greenhouses, i.e., by injection into milled soil followed by covering with a plastic cover, or, by surface fumigation by means of plastic pipes under a plastic cover. Two different formulations (70 % methyl bromide/30 % chloropicrin and 98 % methyl bromide/ 1-2 % chloropicrin) were used and the concentrations of methyl bromide in the air were measured by GC-FID. During injection into soil, values of between 400 and 4000 mg/m^3 (100 and 1000 ppm) were found with peaks up to 12 000 mg/m^3 (3000 ppm) and, in one case, up to 40 000 mg/m^3 (10 000 ppm). However, when preventive measures were taken, values of 800 mg/m^3 (200 ppm) were obtained. During fumigation, concentrations ranged between 400 and 4000 mg/m^3 (100 and 1000 ppm). Using the piped surface fumigation method, concentrations around the treated area were between 320 and 3200 mg/m^3 (80 and 800 ppm) with short-term exposures of the operators to 8000-12 000 mg/m^3 (2000-3000 ppm) when the pipes were being connected.

In another investigation, concentrations of 60-100 g methyl bromide/m^2 were applied under a polyethylene cover (Van Den Oever et al., 1982). Depending on local ventilation, quite a lot of gas escaped into the surrounding atmosphere. The concentration during application varied from 117 to 11 700 mg/m^3 (30 to 3000 ppm). Concentration in the air declined with time to 16 mg methyl bromide/m^3 (4 ppm) five days after application. Removing the plastic sheet involved exposure to peak values as high as 800 mg/m^3 (200 ppm), for a few seconds. On the ninth day after application, milling the soil exposed workers to up to 60 mg/m^3 (15 ppm); on the eleventh day, no methyl bromide was detected in the air.

6. KINETICS AND METABOLISM

6.1 Absorption

6.1.1 Inhalation

6.1.1.1 Animal studies

Uptake of methyl bromide was investigated in male Fischer 344 rats by Andersen et al. (1980). Following whole body exposures to recirculated atmospheres of 390-11 640 mg/m^3 (100-3000 ppm), the uptake (i.e., disappearance from the atmosphere) was rapid and exhibited first-order kinetics without a saturable component, the rate constant being 0.44 kg^{-1} h^{-1}. This rate constant was later recalculated as 0.55 kg^{-1} h^{-1} by Gargas & Andersen (1982).

Medinsky et al. (1985) carried out a nose-only inhalation of 50, 300, 5700, or 10 400 nmol (given as 6.2-1206 mg/m^3) of [^{14}C] methyl bromide/litre of air for 6 h in male F344 rat (5 animals/ group). The results indicated that, at low concentrations (50-300 nmol/litre), about 50% of the inhaled material was absorbed. At 5700 nmol/litre, only 37% was absorbed and, at 10 400 nmol/litre, only 27%. The same amount of methyl bromide (650 μmol/kg body weight) was absorbed at the two higher exposure concentrations. At 10 400 nmol/litre, the total volume inhaled by the rats was reduced (Medinsky et al., 1985).

Raabe (1986) found about 40% uptake of inhaled methyl bromide in studies on beagle dogs. These results are compared in Fig. 6 with those from rats (Medinsky et al., 1985) and those from human volunteers (Raabe, 1988), described below.

6.1.1.2 Human studies

An inhalation study was carried out to determine systemic uptake of low concentrations of methyl bromide from air during nasal or oral breathing (Raabe, 1988). Two male and two female volunteers inhaled about 0.1 mg ^{14}C-labelled methyl bromide/m^3 (25 ppb), once through the nose and once through the mouth. The uptake (% of methyl bromide inhaled) was 55.4% nasally and 52.1% orally.

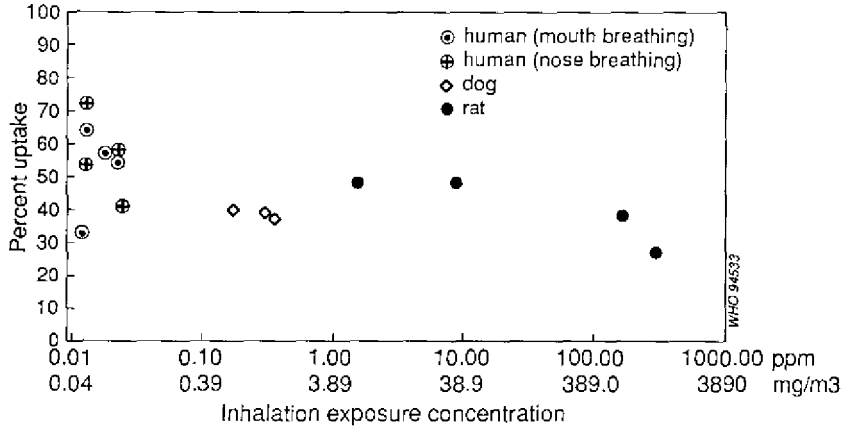


Fig. 6. Methyl bromide inhalation uptake.
Comparison of observed fractions of methyl bromide vapour inhaled by human volunteers (Raabe, 1988), beagles (Raabe, 1986), and Fischer-344 rats (Medinsky et al., 1985) with exposure concentration.

Modified from: Raabe (1988).

6.1.2 *Dermal*

Exclusively dermal exposure has only been observed in human incidents (section 9). There are no data dealing exclusively with dermal exposure in animals.

6.1.3 *Oral*

Methyl bromide (75 or 100 mg/kg) was administered to rats in olive oil by gavage (Miller & Haggard, 1943). The methyl bromide entered the blood stream with only a moderate degree of hydrolysis in the intestine.

6.1.4 Intraperitoneal injection

Methyl bromide (120-180 mg/kg body weight) was administered i.p. in hourly doses to rats (Miller & Haggard, 1943). The percentage of methyl bromide eliminated was between 24 and 45%. Medinsky et al. (1984) administered [^{14}C] methyl bromide i.p., and reported that the major route of elimination was exhalation of $^{14}CO_2$ (46%) (section 6.4).

6.2 Distribution of methyl bromide and bromide in tissues

6.2.1 Animal studies

Methyl bromide is rapidly distributed to all tissues after inhalation and rapidly metabolized. A small percentage is cleared slowly and incorporated into metabolic pools (Jaskot et al., 1988).

At 72 h after oral or i.p. administration of 250 μmol of [^{14}C] methyl bromide/kg body weight, 14-17% of the ^{14}C remained in the rats, the liver and kidney being the major organs of retention (Medinsky et al., 1984).

In rats exposed, nose only, to 337 nmol [^{14}C] methyl bromide/litre air, radioactivity was found widely distributed in tissues immediately following exposures. The lung, adrenal gland, kidney, liver, and nasal turbinates contained the highest concentrations (250, 240, 180, 130, 110 nmol equivalents/g, respectively) (see Table 35). Immediately after exposure, radioactivity in the liver accounted for about 17% and all other tissues about 10% of the absorbed methyl bromide (Bond et al., 1985). Similarly, Jaskot et al. (1988) found that the liver, lung, and kidney were the major organs of [^{14}C] distribution in rats immediately after exposure to [^{14}C] methyl bromide at 214 mg/m^3 (55 ppm) for 3 min.

Honma et al. (1985) measured methyl bromide levels in male Sprague-Dawley rats exposed to 973 mg methyl bromide/m^3 (250 ppm) for 8 h and then sacrificed at successive time intervals. The concentrations found in adipose tissue (maximum 1 μg methyl bromide/g tissue) were much greater than those in blood (max. 0.1 μg/g) and other tissues - brain, liver, muscle, and kidney (maximum about 0.01 μg/g; see Fig. 7). The methyl bromide in all

Table 35. Concentration (nmol/g) of ^{14}C in tissues from rats exposed for 6 h to 337 nmol ^{14}C-methyl bromide/litre air[a,b]

	0 h[c]	8 h	24 h	60 h
lung	250.4 ± 27.7 (3.6)	40.3 ± 5.5 (0.5)	19.5 ± 2.3 (0.2)	19.7 ± 2.3 (0.3)
adrenal	242.0 ± 16.8 (0.9)	25.8 ± 10.2 (0.1)	23.0 ± 1.4 (0.0)	19.5 ± 3.4 (0.0)
kidney	180.4 ± 4.6 (4.3)	76.1 ± 11.4 (1.5)	36.9 ± 2.6 (0.8)	35.1 ± 3.4 (0.7)
liver	129.9 ± 7.0(16.7)	119.6 ± 13.1(11.6)	82.4 ± 10.3 (9.0)	37.8 ± 7.5 (3.9)
turbinates	110.2 ± 6.5 (0.2)	35.2 ± 5.1 (0.1)	13.3 ± 1.4 (0.0)	18.9 ± 3.2 (0.0)
spleen	98.6 ± 3.4 (0.7)	28.8 ± 5.8 (0.2)	15.9 ± 2.1 (0.1)	15.8 ± 1.7 (0.1)
small intestine	96.5 ± 14.6 (2.0)	36.3 ± 0.8 (0.4)	19.9 ± 1.8 (0.2)	15.5 ± 3.2 (0.2)
trachea	84.3 ± 1.4 (0.1)	36.4 ± 6.3 (0.0)	15.5 ± 3.9 (0.0)	18.8 ± 4.3 (0.0)
stomach	80.0 ± 1.8 (1.3)	37.8 ± 5.3 (0.6)	31.9 ± 1.0 (0.5)	27.0 ± 8.3 (0.4)
large intestine	66.3 ± 9.2 (0.9)	43.6 ± 8.6 (0.6)	19.0 ± 2.3 (0.1)	17.8 ± 2.3 (0.2)
testes	65.4 ± 3.6 (2.5)	34.5 ± 3.9 (1.4)	17.1 ± 2.6 (0.6)	12.9 ± 2.3 (0.5)
larynx	61.1 ± 4.9 (0.0)	27.1 ± 5.9 (0.0)	10.5 ± 1.2 (0.0)	11.6 ± 2.0 (0.0)
brain	53.6 ± 9.5 (0.8)	35.8 ± 4.2 (0.6)	8.8 ± 1.1 (0.2)	7.4 ± 0.7 (0.1)
heart	51.7 ± 1.9 (0.6)	35.1 ± 5.3 (0.4)	16.8 ± 1.5 (0.2)	17.6 ± 2.9 (0.2)
thymus	48.4 ± 0.5 (0.2)	33.3 ± 6.7 (0.1)	19.9 ± 2.3 (0.1)	23.4 ± 3.1 (0.1)
urinary bladder	45.6 ± 6.9 (0.1)	27.7 ± 5.5 (0.0)	12.6 ± 1.9 (0.0)	11.8 ± 1.4 (0.0)
thyroid	28.7 ± 24.4 (0.0)	34.8 ± 6.1 (0.0)	16.1 ± 2.6 (0.0)	16.4 ± 1.4 (0.0)

[a] From: Bond et al. (1985).

[b] Values represent the x ± SE of 2-3 rats. Values in parentheses are percentages of the absorbed ^{14}C-methyl bromide.

[c] Time after end of exposure.

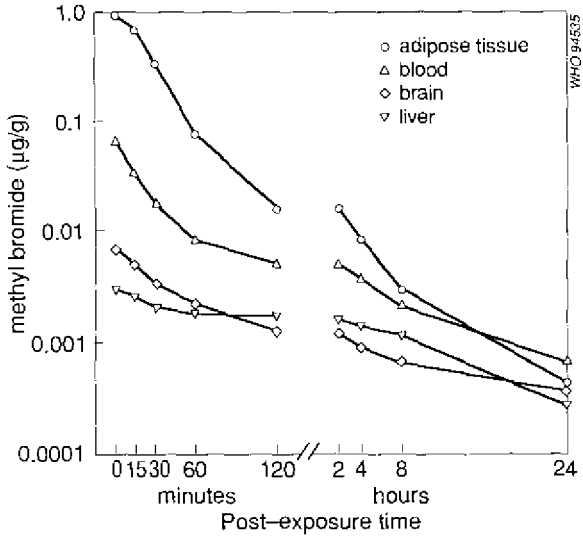


Fig. 7. Time course of CH_3Br concentrations in rat tissues (means of 2 animals) after exposure of rats to 250 ppm CH_3Br for 8 h, measured each time point.

Modified from Honma et al. (1985).

tissues described reached a maximum in 1 h after exposure commenced and maintained almost the same concentrations during exposure. Honma et al. (1985) found peak concentrations of bromine in blood at 4 h after cessation of methyl bromide exposure, and in kidney and liver, 8 h after (Fig. 8).

Calves fed for 49 days on a diet containing about 4650 mg bromide/kg showed bromide concentrations in kidney, liver, and muscle of 1808, 1015, and 465 mg/kg, respectively, on day 49. Serum and organ bromide concentrations decreased markedly 14 days after the feeding of this diet was discontinued (Knight & Reina-Guerra, 1977).

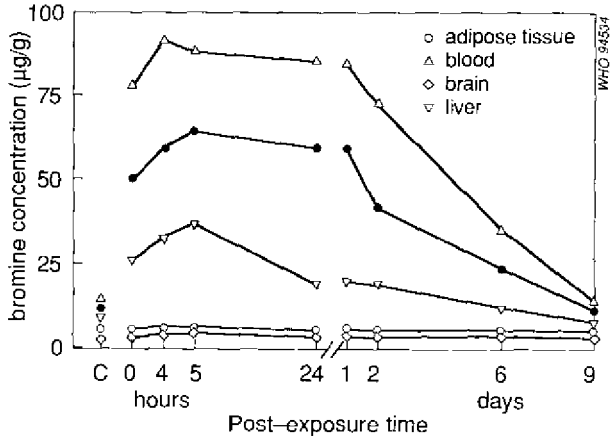


Fig. 8. Time course of bromine concentrations in rat tissues (means of 2 animals) after exposure to 250 ppm CH_3Br for 8 h, with sacrifice at each time point.

Modified from Honma et al. (1985).

6.2.2 Human studies

Data on the concentrations of bromide in various human tissues after methyl bromide poisoning are scarce. In an autopsy study of a methyl bromide-exposed patient, Heimann (1944) reported the following bromide values: lung (127 mg/kg), liver (187 mg/kg), brain (207 mg/kg), and, in a composite sample of heart, kidney, and pancreas (107 mg/kg). Traces of methyl alcohol and formaldehyde were also found in all the tissues examined.

In four lethal cases of people exposed to methyl bromide, Marraccini et al. (1983) found bromide ion concentrations in serum or plasma ranging from 40 to 583 mg/litre. Methyl bromide was detected in the brain of one patient (detection limit < 1 mg/kg).

Values of 0.9 mg/kg in lymph nodes, 3.3 and 5.1 in ovaries and testes, 7.5 in lung, and 8.2 mg/kg wet weight in kidney cortex have been reported in autopsy samples (from accident victims) (Hamilton et al., 1972/73). A study of the levels of bromide in adipose tissue from human subjects in three countries showed the highest levels in the United Kingdom, where 5.6% of the specimens contained levels ranging from 4.0 to 4.5 mg/kg fat; the lowest levels were found in Germany (0-0.9 mg/kg fat) whereas levels of 1-3.7 mg/kg were found in the Netherlands samples (Crampton et al., 1971). Van Leeuwen & Sangster (1987) stated that there was no evidence in humans of bromide concentration in any particular organ that might indicate a specific physiological function of this ion.

6.3 Metabolic transformation

The metabolism of methyl bromide has not been elucidated.

Bromide concentrations in blood (and target organs) were reported to be increased in humans (Clarke et al., 1945; Rathus & Landy, 1961; Hine, 1969) and in laboratory animals (Irish et al., 1940, 1941) after exposure to methyl bromide. Miller & Haggard (1943) postulated that methyl bromide is hydrolysed in the body with the formation of inorganic bromide and methyl alcohol. In part, this hydrolysis may occur intracellularly, resulting in a distribution of bromide that differs from that for bromide given orally as sodium bromide. Sodium bromide and methyl alcohol, given at the levels produced after methyl bromide exposure, did not produce the same toxic and functional response (Irish et al., 1940, 1941). This suggested that the toxicity of methyl bromide was due to the reaction of the halide molecule with the tissue and was not attributable to the hydrolytic products.

Hallier et al. (1990a) measured the cytosolic turnover rate of methyl bromide in both liver and kidney from five different strains of mice and rats, with *in vitro* incubation. The turnover rate in both organs was consistently higher in tissues isolated from females. On the basis of a similar effect with methyl chloride, this effect could be attributed to a higher rate of glutathione conjugation in females.

The reaction products of methyl bromide in wheat were characterized by Winteringham et al. (1955) using ^{14}C- or ^{82}Br-labelled methyl bromide. It was pointed out that, although most

attention is given to the bromide ion because it is the only part of the residue that is easily determined, methyl methionine sulfonium bromide, the methylated histidines, and possibly other residues of methylation were also produced.

6.3.1 Binding to proteins and lipids

Methylation of cysteine-*S* and histidine-*N* residues of haemoglobin in suspended mouse erythrocytes was found after *in vitro* treatment with radiolabelled methyl bromide (Djalali-Behzad et al., 1981). After inhalation of methyl bromide, alkylation of cysteine-*S* residues was seen in mouse haemoglobin and liver proteins (Djalali-Behzad et al., 1981).

Adducts result from reactions between toxic chemicals and amino acids in haemoglobin or other proteins (or nucleosides in DNA - see below). *S*-methyl-cysteine has been studied as a haemoglobin adduct in mice (Iwasaki, 1988a,b) and rats (Xu et al., 1990) and as a serum albumin adduct in human blood samples (Müller et al., 1991, 1992). Both haemoglobin and serum albumin adducts have been studied in blood samples of workers occupationally exposed to methyl bromide and these have been proposed as suitable parameters for the biomonitoring of exposure to the fumigant (Iwasaki et al., 1989; Müller et al., 1991, 1992) (see also section 9.4.4).

In the insect *Triatoma infestans*, Castro et al. (1976) demonstrated that methyl bromide is irreversibly bound to lipids and to proteins in both the nymph adult and eggs and that exposure to methyl bromide significantly decreased the content of sulfhydryl groups in nymph adult and egg proteins.

Studies on methylation by methyl bromide of wool, silk, collagen, and gelatin (Blackburn & Phillips, 1944), wheat flour (Bridges, 1955; Winteringham et al., 1955), and cocoa beans (Asante-Poku et al., 1974) indicated that *N*-, *O*-, and *S*- methylation of proteins occurs (Cova et al., 1986; Starratt & Bond, 1990b). The main site of decomposition of methyl bromide in cocoa beans was shown to be in the alcohol-insoluble proteins of the shell (Asante-Poku et al., 1974). The methyl group of the fumigant became covalently bound to the α-amino group of the various amino acids, the imidazole ring of histidine, and the ε-amino group of lysine.

Winteringham et al. (1955) found that the gluten fraction of whole-wheat flour exposed to [^{14}C]methyl bromide was responsible for 80% of the decomposition of the absorbed fumigant with *N*-methyl, dimethylsulfonium, and methoxyl and thiomethoxyl derivatives accounting for 50, 30, and 20%, respectively, in this fraction. Bridges (1955) reported that 1-*N*-methylhistidine, 3-*N*-methylhistidine and 1,3-*N*,*N*-dimethylhistidine accounted for 75% of the *N*-methyl derivatives, and that 10% was due to probably ε-*N*-methyllysine.

Starratt & Bond (1990a,b) used [^{14}C]methyl bromide to distinguish naturally occurring residues from those formed during the fumigation of a variety of commodities: maize, wheat, oatmeal, peanuts, almonds, alfalfa, potatoes, oranges, and apples. In order to get higher incorporation of the tracer, fumigation was carried out at a level of 48 mg/litre, for 3 days. Methyl bromide was bound both physically and chemically to the commodities. To measure the physically-bound residue, a parallel test was run using unlabelled fumigant. Methyl bromide levels were determined 1 h following fumigation and then at 1, 2, 4, and 10 days. The levels in all the commodities declined rapidly.

Extraction of the [^{14}C]methyl bromide-fumigated commodities with diethyl ether removed very little radioactivity, showing that fats and other non-polar lipids were not methylated during treatment. In maize, fractions corresponding to albumins, glutamines, zein, and glutelin were all methylated.

Methylation of methionine is one of the main reactions forming the relatively unstable methylmethionylsulfonium derivative. Spontaneous decomposition yields dimethyl sulfide. Analysis of the sites of methylation was uncertain as both acidic and basic hydrolysis caused partial decomposition (Starratt & Bond, 1990a,b). The volatile products included methanol, methyl mercaptan, and dimethyl sulfide. Different commodities produced different residues (Starratt & Bond, 1990a,b). In potato and orange extracts, the main methylated components were identified as *S*-methyl-glutathione, gamma-glutamyl-*S*-methylcysteine and *S*-methyl cysteine. These compounds were not found in maize. 1-*N*-methylhistidine and 3-*N*-methylhistidine were the major components from the fumigated maize, almonds and other commodities. The highest level of

histidine methylation occurred in almonds, accounting for about 54% of the chemically-bound residue.

6.3.2 Binding to DNA

Labelled 7-methylguanine was identified in DNA from liver and spleen cells of mice exposed to [^{14}C] methyl bromide (Djalali-Behzad et al., 1981). In *in vitro* experiments with DNA solutions treated with [^{14}C] methyl bromide, predominantly [^{14}C] 7-methylguanine was identified (Starratt & Bond, 1988b).

Calf thymus DNA treated in the solid state with [^{14}C] methyl bromide, showed, on analysis, four major radiolabelled peaks with retention times corresponding to 1-methyladenine, 7-methylguanine, 3-methyladenine, and 3-methylcytosine (Starratt & Bond, 1988b).

The DNA adducts, [^{14}C]3-methyladenine, [^{14}C]7-methylguanine, and [^{14}C]O^6-methylguanine, have been found in the stomach and forestomach of rats after both oral and inhalation exposure of [^{14}C]methyl bromide (Gansewendt et al., 1991).

In maize and wheat, 7-methylguanine and 1-methyladenine were identified as major products after hydrolysis together with lesser amounts of 3-methylcytosine and 3-methyladenine (Starratt & Bond, 1988a). Although the yields of DNA were low, Starratt & Bond (1990a) also found evidence of radioactively-labelled 7-methylguanine and 1-methyladenine in [^{14}C]methyl bromide-fumigated almonds and potatoes.

6.3.3 The role of glutathione in methyl bromide metabolism

6.3.3.1 Mammals

Liver, kidney, lung, and brain from mice, exposed via inhalation for 1 h to methyl bromide concentrations of from 870 to 5930 mg/m^3, were analysed for glutathione and bromide ion (Alexeeff et al., 1985). The liver glutathione levels of the 4700 and 5930 mg/m^3 exposure groups were significantly lower than that of the controls. Bromide ion levels were highest in the liver and kidney and lowest in the whole blood. The lung and brain bromide levels were intermediate.

Methyl bromide has been shown in rats to increase the activity of glutathione *S*-alkyl transferase and decrease the nonprotein sulfhydryl content (Roycroft et al., 1981). A group of male Sprague-Dawley rats were exposed to methyl bromide (117 mg/m^3; 6 h/day; 10 days) and killed immediately after the last dose. Biochemical analyses showed that glutathione *S*-alkyl transferase was significantly increased in the lung (12%), liver (11.9%), and kidney (6.9%). Non-protein sulfhydryl was significantly reduced by 11.4% in the liver and 13.9% in the kidney. Glucose-6-phosphate dehydrogenase was significantly increased in the kidney (8.5%), but not in the lung or liver.

Studies on rats by Davenport et al. (1992) showed that glutathione was depleted and regional brain glutathione-*S*-transferase inhibited by methyl bromide inhalation (584 mg methyl bromide/m^3; 6 h/day; 5 days) [see sections 8.8.2 and 8.10].

In a preliminary report, Thomas & Morgan (1988) reported that treatment of rats with buthionine sulfoximine (BSO) depleted glutathione levels, prior to methyl bromide exposure, and increased the toxicity of methyl bromide. This is in contrast to the findings of Chellman et al. (1986) for methyl chloride in mice, who found that glutathione depletion by BSO decreased methyl chloride toxicity in the brain and kidney. However, the observation is consistent with those of Tanaka et al. (1988), who showed that treatment of rats with glutathione reduced the detrimental effects of methyl bromide on sleep-wakefulness and its circadian rhythm and increased the LD_{50} value (section 8.8.2).

In whole body inhalation studies on rats exposed for 6 h/day, for 5 or 10 days, to 117 mg methyl bromide/m^3 (30 ppm), glutathione (GSH) *S*-transferase and glucose-6-phosphate dehydrogenase (G-6-PDH) activities were increased in the lung. Decreases in GSH-reductase and GSH-*S*-transferase activities were found in the liver (Jaskot et al., 1988).

When human erythrocyte cytoplasm was incubated with methyl bromide or methyl iodide in the presence of excess glutathione (GSH), a spontaneous non-enzymatic conjugation was observed (Deutschmann et al., 1989). This was verified in parallel experiments with boiled cytoplasm and GSH added after boiling.

Enzymatic conjugation of methyl bromide with reduced glutathione to produce *S*-methyl cysteine (the analysis) appears to be isoenzyme-specific, since conjugation was observed in the erythrocyte cytoplasm of a majority (13/20) of the population. The same individuals also conjugated methyl chloride, a reaction that is dependent on glutathione-*S*-transferase rho (GSTρ), a minor form of the enzyme (Hallier et al., 1990b).

Later studies on the properties of the glutathione-*S*-transferase (GST) responsible for methyl bromide conjugation with GSH (measured by methyl bromide depletion) have separated the enzyme GSTσ from human erythrocytes; this new enzyme has not been found in various non-human species (Schröder et al., 1992).

Measurement of methyl bromide disappearance in head-space vials containing whole human blood cultures in an atmosphere of 19 460 mg/m^3 (5000 ppm) at 37 °C indicated that the methyl bromide concentration had fallen to zero within 1 h, in the presence of blood from glutathione conjugators, whereas it had fallen to approximately 5836 mg/m^3 (1500 ppm) at 1 h, in the presence of blood from non-conjugators. Further reduction was slow, the methyl bromide concentration being about 3890 mg/m^3 (1000 ppm) after 6 h (Hallier et al., 1993).

6.3.3.2 *Insects*

Glutathione is depleted and glutathione *S*-transferase can be induced in the larvae of the khapra beetle (*Trogoderma granarium*) by fumigation with methyl bromide at a lethal dose (Shivanandappa & Rajendran, 1987).

Starratt & Bond (1981) demonstrated that, in the granary weevil (*Sitophilus granarius* L.), the major pathway for the detoxication of methyl bromide residues was by conjugation, primarily with glutathione, and that increasing amounts of glutathione in the insects resulted in increasing tolerance to methyl bromide exposure. Both strains of the insect (methyl bromide sensitive and methyl bromide resistant) metabolized methyl bromide primarily to substances that, on thin layer chromatography, behaved consistently with their identification as *S*-methyl glutathione.

6.4 Elimination and excretion in expired air, faeces, urine

The route of administration of methyl bromide affects the pathways of excretion.

Miller & Haggard (1943) investigated the amount of methyl bromide eliminated and the amount of bromide retained in the body after i.p. administration of methyl bromide. Following a single i.p. injection of 60 mg methyl bromide/kg body weight, elimination continued for about 45 min and more than 90% was eliminated in the first 30 min. With lethal i.p. doses of 120-180 mg methyl bromide/kg, 24-45% of the methyl bromide was eliminated; the amounts of fixed and nonvolatile bromide being 94.9-126.6 mg/kg. In rats dosed orally (75-100 mg methyl bromide/kg), similar bromide levels were found, but the methyl bromide eliminated was given as only 2.4-4.6%.

These results have been confirmed by studies using radioactively labelled methyl bromide (Medinsky et al., 1984). In rats dosed intraperitoneally with [^{14}C] methyl bromide, the major route of elimination was the exhalation of $^{14}CO_2$ (46%). In contrast, urinary excretion of [^{14}C] was the major route of elimination (43% of the dose), when methyl bromide was given orally. Very little appeared in the faeces (<3% of the dose), regardless of the route of administration. In rats with bile duct cannulations, 46% of an oral dose appeared in the bile over a 24-h period (Medinsky et al., 1984). The authors suggested that reabsorption of biliary metabolites from the gut played a significant role in the disposition of [^{14}C] methyl bromide.

In inhalation studies on rats exposed for 6 h to 337 nmol [^{14}C] methyl bromide/litre air, Bond et al. (1985) showed that excretion of [^{14}C] as $^{14}CO_2$ was the major route of elimination, about 47% (3900 nmol/rat) of the total [^{14}C] methyl bromide absorbed being excreted by this route. CO_2 excretion exhibited a biphasic elimination pattern with 85% of the $^{14}CO_2$ being excreted with a half-time of 3.9 h and 15% excreted with a half-time of 11.2 h. Half-times for the elimination of ^{14}C in urine and faeces were 9.6 and 16.1 h, respectively; 65 h after exposure, about 75% of the initial radioactivity had been excreted with 25% remaining in the body (Bond et al., 1985). Elimination half-times of [^{14}C] from tissues were 1.5-8 h. In all tissues examined, over 90% of the ^{14}C in the

tissues were methyl bromide metabolites (Bond et al., 1985). The data from this study indicate that, after inhalation, methyl bromide is rapidly metabolized in tissues and readily eliminated.

Male CD rats were exposed (nose only) to [^{14}C]-methyl bromide at 214 mg/m^3 (55 ppm) for 3 min. The liver, lung, and kidney were the major organs of [^{14}C] distribution, immediately after exposure. Up to 32 h after exposure, the major routes of excretion were pulmonary and renal with elimination of 43% and 21% of the total inhaled label, respectively (Jaskot et al., 1988).

Studies into the time course of methyl bromide and bromide elimination in rat tissue have been described by Honma et al. (1985). Male Sprague-Dawley rats were exposed to 973 mg methyl bromide/m^3 (250 ppm) for 8 h and methyl bromide and bromine concentrations measured at successive time intervals (see also section 6.2). The results are shown in Fig. 7 (bromine) and Fig. 8 (methyl bromide). The methyl bromide levels in all tissues described reached a maximum in 1 h following exposure and remained at almost the same levels during exposure. Methyl bromide levels decreased rapidly after exposure; after 30 min only half of the methyl bromide concentrations in adipose tissue and blood were still present (Fig. 7). The methyl bromide levels in the brain and liver were very low, but the elimination of methyl bromide from these organs was slower. Forty-eight hours after exposure, methyl bromide could not be detected in any tissue examined (Honma et al., 1985). In contrast to the methyl bromide study, peak concentrations of bromine in blood, kidneys, and liver occurred 4-8 h after bromide exposure, and the half-life in these tissues was about 5 days.

Honma et al. (1985) carried out a regression analysis of methyl bromide and bromine concentrations in blood, kidney, liver, brain and adipose in male rats after a 2-h exposure to 0, 973, 1946, 2918, or 3890 mg methyl bromide/m^3 (0, 250, 500, 750, or 1000 ppm). Linear relationships were obtained between exposure concentrations and the tissue methyl bromide or bromine values.

Over 95% of the bromide ion in mice exposed to methyl bromide was eliminated within 2.5 days, bringing the concentration close to the control levels and the limit of detection (Alexeeff et al., 1985).

Lactating cows fed a methyl bromide fumigated grain ration (220 mg bromide/kg food) compared with unfumigated diets secreted increased levels of bromide in the milk, i.e., 10-20 mg/litre instead of about 5 mg/litre (Lynn et al., 1963).

6.5 Retention and turnover

The biological half-life of bromide ions in human blood was found to be about 12 days (Söremark, 1960).

The half-lives of bromide in the blood and brain of rats after i.p. injection of methyl bromide were approximately 8.7 and 4.3 days, respectively (Tanaka et al., 1988). In inhalation studies, a half-life of bromide of about 5 days was reported in the blood, kidneys, and liver (Honma et al., 1985). In contrast, methyl bromide concentrations in the blood and adipose tissue were reduced by half after 30 min, though elimination from the brain and liver was much slower (Honma et al., 1985).

6.6 Reaction with body components

Honma et al. (1987) suggested that the main target of methyl bromide in the body was the central nervous system. The norepinephrine content of the hypothalamus and cortex with hippocampus was reduced on exposure to methyl bromide (Honma et al., 1982) and changes in the amino acid content and metabolism in the brain were noted (Honma et al., 1983). The results of further studies suggested that alterations in catecholamine metabolism might be a factor in methyl bromide-induced neurotoxicity (Honma et al., 1987) (see section 8.8). Kato et al. (1986) described histopathological changes in the brain.

Eustis et al, (1986, 1988) found clear species- and sex-related differences in the susceptibility of specific organs and tissues to methyl bromide effects (section 8.8.1). In rats, neuronal necrosis occurred primarily in the cerebral cortex, hippocampus, and thalamus of the brain, whereas in mice, necrosis of the internal granular layer of the cerebellar folia was more frequently observed. Nephrosis occurred in all treated mice. Myocardial degeneration was observed in male and female rats more frequently than male mice. Atrophy of the adrenal cortex and testis and necrosis of the olfactory epithelium

were described. Similar findings were described by Hurtt et al. (1987). Degeneration and regeneration of the olfactory epithelium were also described by Hurtt et al. (1988) and Hastings et al. (1989); Hastings (1990).

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

7.1 Soil microorganisms

Methyl bromide is used commercially to control soil-borne fungi that cause:

- damping off: *Rhizoctonia solani, Pythium* spp., *Sclerotium bataticola (Macrophomina phaseolina), Phytophtora* spp., and *Thielaviopsis basicola.*
- crown rot: *Sclerotium rolfsii* and *Sclerotinia* spp.
- root rot: *Pythium* spp., *Stromatinia, Fusarium* spp., *Sclerotium bataticola, (Macrophomina phaseolina), Rhizoctonia solani, Pyrenochaeta* spp. (corky root, pink root), *Armillaria* and *Phytophthora* spp.
- wilt: *Fusarium* spp., and *Verticillium* spp.

Generally, concentration-time products of methyl bromide required to kill fungi are much higher than those needed to control insect and nematode pests, susceptibility increasing with temperature. To control fungi, methyl bromide is generally used at rates of 40-100 g/m^2 (Davis et al., 1977).

Filip & Roth (1977) demonstrated the efficacy of methyl bromide against *Armillaria* root rot in the stumps of ponderosa pine (*Pinus ponderosa* Laws). The survival of young pine trees in areas infected with such fungi was increased after the elimination of the fungus, using the fumigant.

Heungens & Roos (1982) recovered non-pathogenic fungi (*Penicillium* and *Mucor*) following the application of methyl bromide (300 g/m^2) to pine litter, but no pathogenic fungi were recovered.

After an initial reduction, the numbers of bacteria and fungi in fumigated soil remained high and low, respectively, in comparison with those in untreated soil (Sivasithamparam et al., 1987). In the fumigated soil, *Trichoderma* species rapidly recolonized the soil, becoming the dominant fungus within 15 days. In a study on the microflora in the rhizosphere of wheat, the same authors found that, though there was no difference in the total number of bacteria,

actinomycetes, and fungi, before and after fumigation with methyl bromide, there were some fungal species differences with *Fusarium merismoides*, *T. koningii*, and *T. viride* present in significantly higher numbers, other fungi being less abundant.

Kelley & Rodriguez-Kabana (1979) reported that methyl bromide did not cause any permanent changes in soil enzyme activities or adversely affect the mycorrhizal root development of pine seedlings.

Methyl bromide is used for controlling fungal infections in the poultry industry (Harry et al., 1972; Davis et al., 1977).

Methyl bromide is much less frequently used as a bactericide than as an insecticide (Davis et al., 1977). It is used to control certain soil-borne bacteria, e.g., bacterial canker (*Corynebacterium michiganese*), and bacterial wilt (*Pseudomonas solanacerum*) (Bromine & Chemicals Ltd.,1990). A summary of the acute toxic effects of methyl bromide on bacteria and viruses is given in Table 36.

Methyl bromide, used at a concentration-time product of 800 mg.h/litre at 25 °C, with a relative humidity of 70%, eliminated salmonellae from artificially contaminated poultry foodstuffs (Tucker et al., 1974).

Although there have been many studies on the effectiveness of methyl bromide in reducing diseases produced by pathogenic micro-organisms, there are fewer data on its effects on soil microbes.

Matta & Porta-Puglia (1968) tested methyl bromide on several morphologically and functionally different groups of soil microbes. In isolated soil samples, treated and maintained under constant temperature (22-23 °C) and humidity (16-18%), microorganisms were counted at 2, 21, 54, and 87 days following fumigation with 300 g methyl bromide/m^3. After 2 days, most bacteria were dead; after 87 days, there were very low counts of fungi, aerobic nitrogen-fixing, nitrifying, and cellulolytic bacteria, whereas denitrifying, proteolytic, amylolytic, and ammonifying bacteria showed a marked resurgence in recolonization (Matta & Porta-Puglia, 1968). The selective-action effects of methyl bromide fumigation on a given microbe population in soil appear to be more significant than the effects on microbe number.

Table 36. Effects of methyl bromide fumigation on bacteria and viruses[a]

Organism	Dosage	Conditions	Reference
Vibrio cholera, Shigella dysenteriae, Salmonella typhi, Salmonella paratyphi A, Salmonella paratyphi B	33 g/m^3	10-h exposure LD_{100}	Saiki (1952)
Corynebacterium sepedonicum	10 % bromomethane, 5 % ethylene oxide	18-h exposure LD_{100} 85 % CO_2	Richardson & Monro (1962)
Arabis mosaic virus	0.32 kg/m^3	controlled virus on strawberry plants	Harrison et al. (1963)
Tobacco mosaic virus, Cucumber green mottle virus	640 g/m^3 110 g/m^3 320 g/m^3	inactivated virus inactivated at 27°C inactivated at 14-16°C	Inouye et al. (1967)
Escherichia coli 1257	1000 g/m^3	40°C and 90 % relative humidity provided control	Prishchep & Nikiforova (1969)

Table 36 (continued)

Organism	Dosage	Conditions	Reference
Bacillus larvae, Bacillus paraalvei, Streptococcus apis, Streptococcus pluton, Pseudomonas apisepticus	5000 g/m^3	5-day exposure controlled bacteria in bee honeycombs	Smirnov (1970)
Tobacco mosaic virus	200 g/m^3	inactivated virus in 3 kg soil in which tomatoes were grown	Doraiswamy et al. (1972)
Salmonella typhimurium	800 mg-h/litre	25 °C and 70% relative humidity provided control	Tucker et al. (1974)
Xanthomonas begoniae	0.32 kg/m^3	24-h exposure eliminated bacterial blight from *Rieger begonia*	Strider (1975)

[a] Adapted from: Davis et al. (1977).

In a study on bacterial flora involved in the nitrogen cycle, hot fumigation with methyl bromide at concentrations of 80 g/m^3 was carried out in greenhouses at 6 different sites (Turtura et al., 1988). Seven months after treatment, the total aerobic mesophile bacteria count, aerobic nitrogen-fixing, ammonifying, ammonia-oxidizing, and nitrite-oxidizing bacteria, always showed higher values in fumigated than in unfumigated control soils. Recolonization was more marked in the upper 0-30 cm soil samples in which the development of ammonifying and nitrifying bacteria was highly significant.

Rovira & Ridge (1979) found no long-term effects on aerobic soil bacteria or actinomycetes with application of 22 g methyl bromide/m^2.

Yeates et al. (1991) described the recolonization of soils sterilized in the laboratory and returned to their original pasture and forest sites, under four different types of field conditions. Sampling took place over 166 days (midsummer to midwinter) with two of the sites having a moderate, and two a high, rainfall. Both microbial biomass and dehydrogenase activity recovered rapidly but remained consistently lower in the fumigated than in the untreated samples in all four sites. Bacterial numbers also recovered rapidly. Fungal hyphal lengths were 25% lower in the fumigated soil. Fumigation showed no detectable effects on the subsequent rates of nitrogen mineralization and little effect on nitrification rates. Protozoa were almost completely eliminated by fumigation, numbers recovering most rapidly in moist forest soil and slowly in dry pasture soil. Nematodes were eliminated by fumigation; recolonization was first detected on day 26. Numbers (10 and 62/g, respectively) and species (10 and 31, respectively) remained much lower in fumigated, compared with untreated, soil.

After sterilization of greenhouse soil with methyl bromide (75 g/m^2), there were profound qualitative and quantitative disturbances up to a soil depth of 30 cm (Bourbos & Skoudridakis, 1991); 7-9 species of soil mycoflora were isolated from the fumigated soil compared with 107 from control soils. The 31-40 cm soil layer was not affected by disinfestation. After two months, recolonization had taken place of only 35-40% in species and 60-63% in density of the primary microflora.

The use of methyl bromide as an effective fumigant for greenhouses has been questioned (Bourbos & Skoudridakis, 1991). Certain saprophytic fungi have developed a degree of tolerance. Disinfested soil was quickly contaminated by certain pathogens (*Fusarium* and *Pythium* spp.) and there was also a possibility of reinfection from the lower layer of soil not reached by the fumigant. Some fungi controlled by methyl bromide are listed in Table 37.

7.2 Aquatic organisms

7.2.1 Effect of methyl bromide

LC_{50} (96-h) values of 11 mg methyl bromide/litre and 12 mg methyl bromide/litre for bluegill sunfish, *Lepomis macrochirus* (freshwater) and tidewater silversides, *Menidia beryllina* (saltwater), respectively, have been determined following exposure to methyl bromide (Dawson et al., 1975/77).

The acute toxicity of methyl bromide for carp (*Cyprinus carpio* L.) was determined in studies with a 4-h exposure period (Segers et al., 1984). The 4-h LC_{50} was calculated to be approximately 17 mg/litre. Damage to the gill epithelium was the most pronounced morphological damage, which probably caused the death of the fish by suffocation.

In a short-term study, triplicate groups of 10 fish (*P. reticulata* (guppy) and *Oryzias latipes* (medaka)) were exposed to 0.56, 1.0, or 1.8 mg methyl bromide/litre for 4 days. All methyl bromide-exposed fish displayed abnormal behaviour (reduced activity). Limited mortality was noted in *P. reticulata* exposed to 1.0 and 1.8 mg/litre and *O. latipes* exposed to 1.8 mg/litre, but there was no increase in mortality in the next lower concentration groups (Wester et al., 1988).

Table 37. Some fungi controlled by methyl bromide

Fungus	Dose, Surface application/m^2, commodity fumigation/m^3	Crop/ commodity	Reference
Alternaria sp.	1.6-3.3 g/m^3	pecan	Wells & Payne (1975)
Armillaria melea	4-98 g/m^2	citrus/ grape	Munnecke et al. (1969) Kissler et al. (1973)
Aspergillus sp.	1.6-5 g/m^2	pecan/ honeycomb	Wells & Payne (1975) Smirnov (1970)
Byssochalamy fuloa	60-120 mg/kg	starch	Ito et al. (1972)
Cladosporium sp.	1.6-3.3 g/m^2	pecan	Wells & Payne (1975)
Eumargodes laivgi	24 g/m^2	not stated	Hitchcock (1968)
Fusarium sp.	45-100 g/m^3	tomato	Westeijn (1973) Weihing et al. (1971) Wells & Payne (1975) Perrotta (1968) Vanachter (1974)
Monochaeta sp.	1.6-3.3 g/m^3	pecan	Wells & Payne (1975)
Penicillium sp.	1.6-3.3 g/m^3	pecan	
Pestalotia sp.	1.6-3.3 g/m^3	pecan	

Table 37 (continued)

Fungus	Dose, surface application/m^2, commodity fumigation/m^3	Crop/ commodity	Reference
Phoma sp.	1.6-3.3 g/m^3	pecan	Wells & Payne (1975)
Phytophora parasitica	49 g/m^2	citrus	Grimm & Alexander (1971)
Phytophora capsici	40 g/m^2	green peppers	Alfaro Moreno & Vehg (1971)
Plasmodiophora brassicae	50-150 g/m^2	cabbage	Winstead & Garriss (1960)
Plasmosisphora brassicae	48 g/m^2	cabbage	Wimalajewa (1975)
Pyrenochaeta lycopersici	125 g/m^3	soil	Vanachter (1974)
Rhizoctania solani	50-150 g/m^2	soil	Winstead & Garriss (1960)
Sclerotium rolfsii	50 g/m^2	iris	Kiewnick (1968)
Sclerotina sclerotiorum	50 g/m^2	tobacco	Hartill & Campbell (1973)
Thielaviopsis basicola	50 g/m^3	tobacco	Mounat & Hitier (1959)
Verticillium sp.	45-70 g/m^2	tomato	Perrotta (1968)

In a long-term study, *P. reticulata* and *O. latipes* were exposed for 1 and 3 months to 0.032-3.2 mg methyl bromide/litre (Wester et al., 1988). All guppies died in the 3.2 mg/litre group within 3 days, and, in the 1.0 mg/litre group, within 3 weeks. The NOLC (no observed lethal concentration) and NOEC (no observed effect concentration: behaviour, appearance) values were 0.32 and 0.1 mg/litre, respectively. A significant decrease in weight was noted in both sexes in the 0.32 mg/litre group.

All medaka embryos exposed to 1.8 or 3.2 mg/litre and most of the 1.0 mg/litre group died before hatching. The NOLC after 3 months was 0.32 mg/litre. The NOEC values, on the basis of behaviour and appearance, were 0.56 mg/litre and 0.32 mg/litre after 1 and 3 months, respectively (Wester et al., 1988).

A short-term study with (lethal) concentrations of 0.56, 1.0, or 1.8 mg methyl bromide/litre showed (using scanning electron microscopy) major degenerative and regenerative changes in the superficial epithelia, especially of the gills and oral mucosa, caused, apparently, by the local irritating action of this compound. Necrotic changes were also seen in the thymic cortex and the testis (Wester et al., 1988). In a long-term study on guppies and medakas exposed to the highest concentrations for 1 month and 3 months, respectively, no significant organ or tissue changes could be detected in routine histopathology.

7.2.2 *Effect of bromide ion on aquatic organisms*

The main degradation product of methyl bromide is inorganic bromide.

To evaluate the potential impact of pollution with the bromide ion, Canton et al.(1983) investigated the short-term effects of sodium bromide on various freshwater organisms, using algae (*Scenedesmus pannonicus*), crustaceans (*Daphnia magna*), and fish (*P. reticulata* and *O. latipes*) (Table 38). Depending on the species tested, acute toxic effects were seen at concentrations ranging from 44 to 5800 mg Br^-/litre and, in long-term tests, the NOEC varied from 7.8 to 250 mg Br^-/litre. Bromide ion markedly impaired reproduction in both crustaceans and fish.

Table 38. Effects on aquatic organisms of short-term exposure to sodium bromide[a]

Test species	Parameter	Results (g Br^-/litre) at: 24 h	48 h	72 h	96 h
Scenedesmus pannonicus (alga)	EC_{50} (growth)	5.8	7.8	8.5	10
	NOEC (growth)	2.5	2.5	2.5	2.5
Daphnia magna (crustacea)	LC_{50} (mortality)	11	11	-	-
	EC_{50} (mort./abn. behaviour)	5.8	5.8	-	-
	NOLC (mortality)	7.8	7.8	-	-
	NOEC (mort./abn. behaviour)	4.3	4.3	-	-
Poecilia reticulata (fish)	LC_{50} (mortality)	16	16	16	16
	EC_{50} (mort./abn. behaviour)	0.44	0.14	0.044	0.044
	NOLC (mortality)	7.8	7.8	7.8	7.8
	NOEC (mort./abn. behaviour)	0.25	0.078	0.025	0.025
Oryzias latipes (fish)	LC_{50} (mortality)	26	25	24	24
	EC_{50} (mort./abn. behaviour)	0.44	0.44	0.44	0.44
	NOLC (mortality)	7.8	7.8	7.8	7.8
	NOEC (mort./abn. behaviour)	0.25	0.25	0.25	0.25

[a] From: Canton et al. (1983).
[b] NOE(L)C = no observed (specified) effect concentration.

Further tests were performed on *P. reticulata* (guppy) and *O. latipes* (medaka) following sodium bromide exposure for 1 and 3 months at concentration ranges of 10-32 000 mg/litre (guppy) and 180-56 000 mg/litre (medaka). NOLC values for guppies were 10 000 mg/litre and 1000 mg/litre after 1 and 3 months, respectively. The NOEC value was 32 mg/litre in both studies. Histopathological changes were observed at concentrations of 100 mg/litre or more (Wester et al., 1988). For medakas, the NOLC values were 5600 and 3200 mg/litre after 3 weeks and 3 months, respectively, whereas the NOEC value (behaviour) for both periods was 320 mg/litre (Wester et al., 1988).

The relative susceptibility to sodium bromide of 11 taxonomically different freshwater species was determined in medium-term toxicity tests by Slooff & Canton (1983). The data are summarized in Table 39.

In semi-static, long-term toxicity tests on *Daphnia magna*, EC_{50} and EC_{10} values of 27 and 18 mg/litre, respectively, were determined (Van Leeuwen et al., 1986).

7.3 Terrestrial organisms

7.3.1 Protozoa

Long et al. (1972) studied the effect of methyl bromide on protozoa (*Eimeria tenella* and *E. acervulina*) at a dosage of 5 g/m^3 for 20 h at 25 °C; 100 % control (destruction of oocysts) was achieved.

7.3.2 Plants

Methyl bromide is often applied, as a fumigant, directly to plant seeds, plant cuttings, or harvested plant products to disinfect before, and during, transportation or storage (Davis et al., 1977). Additionally, methyl bromide is used as a soil fumigant to control certain plant pathogens and weed seeds in areas to be planted.

As chloropicrin is phytotoxic, methyl bromide formulations that contain it as a warning agent are not used on nursery stock or other living plants (Bond, 1984).

Table 39. Summary of the results of medium-term toxicity tests using sodium bromide on 11 different freshwater test species[a]

Test species	Exposure time (days)	Criteria	NOL(E)C values[b] (mg/litre)
Pseudomonas fluorescens (bacterium)	0.3	specific growth rate	3200
Microcytis aeruginosa (cyanobacterium)	4	specific growth rate	3200
Scenedesmus pannonicus (alga)	4	growth (biomass)	3200
Lemna minor (plant)	7	specific growth rate	3200
Daphnia magna (crustacea)	21	mortality reproduction	3200 10
Culex pipiens (insect)	25	mortality development	100 100
Hydra oligactis (hydrozoan)	21	specific growth rate	1000
Lymnaea stagnalis (mollusc)	40	mortality reproduction hatching	3200 10 3200
Poecilia recticulata (viviparous fish)	28	mortality mortality and behaviour growth	100 32 320
Oryzias latipes (viviparous fish)	40	mortality mortality and behaviour hatching growth	3200 320 10 000
Xenopus laevis (amphibian)	100	mortality development growth	32 320 320

[a] Adapted from: Slooff & Canton (1983).
[b] NOL(E)C = no observed (specified) effect concentration.

7.3.2.1 Seed fumigation

As shown in Table 40, fumigation with methyl bromide can result in delay in the germination of seeds and some loss of total germinative capacity, depending on the variety, moisture content, and the extent of exposure to the gas (Davis et al., 1977). This was confirmed by Sittisuang & Nakakita (1985) who compared the effects of methyl bromide on the germination of rice seeds (*Oryza sativa* L., Japicona type) and corn (maize) seeds (*Zea mays* L.). No detrimental effect of methyl bromide up to 4 mg/litre was observed in rice seeds at a moisture content of 11%, but as the moisture content and temperature increased, methyl bromide had an increasing effect on germination. Maize seeds were much more tolerant to methyl bromide. Exposure to 5 mg methyl bromide/litre, which caused heavy damage to rice seeds in most cases, did not generally produce any harmful effect on the germination of maize seeds, regardless of the moisture content and temperature. At concentrations higher than 10 mg/litre, the viability of maize seeds declined in a similar way to that of rice seeds. Rice seeds were found to absorb more methyl bromide than corn seeds. Seeds with a higher moisture content absorbed more methyl bromide and seeds with the same moisture content absorbed more methyl bromide at higher temperatures than at lower temperatures. The authors suggested that changes in certain proteins and enzymes were major factors in seed viability.

The effects of methyl bromide fumigation on the germination of different cultivars of wheat seed have been investigated. The germination of all cultivars was reduced following fumigation at a dose of 16 mg/litre for 24 h (11% moisture, temperature not given). The optimal conditions were a moisture content of 9% and a temperature of 18 °C. With increasing moisture or temperature, the percentage germination decreased. At higher levels of moisture, the concentration of methyl bromide appeared to be a more important factor than exposure time at a constant concentration × time product (CTP) of 768 mg.h/litre (Khanna & Yadav, 1987).

Hanson et al. (1987) found that fumigation with methyl bromide not only caused a delay in germination and loss of germinative capacity but also that certain varieties of seed barley were damaged,

Table 40. Effects on germination of seeds fumigated with methyl bromide[a]

Seed	Fumigation conditions	Germination results	Reference
hemp	70-140 g/m^3	5-23 % reduction	Tkalich (1974)
onion	42 g/m^3 for 24 h	95 % reduction in laboratory 11.5% reduction in cool soil	Powell (1975)
peanuts paper container burlap bags	32 mg/litre (24 h, 27°C, 80% relative humidity), applied under cover, aerated 72 h	reduction of: 21.7% 11.4%	Leesch et al. (1974)
oat, wheat, rye, barley	0, 600, or 1200 g.h/m^3 at 8, 11 14, or 18% moisture content	at 18% moisture content: - no germination after 6 years storage	Blackith & Lubatti (1965)
		at 8% moisture content: - 90% germination after 6 years storage[b]	
Picea abies, Picea glauca, Pinus mugo mughus, Pinus sylvestris (seeds)	seeds at various moisture content; 48 g/m^3, 24°C, 2-5 h, then aerated 1-25 h and stored in sealed containers at 7°C for 1 year	germination normal after storage only if seeds aerated 24 h before storage; all but *P. sylvestris* required drying to 5% moisture content before storage	Jones (1968)
tobacco seed	16-32 g/m^3 or 32-48 g/m^3	germination satisfactory at <10 % seed moisture content: germination dcreased at seed moisture contents above 10%	Guthrie & Kincaid (1957)
barley, corn, grain sorghum, oats, wheat	32 g/m^3 (< 24 h, 26°C);	unimpaired germination seed moisture content less than 12%	Whitney et al. (1958)

[a] From: Davis et al. (1977).
[b] Except rye, germinated well only up to 3 years storage.

exhibiting symptoms of albinism and stunted growth. The authors suggested that great care should be taken in the selection of stored barley intended for seed and, in particular, in the fumigation of samples in standard reference collections. A CTP of 200 mg.h/litre is used commercially, but higher concentrations may be attained if the distribution during fumigation is poor.

7.3.2.2 Fumigation of plants or plant products

Direct fumigation of plants or plant products is used to retard, or prevent, pest infestations and to overcome quarantine barriers. Post-harvest fumigation is discussed in section 5.1.4.2.

7.3.2.3 The effects on plants of soil fumigation

Methyl bromide can have adverse as well as positive effects on plants.

The phytotoxic effects of methyl bromide as a soil sterilant can be caused by:

(1) the action on plants of methyl bromide itself;

(2) the action of inorganic bromide formed by the breakdown of methyl bromide in the soil;

(3) indirect action through effects of either methyl bromide or inorganic bromide on soil microflora, soil structure, or composition (Maw & Kempton, 1973).

Where the crops are affected by lack of mycorrhizae, the plants are stunted. Experiments have proved that this problem can be rectified by fertilizing with phosphoric acid in the irrigation water, using a trickle system (Bromine & Chemicals Ltd., 1990).

The phytotoxicity of methyl bromide is thought to be due mainly to the high level of bromide ion. Drosihn et al. (1968) showed that the degree of susceptibility of carnations to methyl bromide fumigation of the soil depends on the intensity of subsequent leaching of the soil. Similar findings were described by Kempton & Maw (1974). In contrast to this, tomato plants were relatively insensitive to bromide; growing tomatoes tolerated up to 0.1 mg bromide/g soil without signs of injury or growth retardation (Maw & Kempton, 1973). These authors found lettuce to be particularly resistant to

inorganic bromide, with some varieties growing in the presence of as much as 5 mg Br^-/g soil.

Reichmuth & Noack (1983) determined the threshold concentration of methyl bromide in air that should not be exceeded in the vicinity of fumigated buildings, in order to protect plants. The test plants (*Lactuca sativa capitata* (lettuce) and *Nasturtium officinale* (water cress)) were exposed to concentrations of between 4 and 1400 mg methyl bromide/m^3 for 72 h. At 400 mg/m^3, yellowing of lettuce leaves became apparent, while no visible effects were observed on water cress up to the highest concentration.

(*a*) *Cultivated plants*

Only a limited number of genera, species, or varieties of plants are susceptible to methyl bromide. Of the 441 species of glasshouse plants tested by Latta & Cowgill (1941), 414 (93.9%) were not affected and only 27 sustained various levels of damage; of these, five species were severely burned. For example, roses showed no pronounced toxic effects, when planted in soils aerated for four days after methyl bromide fumigation, however, carnations were extremely sensitive to both residual methyl bromide gas and inorganic bromide in the soil (Kempton & Maw, 1974). Other crops, such as cotton, celery, pepper, and onion, do not reach adequate growth, when grown in fumigated soil (Bromine & Chemicals Ltd., 1990). Plants, actively growing, are more likely to sustain injury than dormant plants (Bond, 1984).

(*b*) *Weeds*

The phytotoxic effects of methyl bromide on weeds are important in soil fumigation.

Table 11 shows that the recommended dose rates to eradicate weeds is 35-50 g/m^2, though purple nutsedge (nut grass), corms and seeds of horseweed *Erigeron* (*Conyza*), mallow (*Malva*), and legumes are not efficiently controlled at this dose (Bromine & Chemicals Ltd., 1990).

Methyl bromide (40-80 g/m^2) is mentioned as being the best soil fumigant against yellow nutsedge (*Cyperus esculentus* L.), but the

weed was not completely eradicated because dormant tubers below the tillage depth survived (Rotteveel & Naber, 1987).

7.3.3 Soil invertebrates

Soil fumigation with methyl bromide (and chloropicrin) results generally in toxic effects in both target and non-target organisms. The concentrations used are sufficiently high to eradicate populations of a wide variety of organisms. Fumigants, including methyl bromide and chloropicrin, were all strongly nematocidal. Methyl bromide killed virtually all soil arthropods, including mites; Collembola were almost completely eradicated. Methyl bromide was very toxic for symphylids and millipedes (details of dose not given) (Edwards & Thompson, 1973). Methyl bromide (concentration not given) and chloropicrin were very toxic for earthworms, even those that lived in deep burrows (Van Rhee, 1977). Chloropicrin was repellent to most arthropods in soil (Edwards & Thompson, 1973). To control nematodes, methyl bromide is generally used at rates of up to 80 g/m^2 (Table 41).

7.3.4 Insects and arachnids

Methyl bromide is used as a fumigant to control insect pests. Although it is not as toxic for insect species as some other fumigants, such as HCN, acrylonitrile, and ethylene dibromide, its ability to penetrate quickly and deeply into sorptive materials makes it an effective and versatile fumigant (Davis et al., 1977; Sassaman et al., 1986). The commercial dosage for methyl bromide as a storage fumigant ranges from 16 to 100 g/m^3 for up to 3 days (Tables 12 and 13).

The dosage required depends also on the temperature. The threshold concentration levels identified at 15 and 25 °C differed by a factor of two or three. These investigations by Bell (1988) were carried out on the adult beetle. The dosage of methyl bromide required to kill eggs and pupae is greater than that required to kill all adults. Pupae and older larvae of *Tribolium* spp., for example, required CTPs of up to 180 mg.h/litre for control (Hole, 1981). For other species and exposure conditions see Table 42.

Table 41. Effects of methyl bromide on nematodes

Nematode	Effective control concentration	Exposure Conditions	Reference
Anguina agrostis	CTP 600-800 mg.h/litre	12% moisture	Hague (1963)
Belonolaimus longicaudans	98 g/m^2	98% methyl bromide 2% chloropicrin; covered 48 h	Darby et al. (1962)
Ditylenchus dipsaci	CTP 850 mg.h/litre	10-14% moisture	Hague & Clark (1959)
Dorylaimus sp.	2.3 g/m^3	40 h	Van Gundy et al. (1972)
Hemicyclophora parvana	98 g/m^2	98% methyl bromide 2% chloropicrin: covered 48 h	Darby et al. (1962)
Heterodera rostochiensis	Ct 500-1000 mg.h/litre	treatment with water before fumigation enhanced penetration of methyl bromide	Hague (1959)
Heterodera rostochiensis	111 g/m^2	covered 16 days: 98 % methyl bromide and 2% chloropicrin	Whitehead et al. (1972)
Heterodera schachtii	0.5-30 g/m^3	1-21 days	Abdalla & Lear (1975)
Hoplolaimus columbus	23 g/m^2	potted seedlings, covered, aerated for 1 h after 24 h	Bird et al. (1974)
Hoplolaimus tylenchiformis	98 g/m^2	98% methyl bromide 2% chloropicrin: covered 48 h	Darby et al. (1962)

Table 41 (continued)

Nematode	Effective control concentration	Exposure Conditions	Reference
Meloidogyne sp.	50 g/m^2	manure applied prior to fumigation decreased nematocidal effect	Scotto La Massese & Mars (1975)
Meloidogyne incognita	2.3 g/m^3	38 h	Van Gundy et al. (1972)
Meloidogyne incognita	23 g/m^2	potted seedlings, covered, aerated for 1 h after 24 h	Bird et al. (1974)
Meloidogyne incognita	45-67 g/m^2	covered	Raski et al. (1975)
Meloidogyne incognita	0.6-2.5 g/m^3	1-21 days	Abdalla & Lear (1975)
Meloidogyne incognita acrita	17-22 g/m^2	chisel applicator, covered or rolled	Sher et al. (1958)
Meloidogyne javanica	45-67 g/m^2	covered	Raski et al. (1975)
Meloidogyne javanica	22-34 g/m^2	chisel application, covered	Thomason (1959)
Meloidogyne javanica	56-112 g/m^2	98 % methyl bromide and 2% chloropicrin	Milne (1962)
Pratylenchus sp.	45-67 g/m^2	covered	Raski et al. (1975)
Pratylenchus sp.	4.9-9.7 g/m^3	1-3 days	Abdalla & Lear (1975)
Pratylenchus brachynrus	23 g/m^2	potted seedlings, covered, aerated for 1 h after 24 h	Bird et al. (1974)
Pratylenchus brachyurus	25-51 g/m^3	24 hours; 25°C	Minton & Gillenwater (1973)

Table 41 (continued)

Nematode	Effective control concentration	Exposure Conditions	Reference
Pratylenchus penetrans	50 g/m^2	not stated	Chen et al. (1962)
Pratylenchus thornei	49 g/m^2	covered after application for unspecified time	Van Gundy et al. (1974)
Pratylenchus zeae	100 g/m^2	covered for 48 h following fumigation	Oakes et al. (1956)
Trichoderus christiei	98 g/m^2	98% methyl bromide 2% chloropicrin: covered 48 h	Darby et al. (1962)
Xiphinema americanum	45-67 g/m^2	covered	Raski et al. (1975)
Xiphinema index	2.3 g/m^3	28 h	Van Gundy et al. (1972)
Xiphinema index	45-67 g/m^2	covered	Raski et al. (1975)
Xiphinema index	0.2-2.0 g/m^3	1-21 days	Abdalla & Lear (1975)

Table 42. Some insects controlled by methyl bromide[a]

Insect	LD_{50} (g/m^3)	LD_{95} (g/m^3)	LD_{100} (g/m^3)	Reference
Antagenus picus (black carpet beetle)	32			Pence & Morganroth (1962)
Anthonomus grandis (cotton boll weevil)		16-80		Roth & Kennedy (1972)
Anthrenus flavipes (furniture carpet beetle)			32	Pence & Morganroth (1962)
Anthrenus verbasci (varied carpet beetle)			32	
Araecerus fasciculatus	6.2 (eggs) 3.4 (larvae) 7.4 (pupae) 4.5 (adults)			Majumder et al. (1961)
Blatta orientalis (cockroach)			64	Hickin (1961)
Blatella germanica (cockroach)			64	
Bruchus rufimanus (broad bean weevil)			28	Roth & Richardson (1974)

Table 42 (continued)

Insect	LD_{50} (g/m^3)	LD_{95} (g/m^3)	LD_{100} (g/m^3)	Reference
Cadra cautella (almond moth)			32	Leesch et al. (1974)
Callosobruchus chinensis (L) (cowpea weevil)	0.85 (eggs) 2.2 (instar larvae) 0.89 (pupae) 1.17 (adult)	1.25 (eggs) 2.72 (instar larvae) 3.98 (pupae) 1.4 (adult)		Adu & Muthu (1985)
Chilo agamemnon (corn borer)			20 (larvae)	Isa et al. (1970)
Corcyra cephalonica (rice moth)	1.66-1.78 (eggs) 1.10-1.68 (instar larvae) 2.79 (pupae)			El-Buzz et al. (1974)
Curculio caryae (pecan weevil)			32-112	Leesch & Gillenwater (1976)
Ephestia kuehniella (mediterranean flour moth)	2.02-2.46			Mostafa et al. (1972)
Gnorimoschema operculella (potato tuber moth)	11.74 (larvae)			Pradhan et al. (1960)
Gryllotalpa (mole cricket)		70-100 g/m^2		Dzidzariya (1972)

Table 42 (continued)

Insect	LD_{50} (g/m^3)	LD_{95} (g/m^3)	LD_{100} (g/m^3)	Reference
Hemp leaf roller			40-45	Tkalich (1972)
Laspeyresia pomonella (codling moth)			32	Morgan et al. (1974)
			32	Anthon et al. (1975)
Megastigmus aculeatus (dog rose weevil)			50	Vodolagin (1971)
Musca domestica (housefly)			64	Hickin (1961)
Onychuirus hortensis (springtail)			89 g/m^2	Edwards (1962)
Oryzaephilus mercator (merchant grain beetle)			200	Joshi (1974)
			32	Leesch et al. (1974)
Ostrinia nubilalis (corn borer)			20 (larvae)	Isa et al. (1970)
Periplaneta americana (cockroach)			64	Hickin (1961)
Plodia interpunctella (indian meal moth)	5.5 (normal larvae) 10.2 (diapausing larvae)			Sardesai (1972)
			32	Leesch et al. (1974)
Sitophilus oryzae (rice weevil)	5.45-6.19			

Table 42 (continued)

Insect	LD_{50} (g/m^3)	LD_{95} (g/m^3)	LD_{100} (g/m^3)	Reference
Sitotroga cerealella (angoumois grain moth)	1.85-2.21			
Tenebroides mauritanicus (cadelle)	16 25.5-43.3		23	Bond (1956) Monro et al. (1966)
Isoptera (termites; 5 species)			64	Hickin (1961)
Tribolium castaneum (red flour beetle)	0.009 (adults) 3.06-6.19			Mostafa et al. (1972)
Trilobium confusum (confused flour beetle)	3.6 - 91	4.64-145.14 15[b]		Kenaga (1961)
	21.5-23.7			Monro et al. (1966)
Trogoderma granaria (grain beetle)	0.038 (larvae)			Pradhan & Govindan (1954)
Trogoderma variable (warehouse beetle)			32-40 (eggs) 16-56 (instar larvae) 32-72 (pupae) 24-36 (adults)	Vincent & Lindgren (1975)

[a] A range of LD values reflects effects of time, temperature, or pressure.
[b] Preceded by gamma radiation (50 krad).

In an FAO study, it was found that there was a variation in tolerance to methyl bromide in different strains of eight species of stored product beetles collected from different parts of the world (Hole, 1981). Although resistant strains have been identified in the laboratory, there have been no reports of resistance to methyl bromide in practice (Bell, 1988).

The effects of lethal concentrations of methyl bromide (48 g/m^3 for 2 h) on embryos of the codling moth (*Cydia pomonella* L.) were assessed using light microscopy and transmission electron microscopy (Cheetham, 1990). Cell division stopped within one hour in nearly all embryos, a small number of terata being produced.

Methyl bromide is used to eradicate various wood and household pests, particularly in the warmer climates of southern and western USA. The primary targets are drywood termites (Kalotermitidiae). Scheffrahn & Su (1992) have assessed the toxicity of methyl bromide at 27 °C against pseudergates, nymphs, or alates of several species. Estimates of lethal accumulated doses for 50 and 99% mortality ranged, respectively, from 11.4 and 16.5 for *R. hesperus* pseudergates to 45.9 and 75.0 mg h/litre for *C. cavifrons* pseudergates and nymphs. Alates were more susceptible to methyl bromide than pseudergates or nymphs. Boczek et al. (1975) reported three periods in the development of *Acarus siro* that have increased sensitivity to methyl bromide: (*a*) before the beginning of gastrulation movements in the germ band; (*b*) during the formation of the nervous system; and (*c*) the period preceding dorsal closure. For this species, Burkholder (1966) found LD_{100} values ranging from 3.4 to 16.8 g/m^3 at various exposure times at 16 °C and 85% relative humidity whilst achieving the same CTP (65-83 g.h/m^3).

LD_{100} values have been determined for *Rhipicephalus sanguineus* (brown dog tick) ranging from 6 to 96 g/m^3 (3.5 h, 22 °C and 6 h, 11 °C, respectively) (Roth, 1973).

7.3.5 Gastropods

The effects of methyl bromide on various gastropods (slugs, snails, limpets) have been studied. Roth & Kennedy (1973) found an LD_{100} for *Helidella candidula* and *H. conspurcata*, exposed for 24 h at a dosage of 240 g/m^3. Similarly, for *Cochicella barbara* (72 h,

13 °C) and *Theba pisana* (10 h, 13 °C) a dosage of 128 g/m^3 was lethal (Richardson & Roth, 1965).

7.3.6 Birds

Rhode Island Red female hens were fed, from hatching, on diets that had been fumigated with methyl bromide at the concentration recommended for the elimination of salmonellae (800 mg.h/litre) or at 1½ times this value (Cooper et al., 1978). Body weight, egg weight, and egg number were not significantly affected by treatments, but sexual maturity may have been slightly delayed. The egg flavour was adversely affected. The same group had previously shown that the taste of meat from broiler chickens was similarly tainted (Griffiths et al., 1978).

No adverse effects on either the fertility or hatchability of hens' eggs, previously fumigated with methyl bromide at 32 g/m^3 for 24 h, were observed (Devaney & Beerwinkle, 1982).

7.3.7 Other animals

Data are not available on the direct environmental exposure to methyl bromide of other animals. Effects on test animals are given in section 8.

Bromide intoxication was reported by Knight & Costner (1977) after horses, goats, and cattle were accidentally fed oat hay that had been cut from a field treated with methyl bromide the previous autumn. The bromide content of the hay ranged from 6800 to 8400 mg/kg so that the estimated mean daily intake was 9, 49, and 70 g of bromide ion in goats, horses, and cattle, respectively. Signs of intoxication reported included lethargy, weakness, and ataxia. Similar symptoms were noticed between the 7th and 9th days in animals fed this hay on an experimental basis. Signs of in-coordination (between 10th and 12th days) were correlated with serum bromide concentrations of 30 mEq/litre (2.4 g/litre) or more (Knight & Reina-Guerra, 1977). Serum bromide concentrations and the associated neurological signs subsided markedly 14 days after feeding discontinued (Knight & Reina-Guerra, 1977). Methyl bromide is not approved for use prior to the planting of forage crops.

7.4 Population and ecosystem effects

Application of methyl bromide as a soil fumigant resulted in the almost complete eradication of populations of a wide variety of microflora and fauna, as well as other soil organisms, thus altering, at least temporarily, the trophic structure of the soil environment (Sassaman et al., 1986).

Treatment with 100% methyl bromide and other methyl bromide/chloropicrin formulations reduced populations of *Fusarium*, *Pythium*, and *Rhizooctonia* species in soil. Nine weeks after application, populations were still significantly lower. Seedlings grown in treated plots had the least amount of damping off and root rot (Enebak et al., 1988).

Methyl bromide dosed under plastic sheeting at a rate of 300 g/m^3 (for 30 cm depth 100 g/m^2) killed all insects, though small numbers of soil nematodes and mites were collected during subsequent sampling (Heungens & Roos, 1982).

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

8.1.1 Oral

A summary of acute oral toxicity data is given in Table 43. Very few studies have been carried out, mainly because methyl bromide is a gas at temperatures above 4 °C. The minimum lethal oral dose of methyl bromide for rabbits was found to be 60-65 mg/kg body weight (Dudley et al., 1940; Dudley & Neal, 1942). Miller & Haggard (1943) found that all rats given a single oral dose of 100 mg/kg body weight in olive oil died in 5-7 h.

8.1.2 Inhalation

8.1.2.1 Guinea-pig and rabbit

Single exposure toxicity tests conducted on various mammalian species have shown that methyl bromide is highly toxic. A summary of the acute toxicity data is presented in Table 44.

Studies on guinea-pigs (Sayers et al., 1929) and rabbits (Irish et al., 1940) were carried out. Rabbits were exposed to concentrations of 420, 852, 1000, 2000, 10 000, 20 000, and 50 000 mg methyl bromide/m^3. Table 45 shows the exposure times giving 100% survival and 100% mortality. Concentrations of methyl bromide above 10 000 mg/m^3 sometimes caused the rabbits to close their eyes; otherwise they appeared normal until they became too weak to hold up their heads (Irish et al., 1940). Rabbits that survived 1000 mg methyl bromide/m^3 for 2 days after exposure usually became paralysed (Irish et al., 1940).

Table 43. Acute and short-term oral (gavage) toxicity

Species/ strain	Number of animals/ group[a]	Exposure time	Dose (mg/kg body weight)	Effect	Reference
rabbit	n.d.	single	56-71	all rabbits given an oral dose of 63.9 mg/kg died; one rabbit receiving 56.3 mg/kg died; all rabbits given 56.1 mg/kg or less survived; destruction of superficial layers of stomach and duodenum with accompanying haemorrhage and hyperaemia; minimal lethal dose: 60-65 mg/kg body weight	Dudley et al. (1940) Dudley & Neal (1942)
rat	n.d.	single	100	all died in 5-7 h	Miller & Haggard (1943)
rat	n.d;	single	190-239	LD_{50}, 214 mg/kg	Danse et al. (1984)
rat	n.d.	4 weeks; 7 days/week	50	epithelial hyperplasia, hyperkeratosis and ulceration of the forestomach	
rat (Wistar)	10 (male) 10 (female)	13 weeks; 5 days/week	0 0.4 2 10 50	10 and 50 mg/kg: proliferative alterations of forestomach mucosa; 50 mg/kg: haematological changes 13/20 squamous cell carcinomas of forestomach	

Table 43 (continued)

Species/ strain	Number of animals/ group	Exposure time	Dose (mg/kg body weight)	Effect	Reference
rat	15	13-25 weeks; 12 weeks recovery for some groups	0 50	treated group: week 13: forestomach acanthosis, fibrosis, pseudoepitheliomatous hyperplasia; week 25: hyperplastic lesions of forestomach recovery group: regression of stomach lesions, but adhesions, fibrosis, and mild acanthosis remained; evidence of malignancy in one rat	Boorman et al. (1986)
rat (n.d.)	n.d.	4,8,13, and 17 weeks; 5 days/week	0 25 50	treated groups: forestomach ulceration pseudoepitheliomatous hyperplasia	Hubbs & Hartington (1986)
	n.d.	13 weeks; 5 days/week recovery for 4-8 weeks	0 25 50	recovery period: marked but incomplete regression of lesions; no evidence of malignancy	

[a] n.d. = no details given.

Table 44. Single exposure inhalation studies of methyl bromide on mammals[a]

Species	Concentration (mg/m^3)	Length of exposure (min)[b]	Effect	References
mouse	94 950	25	100 % died within 6 h	Bachem (1927)
mouse	700	n.d.	100 % survived	Bachem (1927)
rat	20 000	6 24	100 % survived 100 % died	Irish et al. (1940)
rat	43 000	3	survived	Clarke et al. (1945)
rat	50 000	3 6	100 % survived 100 % died	Irish et al. (1940)
rabbit	70	40	change in motor reflex behaviour	Balander & Polyak (1962)
rabbit	19 000	25	deep (fatigued) breathing	Beyne & Goett (1934)
rabbit	20 000	36	100 % survived	Irish et al. (1940)
rabbit	20 000	84	100 % died	
rabbit	25 000	30	died	Beyne & Goett (1934)
rabbit	31 600	5	died after 8-10 h	Duvoir et al. (1937)
rabbit	36 000	25	died	Beyne & Goett (1934)
rabbit	50 000	12 30	100 % survived 100 % died	Irish et al. (1940)
dog	10 000	5-6 h	died	Beyne & Goett (1934)
dog	17 000	n.d.	died	Merzbach (1928)
dog	19 000	n.d.	died	Beyne & Goett (1934)
dog	34 000	60	died	Merzbach (1928)
dog	48 000	40	died	Duvoir et al. (1937)
dog	50 000	45	died	Merzbach (1928)

[a] Adapted from Henschler (1990).
[b] n.d. = no details given.

Toxicity is a function of the concentration levels and the exposure times (see also Table 45). The steep dose-mortality response to methyl bromide found by many authors can be seen in Fig. 9.

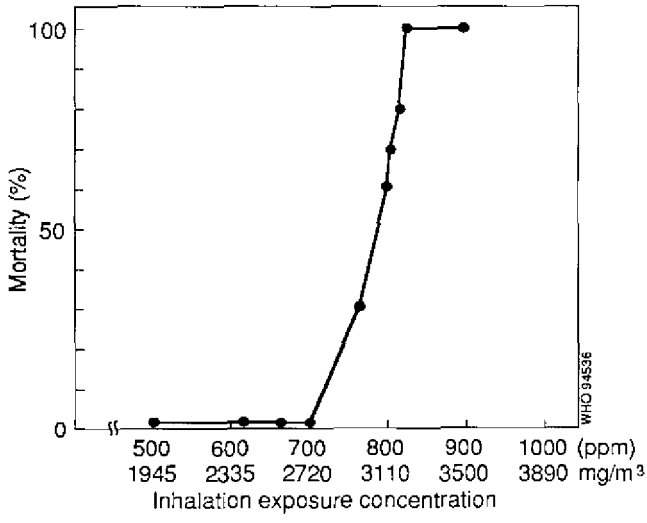


Fig. 9. Dose-mortality response curve after 4 h methyl bromide inhalation exposure of male rats. (From: Kato et al., 1986)

Table 45. Acute inhalation toxicity of methyl bromide for rats and rabbits[a]

Concentration (mg/m³)	Exposure time in hours			
	Rats		Rabbits	
	100 % fatality	100 % survival	100 % fatality	100 % survival
50 000	0.1	0.03	0.5	0.2
20 000	0.4	0.1	1.4	0.6
10 000	0.7	0.4	2.2	1.0
2 000	6	2	11	6
1 000	22	8	24	15
852	26	12	32	20
420	.[b]	22	.[b]	.[b]

[a] From: Irish et al. (1940).
[b] No data.

8.1.2.2 Mouse

The results of single exposure inhalation studies on mice, carried out by Alexeeff et al. (1985), Yamano (1991), and the Japanese Ministry of Labour (1992), are given in Tables 46 and 47. The sharp onset of lethal toxicity was shown in all cases. Alexeeff et al. (1985) exposed male mice to methyl bromide (870-5930 mg/m^3) for 1 h and observed that clinical signs and mortality were dose related, with the possibility of delayed effects in target organs, such as the kidney.

Table 46. LC_{50} values for methyl bromide

Species	Concentration (mg/m^3)	Exposure time	Reference
mouse	6 600	30 min	Bakhishev (1973)
mouse	4 680	1 h	Alexeeff et al. (1985)
mouse	1 540	2 h	Balander & Polyak (1962)
mouse	1 575	4 h	Yamano (1991)
rat	11 000	30 min	Bakhishev (1973)
rat	7 300	1 h	Zwart (1988); Zwart et al. (1992)
rat	3 034	4 h	Kato et al.(1986)
rat	1 175	8 h	Honma et al. (1985)

Further details of target organ studies and biochemical findings from the series of mouse studies (Alexeeff et al., 1985) are given in sections 8.8 and 6.3, respectively.

An LC_{50} of 1575 mg methyl bromide/m^3 (405 ppm $\pm$ 20) was determined after a 4 h exposure (Yamano, 1991). In a further study, the author exposed mice to 1945 mg methyl bromide/m^3 (500 ppm). After 2 h of exposure, there were no deaths, but, after a further 30 min, there was 85% mortality. Mice treated prior to exposure with glutathione (500 mg/kg i.p.) showed only 5.3% mortality after this time.

Groups (10 male+10 female) of BDF1 mice were exposed to methyl bromide (99.9% pure) concentrations of 389, 584, 873, 1315, 1970, or 2950 mg/m^3 (100, 150, 225, 338, 506, or 760 ppm) for 4 h

Table 47. Some single exposure inhalation studies

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects[a]	Reference
mouse (Swiss-Webster)	6 (male)	(nose only) 1 h, surviving mice sacrificed one week later	0		Alexeeff et al. (1985)
			870	(+); no toxic response	
			1720	(+); no toxic response	
			2200	(+); significantly decreased lung and liver weights	
			2720		
			3500	(+); additionally enlarged, pale kidneys and kidney lesions	
			3820	(-); additionally abnormal clinical signs, weight loss and mortality; cerebral haemorrhage	
			4700	(-); additionally liver lesion, liver congestion and haemorrhage	
			5770	(-); additionally decreased motor coordination; cerebral congestion; colonic haemorrhage; congested kidneys	
			5930	(-); all effects mentioned above	
				(1 h-LC_{50} of 4680 mg/m^3 determined)	

[a] (+) = Able to recall a single task passive avoidance test.
[b] (-) = Not able to recall a single task passive avoidance test.

Table 47 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
mouse (Crj: BDF1)	10 (male) 10 (female)	4 h	389	0% mortality	Japanese Ministry of Labour (1992)
			584	0% mortality	
			873	0% mortality	
			1315	0% mortality **Pathology**: respiratory metaplasia of the olfactory epithelium of the nasal cavity (female)	
			1970	80% mortality (male) and 100% mortality (female) **Clinical signs**: decrease in locomotor movement, tremor, convulsion, diarrhoea, bradypnoea, dyspnoea (dead) **Pathology**: Dead: congestion of the lung, necrosis and degeneration of the liver, tubular necrosis of the kidney, karyorrhexis of the thymus and lymph node, necrosis of the olfactory epithelium of the nasal cavity Survived: tubular necrosis and regeneration of the kidney, necrosis and respiratory metaplasia of the olfactory epithelium of the nasal cavity	
			2950	100% mortality clinical sign and pathology: same as 1970 mg/m^3 dead animals	

Table 47 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
mouse		1 h 45 min	1945	0% mortality	Yamano (1991)
		2 h		0% mortality	
		2 h 10 min		11% mortality	
		2 h 20 min		15% mortality	
		2 h 30 min		85% mortality	
		3 h		90% mortality	
rat (F344/DuCrj)	10(male) 10(female)	4 h	584	0% mortality	Japanese Ministry of Labour (1992)
			875	0% mortality **Pathology**: disarrangement and respiratory metaplasia of the olfactory epithelium of the nasal cavity	
			1315	0% mortality; **Pathology**: same as 875 mg/m^3	
			1970	0% mortality; **Pathology**: same as 875 mg/m^3	
			2956	100% mortality **Clinical signs**: closed eyelid, decrease in locomotor movement, ataxic gait, serous discharge of nose, lacrimation, diarrhoea, irregular breathing and bradypnoea **Pathology**: congestion of the lung, degeneration of the liver, tubular necrosis of the kidney, haemorrhage of heart, haemorrhage or necrosis of the adrenal glands, necrosis of the olfactory epithelium of the nasal cavity, congestion of the thymus	
			4435	100% mortality **Clinical signs and pathology**: same as 2956 mg/m^3	

Table 47 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
rat (SPF-Wistar)	2 (male)	5.2-86 min	7500-57 000	1-h LC_{50} was 7300 mg/m^3. **Range**[c]: 3.5-min LC_{50} = 75 700 mg/m^3 480-min LC_{50} = 1300 mg/m^3	Zwart (1988) Zwart et al. (1992)
rat (Sprague-Dawley)	5 (male)	8 h	1042-2085	LC_{50} = 1175 mg/m^3	Honma et al. (1985)
rat (Sprague-Dawley)	8 (male)	8 h	245-972	locomotor activity decreased at 731 mg/m^3; rectal temperature fell 2°C at 486 mg/m^3; decrease in feed consumption and body weight gain at 486 mg/m^3; all animals lost righting reflex at 245 mg/m^3	
rat (F-344)	8 (male)	6 h	778	extensive destruction of the olfactory epithelium	Hurtt et al. (1988)

[c] Total of 23 combinations of time and dosage; the animals were observed for up to 2 weeks.

(Japanese Ministry of Labour, 1992). Mice exposed to concentrations of 1970 and 2950 mg/m^3 showed decreased locomotor activity, tremor, convulsions, diarrhoea, dyspnoea, and bradypnoea. In the 2950 mg/m^3 group, all the mice died; at 1970 mg/m^3, 2 males survived. Mice exposed to concentrations of between 389 and 1315 mg/m^3 did not exhibit any abnormal clinical signs.

Pathology in a female mouse exposed to 1315 mg/m^3 showed metaplasia of the olfactory epithelium. In the 2 male mice surviving exposure to 1970 mg/m^3, there was renal tubular necrosis and regeneration, and necrosis and metaplasia of the olfactory epithelium. In the other mice exposed to 1970 and 2950 mg/m^3, there was pulmonary congestion, hepatic degeneration and necrosis, renal tubular necrosis, karyorrhexis of the thymus and lymph nodes, and necrosis of the olfactory epithelium.

8.1.2.3 *Rat*

Irish et al. (1940) exposed rats to concentrations of 420, 852, 1000, 2000, 10 000, 20 000, or 50 000 mg methyl bromide/m^3. Table 45 shows the exposure time in hours resulting in 100 % survival and 100 % fatality. Rats exposed to concentrations below 10 000 mg/m^3 showed roughening of the fur, hunching of the back, drowsiness, heavy breathing, and sometimes lacrimation. At higher concentrations, the first signs were nose irritation and lacrimation followed by the reactions already mentioned. Those exposed for 20 h to 1000 mg methyl bromide/m^3 often became hyperactive until exhausted.

As well as neurological manifestations of toxicity in rats, methyl bromide at concentrations of 1000-20 000 mg/m^3 caused irritation of the lungs, producing acute congestion and oedema (Irish et al., 1940).

Groups (10 male + 10 female) of F344 rats were exposed to methyl bromide (99.9% pure) concentrations of 584, 875, 1315, 1970, 2956, or 4435 mg/m^3 (150, 225, 338, 506, 760, or 1140 ppm) for 4 h in a chamber (Japanese Ministry of Labour, 1992). At concentrations of 1315 mg/m^3 and above, there was decreased locomotor activity, ataxia, nasal discharge, lacrimation, diarrhoea, and irregular breathing and bradypnoea. In the 2956 and 4435 mg/m^3 exposure groups, all the rats died. Pathology of these

groups showed pulmonary congestion, hepatic degeneration, renal necrosis, myocardial haemorrhages, haemorrhage and necrosis of the adrenal glands, and congestion of the thymus. In rats exposed to 875, 1315, or 1970 mg/m^3, there was metaplasia of the olfactory epithelium and, in those exposed to the two highest doses, also necrosis of the olfactory epithelium.

A single 6-h exposure of rats to 780 mg methyl bromide/m^3 caused extensive destruction of the olfactory mucosal epithelium (Hurtt et al., 1988).

Kato et al. (1986) determined a 4-h LC_{50} for methyl bromide in male Sprague-Dawley rats (Fig. 9). Groups of 5 rats were exposed for 4 h to methyl bromide at concentrations of 1952, 2420, 3108, or 3485 mg/m^3 (502, 622, 799, or 896 ppm), and approximate values of 100% survival and 100% lethal concentration were determined (2529 and 3501 mg/m^3, respectively). In a further test, 10 rats each were exposed to 2727, 2984, 3143, 3178, or 3236 mg/m^3 (701, 767, 808, 817, or 832 ppm). An LC_{50} value of 3034 mg/m^3 (780 ppm) was calculated from mortality at one week after exposure (Kato et al., 1986).

The dependence of methyl bromide toxicity on time and concentration was demonstrated in studies performed by Zwart (1988) and Zwart et al. (1992). Male SPF-Wistar rats were exposed to a total of 23 combinations (2 rats each) of time and concentration and LC_{50} values were determined at seven time points ranging from 3.5 to 480 min. LC_{50}s ranged from 75 700 mg/m^3 at 3.5 min to 1300 mg/m^3 at 480 min. The 1-h LC_{50} was 7300 mg/m^3. Most animals showed some incoordination, decreased response to stimuli, and had lame limbs, directly after exposure. All mortalities occurred during the first week and, on examination, red discoloured lungs and red/black spots in the thymus were found in most dead rats. After two weeks, the surviving animals were sacrificed. Some of these rats showed clear or light red stained fluid in the lungs (Zwart, 1988).

Honma et al. (1985) carried out various investigations into the effects of a single, 8-h exposure to methyl bromide on male Sprague-Dawley rats. An acute toxicity study was carried out with five groups of five animals exposed to 1042, 1303, 1564, 1824, or 2085 mg/m^3 (268, 335, 402, 469, or 536 ppm), respectively. An 8-h LC_{50} of 1175 mg/m^3 (302 ppm) with 95% confidence limits of 1040-1323 mg/m^3 (267-340 ppm) was determined.

Body temperature was measured in four groups of five rats each exposed to 245, 486, or 972 mg methyl bromide/m^3 (63, 125, or 250 ppm). Exposure to 245 mg/m^3 did not effect rectal temperature, while 8-h exposure at 486 or 972 mg/m^3 decreased body temperature by about 2 °C; however, this normalized within one day (Honma et al., 1985).

The effects of methyl bromide on body weight gain were investigated. Food deprivation (feeding only twice a day) was started at least 2 weeks before exposure. Rats were exposed to 245, 486, or 972 mg methyl bromide/m^3 (63, 125, or 250 ppm) for 8 h and feed was provided immediately afterwards. Decrease in food consumption and depression in body weight gain were observed in groups exposed to 486 and 972 mg methyl bromide/m^3, but not in groups exposed to 245 mg methyl bromide/m^3. The control group gained 15 g/day whereas with exposure to 972 mg methyl bromide/m^3, weight gain was almost fully suppressed and was still partially depressed (+10 g) the following day (Honma et al., 1985).

8.1.3 Dermal

Toxicity studies concerning the dermal route of exposure in animals have not been reported.

8.1.4 Subcutaneous administration

For a single subcutaneous administration in Sprague-Dawley male rats (9 rats/group) an LD_{50} for methyl bromide was found to be 135 mg/kg body weight (range 75-250 mg/kg body weight) (Tanaka et al., 1988).

8.2 Short-term exposure

8.2.1 Oral

A summary of studies concerned with oral exposure to methyl bromide by gavage is given in Table 43.

A group of 12 rabbits was fed a mixed diet that had been fumigated with methyl bromide for 24 h. The rabbits were fed immediately after the fumigation was completed and the content of methyl bromide in the feed was 3865 mg/kg. The first animal died

3 days after feeding was begun and the last in 13 days. All were paralysed prior to death and all showed pulmonary damage. No changes in the gastrointestinal tract were found (Dudley et al., 1940).

Studies on rats (8-week preliminary test, 16-week, and 20-week test) and rabbits (52 weeks) were carried out by Dudley & Neal (1942). Results from the rat study showed that, when high (5290-6200 mg Br/kg food) amounts of organic and inorganic bromides were present in food after fumigation with methyl bromide, mortality increased, body weight gain and activity were reduced, and general health and reproductivity were adversely affected. When feed containing 240-300 mg Br/kg, following fumigation with 58 g methyl bromide/m^3 for 24 h, was fed, or when fumigated fruits and vegetables were fed, few or no deleterious effects were noted (Dudley & Neal, 1942). Activity, general condition, body weight gain, and reproductivity were normal. Dudley & Neal (1942) carried out similar studies on rabbits. All 12 rabbits died within 2 weeks of being fed a diet containing about 3000 mg Br/kg. However, the 12 rabbits fed a diet of 60-100 mg Br/kg for 52 weeks showed few or no deleterious effects.

No apparent effects on appearance and general behaviour were observed in Wistar rats (male and female) given doses, by gavage, of up to 50 mg methyl bromide/kg body weight in a 90-day study (Danse et al., 1984). Body weight gain in the male rats was significantly less than that of controls, though this was not the case for females. There were slight haematological changes and, in the two higher dosage groups, several animals showed proliferative alterations of the forestomach mucosa, characterized by hyperkeratosis and papilloma (section 8.7).

A study by Boorman et al. (1986), based on a study design by Danse et al. (1984), included dose groups with a recovery period, in order to study the progression or regression of lesions. Details are given in section 8.7 and Table 43. Boorman et al. (1986) found forestomach lesions similar to those described by Danse et al. (1984), but these lesions regressed in the 60-day recovery period.

Similar findings were reported by Hubbs & Harrington (1986). They administered methyl bromide in peanut oil to rats at doses of 0, 25, or 50 mg/kg body weight per day for up to 120 days. In a regression study, some of the rats were treated for 90 days and then allowed to recover for 30-60 days (Table 43 and section 8.7).

Three groups of four beagle dogs (3 male, 1 female) were fed methyl bromide-fumigated food for 6-8 weeks in doses equivalent to an average daily ingestion of 35, 75, or 150 mg/kg body weight of bromide ion, respectively (Rosenblum et al., 1960). A further group of 4 dogs received 128 mg sodium bromide/kg per day (equivalent to 100 mg bromide ion/kg per day). A control group of 6 dogs (3 male and 3 female) received only dog chow. After one year of observation and monthly blood and urine tests, the remaining dogs were killed, the organs weighed, and histological studies carried out. No evidence of toxicity that could be attributed to bromide was observed in animals that received 35 or 75 mg bromide/kg per day. Dogs in the group receiving 150 mg/kg per day became lethargic and had occasional episodes of salivation and diarrhoea. No significant effects on blood chemistry, haematology, or urinary values were reported, nor were treatment-related deaths or histological lesions noted.

8.2.2 *Inhalation studies*

8.2.2.1 *Guinea-pig, rabbit, monkey*

A summary of short-term exposure studies is given in Table 48.

Irish et al. (1940) carried out extensive studies into the long-term exposure of animals to methyl bromide. A total number of 135 rats, 98 guinea-pigs, 104 rabbits, and 13 monkeys were exposed to 65, 130, 250, 420, or 850 mg methyl bromide/m^3, 7-8 h/day, 5 days/week for 6 months, or, until the majority had either died or shown a severe reaction (Table 49).

8.2.2.2 *Mouse*

In the short-term studies on male and female B6C3F1 mice, exposed 6 h/day for 10 days over 14 days (778 mg methyl bromide/m^3), described by NTP (1992), five mice/dose group per sex were evaluated for haematology, serum pseudocholinesterase activity, and pathology. Necropsied animals from the two highest dosage groups were examined histopathologically. The results are summarized in Table 48.

Eustis et al. (1988) carried out a special target organ study on B6C3F1 mice (and F344/N rats). Male and female B6C3F1 mice were exposed to either 622 mg methyl bromide/m^3 (160 ppm) or air for 6 h/day, 5 days/week. The animals were scheduled for sacrifice after 3, 10, or 30 exposures. When 50% mortality was observed in any group, the surviving animals in that group were sacrificed. Mice were evaluated for body weight, mortality, organ weights, haematology, and histopathology. In addition to these end-points, urine chemistry and plasma enzymes were assessed in the rats. Significantly different mortality rates were observed between the two species, with the mice demonstrating a higher sensitivity to 622 mg methyl bromide/m^3 than rats. Body weight differences were exposure-related (Eustis et al., 1988). The results are summarized in Table 48. Mortality exceeded 50% after 8 and 6 exposures in male and female mice, respectively. The remaining male mice were killed after 10 exposures and the females after 8 exposures. There were significant reductions in body weight and corresponding reductions in organ weights in both sexes, whereas there were sex differences in the haematological parameters. The responses to exposure were minimal in males, but marked in females, in which there were large and significant reductions in RBC, haemoglobin, haematocrit values, and mean corpuscular haemoglobin concentrations, and increases in WBC and mean corpuscular volume (Eustis et al., 1988). Histopathological changes in target organs are described in section 8.8.

BDF1 mice (groups 10 males/10 females) were exposed to methyl bromide at concentrations of 599, 778, 1011, 1315, or 1712 mg/m^3 (154, 200, 260, 338, or 440 ppm) 6 h/day, 5 days/week, for 2 weeks (Japanese Ministry of Labour, 1992). Survival was reduced at all exposure concentrations and none of the mice exposed to 1315 or 1712 mg methyl bromide/m^3 survived. At all exposure concentrations, mice exhibited decreased locomotor activity, piloerection, lacrimation, ataxia, and tremor.

Table 48. Short-term exposure inhalation studies

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
Mouse (B6C3F1)	10 (male) 10 (female)	6 h/day; 5 days/week; 2 weeks	47 97 195 389 778	778 mg/m^3 group: 9 male, 6 female died; All groups: no body weight changes; bloody urine; trembling, jumpiness, paralysis in all groups, but most pronounced in highest dosage groups; haematology parameters/ pseudo cholinesterase activity - no consistent dose-related effects 1 female mouse showed minimal hyperaemia of lungs, liver, kidneys	NTP (1992)
Mouse (B6C3F1)	20 (male) 20 (female)	6 h/day; 5 days/week; 10 exp. days for males and 8 exp. days for females	622	50% mortality (male) after 8 exp. days, 50% mortality (female) after 6 exp. days; exposure-related lesions were seen in the brain, heart, kidneys, thymus, and spleen of both sexes; in the testes, nose, and lungs of males, and in the adrenal glands of females	Eustis et al. (1988)

Table 48 (continued)

Mouse (B6C3F1) (continued)	15 (male) 15 (female)	6 h/day; 5 days/week; 6 weeks	0 622	lethargy; curling and crossing of hind-limbs, forelimb twitching and tremors; decrease in body weight gain after 5 days; decrease in organ weight (lung, heart, thymus, brain, liver) neuronal necrosis; nephrosis; atrophy of inner zone of adrenal cortex; testicular degeneration; decrease in RBC, increase in WBC (females only)	Eustis et al. (1988)
Mouse (B6C3F1)	18-30 (males) 18-30 (female)	5 days/week; 6 h/day; 13 weeks	0 39 78 156 311 467	All dose groups: no significant organ weight effects; decrease in Hb and MCV, increase in RBC (males); decrease in Hb and MCV, increase in RBC (males); 17 % mortality in males; decrease in body weight, additionally severe curling and crossing of hindlimbs and twitching of forelimbs (male > female)	NTP (1992)
Mouse (Crj:BDF1)	10 (male) 10 (female)	6 h/day; 5 days/week 13 weeks	0 29 58 117 234	 no toxic effects; no toxic effects; no toxic effects; depression of body weight gain; **Haematology**: increase in MCV in females; **Urinalysis**: increased protein in females	Japanese Ministry of Labour (1992)

Table 48 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
Mouse (Crj:BDF1) (continued)	10 (male) 10 (female)	6 h/day; 5 days/week 2 weeks	599	10% mortality (male) and 0% (female) depression of body weight gain; **Clinical signs:** **Dead mice**: decrease in locomotor activity, piloerection, lacrimation, bradypnoea, opacity of eye, diarrhoea **Surviving mice**: decrease in locomotor activity, bradypnoea, ataxic gait, sub-normal temperature, tremor, lacrimation, soiled, pallor, hunched posture, piloerection **Pathology:** **Dead mice**: tubular necrosis of the kidney, ulcer of the stomach, testicular atrophy, atrophy of the spleen, atrophy and karyorrhexis of the lymph node, myocardial necrosis **Surviving mice**: degeneration of the granular layer of the cerebellum, tubular necrosis and regeneration of the kidney, necrosis and respiratory metaplasia of the olfactory epithelium	Japanese Ministry of Labour (1992)

Table 48 (continued)

Mouse (Crj:BDF1) (continued)	778	50% mortality of males and 80% mortality of females, depression of body weight gain; **Clinical signs**: same as 599 mg/m^3 group **Pathology: Dead mice**: degeneration of the granular layer of the cerebellum, tubular necrosis and regeneration of the kidney, extramedullary haematopoiesis and atrophy of the spleen, karyorrhexis of the thymus, myocardial necrosis, necrosis of the olfactory epithelium	Japanese Ministry of Labour (1992)
	1011	90% mortality (male and female) depression of body weight gain; **Clinical signs**: same as 599 mg/m^3 Pathology: degeneration of the granular layer of the cerebellum, congestion of the lung, hyaline droplet and tubular necrosis of the kidney, atrophy of the heart, extramedullary haematopoiesis and atrophy of the spleen, myocardial necrosis, necrosis and respiratory metaplasia of the olfactory epithelium of the nasal cavity	
	1315	100% mortality (male and female); **Clinical signs**: same as mice dying in 599 mg/m^3 group **Pathology**: congestion of the lung, degeneration of the liver, hyaline droplet and tubular necrosis of the kidney, karyorrhexis of the thymus and spleen, myocardial necrosis, necrosis of the olfactory epithelium.	

Table 48 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
Mouse (Crj:BDF1) (continued)			1712	100% mortality (male and female); **Clinical signs**: same as mice dying in the 599 mg/m^3 group **Pathology**: congestion of the lung, degeneration of the liver, tubular necrosis of the kidney, karyorrhexis of the thymus and spleen.	Japanese Ministry of Labour (1992)
			467	mortality, 10% in males and 90% in females; depression of body weight gain; **Clinical signs**: ataxic gait; **Haematology**: increased MCV in males; **Urinalysis**: same as 234 mg/m^3 group; **Pathology**: degeneration of the granular layer of the cerebellum, necrosis of the brain, congestion of the lung, karyorrhexis and atrophy of the thymus, tubular necrosis of the kidney, necrosis of the heart, vacuolic change of the adrenal glands	
Rat (SPF Wistar)	6 (male)	6 h/day; 5 days (week 1) 6 h/day; 3 days (week 2)	0 150 375 750	brain weight depression 4-5% (dose related) at 750 mg/m^3; additionally, marked growth retardation; tremors, motor incoordination; liver weights decreased by 26%; no distinct microscopic changes in eight organs (but lungs of three high-dose rats were hyperaemic)	NTP (1992)

Table 48 (continued)

Rat (SPF Wistar)	6 (male) 6 (female)	6 h/day; 5 days/week (week 1,2,3) 6 h/day; 7 days/week (week 4)	0 70 200 600	no toxic effects; no toxic effects (marginal no-effect level); decrease in feed consumption, decrease in body weight gain; disturbed gait and tremors; histopathological changes in heart and lungs, 8 rats died before end of study	NTP (1992) (Dutch Study)
Rat (Wistar)	10 (male) 10 (female)	6 h/day; 5 day/week; 13 weeks	0 4 25 166	no deaths; no clinical findings; no change in body weight minimal changes in liver	Wilmer et al. (1983)
Rat (F344/DuCrj)	10 (male) 10 (female)	6 h/day; 5 days/week; 2 weeks	599 778 1011	depression of body weight gain in females; **Pathology**: disarrangement and respiratory metaplasia of the olfactory epithelium depression of body weight gain; **Pathology**: disarrangement and respiratory metaplasia of the olfactory epithelium of the nasal cavity, cellular vacuolization in the adrenal glands depression of body weight gain; **Clinical signs**: piloerection, soiled, bloody nose discharge; **Pathology**: disarrangement, necrosis and respiratory metaplasia of the olfactory epithelium of the nasal cavity, vacuolic change of the adrenal glands, myocardial damage	Japanese Ministry of Labour (1992)

Table 48 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
Rat (F344/DuCrj) (continued)	10 (male) 10 (female)	6 h/day; 5 days/week; 2 weeks	1315	70% mortality in males and 10% mortality in females; **Dead mice**: depression of body weight gain; **Clinical signs**: decrease in locomotor movement, soiled, piloerection, lacrimation, serous or bloody nose discharge, diarrhoea, pallor, irregular breathing; **Dead and surviving mice**: decrease in locomotor movement, hunched posture, soiled, piloerection, haemorrhagic discharge of nose, lacrimation **Pathology**: interstitial pneumonia, karryorrhexis of of the thymus, myocardial damage, cellular vacuolization of the adrenal glands, disarrangement and respiratory metaplasia of the olfactory epithelium	Japanese Ministry of Labour (1992) (continued)
			1712	100% mortality; **Clinical signs**: same as 338 ppm group dead rats; **Pathology**: congestion and haemorrhage of the lung, congestion, necrosis, and fatty changes in the liver, tubular necrosis of the kidney, myocardial necrosis, haemorrhage, necrosis and cellular vacuolization of the adrenal glands, necrosis and respiratory metaplasia of the olfactory epithelium, congestion of the thymus, inflammation of the bone marrow	

Table 48 (continued)

Rat (Sprague-Dawley)	10-12 (male)	4 h/day; 6 weeks	584 778 1167 1556	decrease in body weight, no clinical changes; decrease in body weight, no clinical changes; 3/12: paralysis of hindlimbs; 5/10: ataxia after 2 weeks, paralysis after 3 weeks, 1/10: died after 4 weeks, 3/10: died after 5 weeks; **Haematology**: no change in RBC, Hb, Hct, WBC 1167 mg/m^3 group: increase in serum enzyme activities; **Organ weights**: decrease in all groups, but no clear dose dependency; **Residual bromide**: increase in all groups 584 mg/m^3: spleen > kidney > liver; higher dosage groups: kidney > spleen > liver; **Histopathological changes**: in brain, heart and testes	Kato et al. (1986)
Rat (Sprague-Dawley)	5 (male)	3 weeks	4 20 39	biochemical changes	Sato et al. (1985)

Table 48 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
Rat (F-344)	10 (male)	6 h/day; 5 days	350 680 973 1264	no observable effects; dose-dependent vacuolar degeneration of zona fasciculata (adrenal gland), cerebellar granular cell degeneration and olfactory sensory cell degeneration; as above, plus: diarrhoea, haemoglobinuria, some gait disturbances and convulsions; hepatocellular degeneration (at 1264 mg/m^3 only) - cerebral cortical degeneration and minor alterations in testicular histology	Hurtt et al. (1987)
Rat (F-344)	total 84 (male)	6 h/day; 5 days	778	increase in mean body weight; degeneration and regeneration of olfactory epithelium	Hurtt et al. (1988)
Rat (F-344)	40 (male); 10 (male) killed on each of day 1,3,5 and 8	6 h/day; 5 days	778	decrease in plasma testosterone concentration and nonprotein sulfhydryl contents of liver and testis	Hurtt & Working (1988)
	35 (male); 5 killed on each of day 6, 10, 17, 24, 38, 52, 73	6 h/day; 5 days			

Table 48 (continued)

Rat (F-344)	5 (male) 5 (female)	6 h/day (3 days)	622	50 % mortality in males after 14 exp. days; remaining males sacrificed; females killed after 6 weeks;clear sex-related differences in susceptibility of specific organs to CH_3Br:brain, kidney, nasal cavity, heart, adrenal, liver, and testis; neuronal necrosis in cerebral cortex, hippocampus and thalamus of brain; necrosis of olfactory epithelium; myocardial degeneration; testicular degeneration	Eustis et al. (1988)
	5 + 10 (male) 5 (female)	6 h/day, 5 days/week (2 weeks)			
	10 (female)	6 h/day, 5 days/week (6 weeks)			
Rat (F-344/N)	18 (male) 18 (female)	6 h/day; 5 day/week; 13 weeks	0 117 234 467	**All dose groups:** no deaths or clinical signs; no consistent organ weight effects; ↓ body weight (females) ↓ body weight (both sexes); minor neurobehavioural changes; (females) ↓ Hct, ↓ Hb, ↓ RBC; olfactory epithelial dysplasia and cysts	Haber et al. (1985)[abstract] NTP (1990)
Rat (CD)	36 (male)	6 h/day; 5 and 10 days	117	GSH and G-6-PDH activities: increase in lung and decrease in liver; serum: decrease in cholinesterase, BUN, uric acid, cholesterol, increase in leucine amino-peptidase	Jaskot et al. (1988)

Table 48 (continued)

Species/ strain	No. of animals/exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
Rat (Long-Evans)	total 30 (15 control)	4 h/day; 4 days/week, 2 weeks	778	damage of olfactory epithelium; repair by day 4; impaired nasal function recovered after 4 days	Hastings (1990)
Rat	10 (male) 10 (female)	6 h/day; 5 day/week; 13 weeks	0		Japanese Ministry of Labour (1992)
			29	no toxic effects	
			73	**Blood biochemistry:** ↓ K (male), ↑ total cholesterol (female)	
			183	**Blood biochemistry:** ↓ in potassium (male) ↑ in total cholesterol, GOT, GPT (female)	
			455	↓ of body weight gain **Haematology:** ↑ Hct, ↑ MCV, ↑ platelet (male) ↑ MCV (female) **Blood biochemistry:** ↓ K (male), ↑ total ↑ total cholesterol, GOT, GPT ↓ glucose, creatinine (female)	

Table 48 (continued)

Rat (continued)	1140	100% mortality; **Clinical signs:** ↓ locomotor activity, hunchback position, piloerection, soiled, ataxic gait, tremor, convulsion, loose stool or diarrhoea, cyanosis, haematuria, serous or haemorrhagic discharge of nose, haemorrhagic discharge of eye, lacrimation, irregular breathing pathology: degeneration of the granular layer of the cerebellum, necrosis of the brain, karyorrhexis, haemorrhage and atrophy of the thymus, tubular necrosis of the kidney, atrophy of the testis, foamy cell accumulation and interstitial pneumonia, myocardial damage, cellular vacuolization of the adrenal glands, pigmentation of the Harderian glands, necrosis, disarrangement and respiratory metaplasia of the olfactory epithelium	Japanese Ministry of Labour (1992) (continued)

GSH = glutathione S transferase; G-6-PDH = glucose-6-phosphate dehydrogenase; BUN = blood urea nitrogen; RBC = red blood cell count; exp. = exposure; p.c. = post copulation.

Histopathology showed degenerative cerebellar changes, renal tubular necrosis and regeneration, and metaplasia and necrosis of olfactory epithelium in all exposed groups. In male mice exposed to 599 mg/m^3, there were also stomach ulceration, testicular atrophy, atrophy of the spleen, and atrophy and karyorrhexis in the lymph nodes. At concentrations above 778 mg/m^3, there were, also karyorrhexis of the thymus, and myocardial necrosis. Hepatic degeneration and pulmonary congestion were found at 1315 and 1712 mg methyl bromide/m^3. For further details see Table 48.

B6C3F1 mice were exposed to methyl bromide concentrations of 0, 39, 78, 156, 312, or 468 mg/m^3 for 6 h per day on five days a week for 13 weeks (NTP, 1992). There were reductions in survival and body weight gain among male mice exposed to 468 mg/m^3. No reduction was observed among males in the other groups or in female mice in any group. Clinical findings in the high-dose group were severe curling and crossing of the hindlimbs and twitching of the forelimbs. These signs were more severe among male than among female mice. Mild behavioural test response deviations reached a maximum after about 6 weeks with no further increase in severity in the later 7 weeks of the study. Plasma cholinesterase activity was unaffected by treatment. No exposure-related histopathological changes were described.

BDF1 mice (groups 10 males/10 females) were exposed to methyl bromide at concentrations of 0, 29, 58, 117, 234, or 467 mg/m^3 (0, 7.5, 15, 30, 60, or 120 ppm) for 13 weeks, 6 h/day, and 5 days/week (Japanese Ministry of Labour, 1992). At 467 mg/m^3, there was a mortality rate of 10% (males) and 90% (females). Ataxia was noted in mice exposed to 467 mg/m^3. There were no abnormal clinical signs at concentrations of between 29 and 234 mg/m^3. Slight increases in mean corpuscular volume (MCV) in female mice exposed to 234 mg/m^3 and in male mice exposed to 467 mg/m^3 were not accompanied by other haematological effects. Blood biochemistry showed no abnormalities. No treatment-related, histopathological effects were observed in the 29 and 234 mg/m^3 groups. In the mice that did not survive exposure to 467 mg/m^3, there were cerebellar degeneration and brain necrosis, pulmonary congestion, thymic atrophy, myocardial damage, renal tubular necrosis, and vacuolization of the adrenal glands (Table 49).

Table 49. Long-term exposure inhalation studies

Species/ strain	No. of animals per exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
mouse (B6C3F1)	86 (male) 86 (female) (planned; because of high mortality, regime altered)	5 days/week; 6 h/day; 2 year (interim sacrifice at 6 and 15 months)	0 39 128 389	**All dose groups**: no biologically significant haematology values; no carcinogenic effects; increased incidence of nonneoplastic lesions in brain, bone, heart, and nose **389 mg/m^3 dosage group**: high mortality (40/86 males and 9/86 females) after 20 weeks; decrease in body weight and in thymus weight; tremors, abnormal posture and limb paralysis; significant behavioural differences at 3 months (males), less so in females	NTP (1992)
mouse (Crj:BDF1)	50 (male) 50 (female)	6 h/day; 5 days/ week; 2 years	0 16 62 250	no toxic effects; no toxic effects; no mortality change; depression of body weight gain **Blood biochemistry**: increase in CPK, inorganic phosphorus (male), chloride; decrease in albumin (female); **Pathology**: atrophy of the granular layer of the cerebellum no increase in neoplastic change was considered	Japanese Ministry of Labour (1992)

Table 49 (continued)

Species/ strain	No. of animals per exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
rat (Wistar)	90 (male) 80 (female)	6 h/day; 5 days/ week; 29 months	0 12 117 350	**All dose groups:** degenerative and hyperplastic lesions in nasal mucosa; no tumours induced by methyl bromide; **350 mg/m^3 group:** ↓ body weight gain; ↓ absolute brain weight; hyperkeratosis in oesophagus and forestomach; ↑ incidence of haemothorax, myocardial degeneration; thrombi in the heart; and increased mortality	Dreef-van der Meulen et al. (1989) Reuzel et al. (1991)
rat (F344/DuCrj)	50 (male) 50 (female)	6 h/day; 5 days/ week; 2 years	16 78 389	**Pathology:** ↑ incidence and severity of inflammation of the nasal cavity (male); **Urinalysis:** ↓ in protein (male); **Pathology:** same as 16 mg/m^3 no mortality change, ↓ body weight gain; **Haematology:** ↑ RBC, Hb, Hct (male) ↑ Hb, Hct (female); **Blood biochemistry:** ↓ LDH, CPK, Na^+, K^+, Cl^- (male), ↓ Glu, CPK, Ca^{2+}, ↑ LAP (female);	Japanese Ministry of Labour (1992)

Table 49 (continued)

Species/ strain	No. of animals per exposure group	Exposure time	Concentration (mg/m^3)	Observed effects	Reference
rat (F344/DuCrj) (continued)				**Urinalysis:** ↓ protein **Pathology:** ↑ incidence of necrosis and respiratory metaplasia of the olfactory epithelium; ↑ incidence and severity of inflammation of the nasal cavity (male); marginal ↑ necrosis of the olfactory epithelium and inflammation of the nasal cavity (female); no increase in neoplasms observed	
rat (Sprague-Dawley)	8 32 (n.g.)[b]	6 h/day; 5 days/ week; 36 weeks over 12 months	0 214	no effect on nerve conduction velocity, open field activity, or coordination	Anger et al. (1981)

[a] RBC = red blood cell count; Hb = haemoglobin; Hct = haematocrit; WBC = white blood cell count; MCV = mean cell volume.
[b] n.g. = sex not given.

8.2.2.3 Rat

F344-rats (groups 10 males/10 females) were exposed to methyl bromide at concentrations of 599, 778, 1011, 1315, or 1712 mg/m^3 (154, 200, 260, 338, or 440 ppm) 6 h/day, 5 days/week, for 2 weeks (Japanese Ministry of Labour, 1992). All rats in the 1712 mg/m^3 group and 7 males and one female in the 1315 mg/m^3 group died before the end of the study. Piloerection and haemorrhagic nasal discharge were reported at exposure concentrations of 1011, 1315, and 1712 mg/m^3. In addition, decreased locomotor activity, a hunched position and lacrimation were observed in rats that survived exposure to 1315 mg/m^3. Diarrhoea and irregular breathing were noted in the rats that died following exposure to 1315 and 1712 mg/m^3.

Pathology showed metaplasia of the olfactory epithelium at methyl bromide concentrations of 599 and 778 mg/m^3, plus necrosis at concentrations between 1011 and 1712 mg/m^3. Vacuolization of the adrenal glands was found at concentrations of 778, 1011, and 1315 mg/m^3 with necrosis at 1712 mg/m^3. Myocardial damage was reported at concentrations between 1011 and 1712 mg/m^3. In the rats exposed to 1315 and 1712 mg/m^3, there was also pulmonary congestion and haemorrhage, renal tubular necrosis and congestion of the thymus; bone marrow inflammation was reported at 1712 mg/m^3 (Table 48).

Two short-term range finding studies were conducted in SPF Wistar rats (NTP, 1992). In the first study, groups of six male rats were exposed to up to 750 mg methyl bromide/m^3 for 6 h/day for 2 weeks (see Table 48). In the second range-finding study, groups of six male and six female rats were exposed to up to 600 mg methyl bromide/m^3 for 4 weeks. Five male and three female rats in the high-dose group died before the end of the study. The most important histopathological changes occurred in the heart and lungs of animals in the high-dose group. Diffuse fatty vacuolization and diffuse myocardial fibre degeneration appeared. The lungs showed hyperaemic and dilated alveoli; in some animals, interstitial pneumonia was noted (NTP, 1992).

Male Sprague-Dawley rats were exposed to up to 1556 mg methyl bromide/m^3 for 4 h/day for 6 weeks (Kato et al., 1986). Changes in body weight, general condition, haematology parameters, organ weight, tissue bromide ion concentration, and the

histopathology of several organs were determined. Suppression of body weight gain, abnormal clinical signs, and severe weakness were observed at 1556 mg methyl bromide/m^3. Bromide ion accumulation was seen, especially in the kidney and spleen, without significant dose-related change. Pronounced histopathological changes were noted in the brain (section 8.8) and multiple small necrotic foci in the heart.

Other short-term, inhalation exposure studies concentrated on one aspect/target organ of methyl bromide exposure.

Sato et al. (1985) described biochemical findings in rats exposed to 4, 20, or 39 mg methyl bromide/m^3, continuously, for 3 weeks. After sacrifice, the organs were weighed and biochemical examinations were performed on the blood and a homogenate of heart, liver, and lungs. The results showed no differences between the 4 mg/m^3 and the control group. In the 20 mg/m^3 group, several changes were observed; serum creatine phosphokinase (CPK), phospholipids (PL), and blood glucose levels, and thymus weight decreased, while blood haemoglobin (Hb), reduced glutathione (GSH), serum total protein, and lung gamma-glutamate-pyruvate transaminase (GTP) levels increased after exposure. In the 39 mg/m^3 group, increases were observed in serum glutamate oxaloacetate transaminase (GOT), lactate dehydrogenase (LDH), alpha-hydroxybutyrate dehydrogenase (α-HBDH), total protein, blood Hb, GSH, lung acid phosphatase (AcP), gamma-GTP, LDH total, liver PL, and triglycerides (TriG), while decreases were noted in serum cholinesterase (ChE), CPK, PL, TriG, lung alkaline phosphatase (AlP), free-cholesterol (f-Chol), lactate, blood glucose, heart lactate, glucose, lung AlP, liver free fatty acids (FFA), and glycogen. Pulmonary haemorrhage was observed in almost all animals in this group.

The effects of short-term inhalation exposure to 1264 mg methyl bromide/m^3 (6 h/day for 5 days) including those on the target organ histopathology of male F-344 rats were studied by Hurtt et al. (1987). Clinical changes (noted only in the 973 and 1264 mg/m^3 groups) were diarrhoea, haemoglobinuria, and, in a few cases, gait disturbances and convulsions. A dose-dependent vacuolar degeneration of the zona fasciculata of the adrenal glands, cerebellar granule cell degeneration, and olfactory sensory cell degeneration were seen in the 680, 973, and 1264 mg/m^3 groups. Cerebral cortical

degeneration and minor alterations in testicular histology were seen only in the 1264 mg/m^3 group whereas hepatocellular degeneration was also found in the 973 mg/m^3 group. No changes were found in the kidneys or epididymides.

In a further study, the degeneration and regeneration of the olfactory epithelium were examined following exposure of a total of 84 rats to 778 mg methyl bromide/m^3 for 6 h/day for 5 days (Hurtt et al., 1988). Groups of five rats were sacrificed after days 1, 3, and 5 and after exposure weeks 1, 2, 3, 5, and 10. Cell replication rate and histopathology were used to assess the kinetics of repair. In addition, olfactory function was assessed using a buried food test. Extensive damage to the olfactory epithelium was evident in animals killed directly after 6 h of exposure. The specific site of damage appeared to be in the olfactory sustentacular cells and mature sensory cells, the basal cells generally being unaffected. By day 3, despite continuous exposure, there was replacement of the olfactory epithelium by a squamous cell layer that increased in thickness and basophilic staining over the next 2 days. One week after exposure, the epithelial region was covered by a layer of polyhedral, basophilic cells and from 2 to 10 weeks exposure, the epithelium exhibited progressive reorganization to restore the original olfactory epithelium pattern; 75-80% of the olfactory epithelium appeared morphologically normal by week 10.

In the same study, the ability of the rats to locate feed was not affected by exposure to 350 mg methyl bromide/m^3, but treatment with 778 mg methyl bromide/m^3 rendered all animals temporarily incapable of locating buried pellets, though they demonstrated searching activity. Four to six days after treatment the animals recovered sufficient olfactory function to find food pellets.

Similar results were reported by Hastings et al. (1989) and Hastings (1990). Studies on Long-Evans rats showed that, after 4 h exposure to methyl bromide (778 mg/m^3), recovery of buried food was greatly impaired but, even with continuous exposure, recovery occurred until, by day 4 of exposure, olfactory function was essentially normal. Extensive damage to the olfactory epithelium was evident after day 1 of exposure; repair of the epithelium was in progress by day 4. The specific site of damage appeared to be in the olfactory sustentacular cell population while the respiratory epithelium was largely spared (Hastings et al.,1989; Hastings,

1990). Bolon et al. (1990) suggested that prior exposure to methyl bromide as well as caging conditions (e.g., inhalation of ammonia from soiled bedding) could influence the olfactory epithelial response.

Evans & Hastings (1992) reported that methyl bromide induced an olfactory function deficit in rats. The olfactory threshold to ethyl acetate was measured in six rats using a conditioned suppression behavioural protocol. Three out of the six rats showed an increase in absolute threshold or threshold response variability after a single, 6-h exposure to 778 mg methyl bromide/m^3.

F-344 rats (20 male + 20 female) were exposed (6 h/day; 5 days/week) to 0 or 622 mg methyl bromide/m^3 (0 or 160 ppm) for 3, 10, or 30 days (Eustis et al., 1988). Toxicological end-points assessed included clinical observations, mortality, body and organ weights, haematology, clinical chemistry, urinalysis, gross pathology, and histopathology. There were no apparent treatment-related changes in any of the clinical chemistry and urinalysis analytes measured. Treatment-related effects in rats included neuronal necrosis in the brain, myocardial degeneration, olfactory epithelial degeneration and atrophy, and testicular degeneration and atrophy.

A study by Eustis et al. (1988) confirmed the very steep concentration-response curve for methyl bromide in rats (and mice). The authors also found clear species and sex differences in sensitivity to methyl bromide toxicity. When rats were compared with mice, the order of susceptibility was female mice > male mice > male rats > female rats. Species and sex-related differences in the histopathology of certain organs were also observed.

Kato et al. (1986) exposed Sprague-Dawley rats for 11 weeks, 4 h/day, to 584 mg methyl bromide/m^3. No abnormal clinical signs were reported. Small necrotic foci and fibrosis were observed in the heart muscle.

F-344 rats (groups 10 males/10 females) were exposed to methyl bromide at concentrations of 0, 29, 73, 183, 455, or 1140 mg/m^3 (0, 7.5, 18.8, 46.9, 117, or 293 ppm) for 13 weeks for 6 h/day, 5 days/week (Japanese Ministry of Labour, 1992). At 1140 mg/m^3, there was 100% mortality. At this concentration of methyl bromide, rats exhibited decreased locomotor activity, piloerection, ataxia, tremor, cyanosis, haematuria, and nasal and ocular discharge. No clinical signs were reported at lower doses.

Haematological studies showed increased MCV in male and female rats exposed to 455 mg/m^3; there was also an increased number of platelets in the male rats. Serum potassium was decreased in male rats exposed to concentrations of 73 mg/m^3 or more. Glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels were significantly increased in female rats exposed to concentrations of 183, 455, and 1140 mg/m^3. Serum glucose and creatinine levels were significantly decreased in female rats at 455 mg/m^3.

There were no abnormal histopathological findings in rats exposed to methyl bromide concentrations of between 29 and 455 mg/m^3. Rats exposed to 1140 mg/m^3 exhibited cerebellar degeneration and brain necrosis, thymic haemorrhages and atrophy, renal tubular necrosis, pneumonitis, myocardial damage, adrenal vacuolization, Harderian gland pigmentation and metaplasia, and necrosis of the olfactory epithelium (Table 49).

Thirteen-week inhalation toxicity studies were conducted in which groups of ten male and ten female Wistar rats were exposed to methyl bromide at target concentrations of up to 166 mg/m^3 for 6 h/day, 5 days/week (Wilmer et al., 1983). No deaths occurred, and no abnormal clinical findings were observed. Body weight gain was not affected in any of the exposed groups. Leukocyte counts were 22% higher in high-dose males than in male control animals. Plasma alkaline phosphatase activity was lower in both high-dose males (32%) and females (53%) than in controls, and the plasma albumin concentration was 10% higher in high-dose females than in controls. The absolute and relative liver weights were up to 16% lower for high-dose males and females compared with controls. The only exposure-related histopathological change, which occurred in the liver of high-dose male and female rats, was characterized by small hepatocytes with homogeneous eosinophilic cytoplasm. This alteration varied in extent from slight to severe and was seen in 6/10 males and 7/10 females. The no-adverse-effect level for these 13-week inhalation toxicity studies was considered to be 25 mg/m^3.

Groups of 18 rats of each sex were exposed to up to 467 mg/m^3 for 6 h/day and 5 days/week over 13 weeks (NTP, 1992). All rats survived to the end of the studies, few or no clinical effects of exposure to methyl bromide could be seen. Significant decreases in body weight gain were noted in both sexes at 467 mg/m^3 and in

females at 234 mg/m^3. No consistent organ weight effects were observed. Minor neurobehavioural changes were noted in both sexes in the highest dosage group. Females, but not males, of this group had significantly lower haematocrit, haemoglobin levels, and erythrocyte counts compared with those of controls. Olfactory epithelial dysplasia and cysts, characterized by irregularity in mucosal thickness and focal cavitated spaces, respectively, were seen in both sexes at 467 mg/m^3.

8.2.3 Dermal

There are no reports of studies on short-term dermal exposure.

8.3 Skin and eye irritation

Irish et al. (1940) noticed lacrimation in rats after inhalation of methyl bromide levels above 10 000 mg/m^3. Irritation of the eye membranes in mice at concentrations of 3200 mg methyl bromide/m^3 was described by Balander & Polyak (1962). There are no reports on skin effects in animals.

8.4 Long-term exposure

8.4.1 Oral

8.4.1.1 Rat

Rats were fed for 7-8 months on wheat grain or peanuts fumigated with methyl bromide having residual bromide levels of 20 and 22-46 mg/kg, respectively. There were no effects on weight gain of the animals, haemoglobin content, or red or white blood cell numbers. However, a decrease in iodine and calcium levels in the blood and abnormal changes in the thyroid and parathyroid glands were reported (Vitte et al., 1970).

A two-year, oral, long-term toxicity and carcinogenicity study was carried out on 60 male and 60 female F-344 rats per group fed diets fumigated with methyl bromide (Mitsumori et al., 1990). Diets containing 80, 200, or 500 mg total bromide/kg food (methyl bromide concentration <20 mg/kg food) were fed, the controls receiving commercial basal diet (containing 30 mg bromide/kg) and

a diet containing 500 mg potassium bromide/kg. No effects were observed on the behaviour of the rats in any of the groups fed the fumigated or KBr- containing diets. In rats fed the diets fumigated with methyl bromide, there were no marked toxic changes, except for a slight depression in body weight from week 60 onwards in males in the 500 mg/kg group. Tumour incidence was unaffected. Rats given a diet containing KBr did not show any treatment-related changes. The no-effect level was 200 mg/kg (equivalent to 6.77 mg total bromine/kg body weight per day) in males. No effects were observed in females at the doses studied.

8.4.2 Inhalation studies

Long-term exposure inhalation studies are summarized in Table 49.

8.4.2.1 Mouse

In a carcinogenicity study, 86 B6C3F1 mice/sex were exposed to 39, 128, or 389 mg methyl bromide/m^3 for 6 h/day, 5 days/week, for 2 years with scheduled interim sacrifices at 6 months and 15 months (NTP, 1992). Because of the high mortality early in this study in the 389 mg/m^3 group (27/86 males, 7/86 females), the exposure to methyl bromide at this level was stopped at 20 weeks and the surviving mice were exposed to air for the rest of the study.

Terminal survival rates (Kaplan-Meier determinations) in the control, 39 mg/m^3, 128 mg/m^3, and 389 mg/m^3 groups were: males 82%, 74%, 80%, and 23%; and females, 71%, 82%, 90%, and 65%, respectively. Significantly lower mean body weights of the highest dosage group compared with controls appeared by week 11 and persisted after termination of dosing at week 20 until the end of the studies. The only biologically significant change appeared to be reduced absolute and relative thymus weights in both sexes. Neurological signs were also observed, mostly in the highest dosage group, including tremors, abnormal posture (lateral curvature of the spine), and limb paralysis. These symptoms generally persisted (NTP, 1992). Exposure-related histological lesions occurred primarily in the 389 mg/m^3 exposure group and included degeneration in the cerebellum, cerebrum and heart, chronic cardiomyopathy, sternal dysplasia, and either necrosis or metaplasia of the olfactory

epithelium. There were no neoplasms attributed to exposure to methyl bromide.

Quantitative neurobehavioural testing showed significant differences in the behaviour of the high-dose males at 3 months. The animals were less active and demonstrated a reduction in startle response latency. Because of the high early mortality in high-dose males, only males in the controls and two lower dosage groups were tested after 3 months. After 6 months of exposure, the 389 mg/m^3 females had significantly lower activity scores than females in other groups, but their higher startle responses had disappeared. Although at 9 months of exposure no behavioural differences were apparent, lower activity and heightened startle response were again noted at the 2-year testing time (NTP, 1992).

Toxicity and carcinogenicity studies were conducted by inhalation exposure of groups of 50 male and 50 female Crj:BDF1 mice (6 h/day, 5 days/week) to methyl bromide (99.9% pure) for 104 weeks (Japanese Ministry of Labour, 1992). Methyl bromide concentrations of 0, 16, 62, and 250 mg/m^3 were used.

Body weight gains in male and female mice exposed to 250 mg/m^3 were lower than those in chamber controls. No significant differences in survival were observed between exposed and control groups of either sex. Increased incidences of atrophy (slight) of the granular layer of the cerebellum were observed in male and female mice exposed to 250 mg/m^3. There were no treatment-related neoplasms in male or female mice.

8.4.2.2 Rat

Toxicity and carcinogenicity studies were also conducted by inhalation exposure to methyl bromide (99.9% pure) of groups of 50 male and 50 female F344/DuCrj rats (6 h/day, 5 days/week) for 104 weeks (Japanese Ministry of Labour, 1992). Methyl bromide concentrations of 0, 16, 78, and 389 mg/m^3 were used. Body weight gains in males and female rats exposed to 389 mg methyl bromide/m^3 were lower than those in chamber controls. No significant differences in survival were observed between exposed and control groups of either sex. Increased incidences of necrosis and respiratory metaplasia of the olfactory epithelium of the nasal cavity were observed in male rats exposed to 389 mg methyl bromide/m^3, and

increased incidence and severity of inflammation of the nasal cavity were observed in male rats exposed at all concentrations used. Necrosis of the olfactory epithelium and inflammation of the nasal cavity were marginally increased in female rats exposed to 389 mg methyl bromide/m^3. There were no exposure-related increased incidences of neoplasms in male and female rats.

In a long-term inhalation study, a total of 360 male and 360 female rats (Wistar) were exposed to concentrations of up to 350 mg methyl bromide/m^3 for 6 h/day, 5 days/week for 29 months (Dreef-van der Meulen et al., 1989; Reuzel et al., 1991). Non-neoplastic and neoplastic lesions were scored in all control and high-level animals of the main group, and the nose examined histopathologically at all exposure levels. Mortality was higher in males and females at the 350 mg/m^3 level than in controls from the end of the second year onwards. Body weights in the 350 mg/m^3 group (both sexes) were slightly lower than controls from week 4 onwards. No essential differences between groups were observed in haematology, clinical and blood chemistry, and urine analysis at three months and one year. The absolute brain weight was decreased in females at 350 mg/m^3. A higher incidence of haemothorax was seen in males and females at 350 mg/m^3 than in controls. In the heart there was an increased incidence of thrombi and myocardial degeneration in rats exposed to 350 mg/m^3. There was hyperkeratosis of the oesophagus and forestomach. The incidences of neoplastic lesions did not differ significantly among the groups.

8.5 Reproduction, embryotoxicity, and teratogenicity

8.5.1 *Reproduction and embryotoxicity*

McGregor (1981) conducted a sperm abnormality assay exposing groups of 10 male B6C3F1 mice to air containing 0, 78, or 272 mg methyl bromide/m^3 (0, 20, or 70 ppm) for 7 h/day, for 5 days. No sperm abnormalities were found at these concentrations.

Atrophy of seminal epithelium, incomplete spermatogenesis, and giant cells in the seminal tubules, were detected unilaterally in one rat (group of 10) after inhalation of 778 mg methyl bromide/m^3 (200 ppm) (4 h/day; 5 days/week for 6 weeks) and in six rats (group of 10) after inhalation of 1167 mg methyl bromide/m^3 (same length of exposure). In the tubules of the epididymis adjacent to the

atrophied testis, necrotic spermatocytes had accumulated in seminal fluid, but spermatozoa were not seen (Kato et al., 1986).

Spermatogenesis and sperm quality were evaluated in the rat (F-344/N) following exposure to 778 mg methyl bromide/m^3, 6 h/day for 5 days (Hurtt & Working, 1988). Although methyl bromide caused a transient decrease in plasma testosterone and testicular nonprotein sulfhydryl concentrations during acute exposure, no other reproductive indices, including testis weight, daily sperm production, cauda epididymal sperm count, sperm morphology, percentage motile sperm, linear sperm velocity, and epididymal and testicular histology, were affected by methyl bromide exposure.

Testicular degeneration and atrophy occurred in several rats and mice following repeated (6 h/day, 5 days/week for up to 6 weeks) inhalation exposure to 622 mg methyl bromide/m^3 (Eustis et al., 1988). In rats, degeneration included separation and sloughing of spermatocytes and late stage spermatids and/or formation of intratubular multinucleate giant cells. Atrophy was characterized by variable loss of all components of the spermatogenic epithelium. In exposed mice, degeneration of testes occurred frequently, but it was not always severe.

Thirteen-week inhalation studies on sperm morphology and vaginal cytology examinations (SMVCEs) in $B6C3F_1$ mice and F-344 rats were carried out by Morrissey et al. (1988). Results from mouse studies (inhalation of 39, 156, or 467 mg methyl bromide/m^3) showed a decrease in terminal body weight, and a relative increase in the weight of epididymis and testis. A decrease in sperm density and an increase in the percentage of abnormal sperm were also noted. In rats that inhaled 117, 233, or 467 mg methyl bromide/m^3, a decrease in terminal body weight as well as a decrease in the weight of the cauda epididymis, and a relative increase in the weight of the testis were noted. A decrease in sperm motility was also observed. In females, exposure to methyl bromide did not affect the length of the estrous cycle (Morrissey et al., 1988).

Female rats exposed to 272 mg methyl bromide/m^3 (70 ppm) for up to 40 days survived and reproduced without impairment (Hardin et al., 1981; Zikov et al., 1981).

In a dominant lethal assay carried out in rats (McGregor, 1981), groups of 10 male, adult CD rats were exposed to 0, 78, or 272 mg

methyl bromide/m^3 for 7 h/day on five consecutive days, then serially mated at weekly intervals for 10 weeks with untreated virgin females in the ratio one male: two females. When the females were sacrificed, their ovaries were examined for corpora lutea graviditatis and the uteri were opened and examined for live implantations, late deaths, and early deaths. The frequency of pregnancy was determined by (*a*) females with corpora lutea graviditatis and (*b*) females with implantations. With either method, methyl bromide did not cause a significant decrease in the frequency of pregnancy, and the number of corpora lutea per pregnancy and the frequency of early deaths were unaffected.

The effects of inhalation exposure to 0, 12, 117, or 350 mg methyl bromide/m^3 for 6 h/day, 5 days/week, for around 8 months, on the growth, reproduction, and offspring in two consecutive generations of CD Sprague-Dawley rats were investigated (American Biogenics Corporation, 1986). Body weight depressions were noted in the males in the highest concentration group at 5 of the 10 pre-mating collection intervals and at final sacrifice. The pre-mating and total weight gains were also less than those of the untreated control males. In the F1 generation, parental body weight was comparable in exposed and control animals. In the F2a litter, a slight body weight depression was noted in gestating and lactating dams in the highest concentration group compared with controls. Otherwise, maternal body weights were comparable with those of the controls.

There was a marginal reduction in female fertility index in the two top dose groups of the F2a litter. The mean numbers of pups delivered viable were comparable with controls. Survival of the pups was reduced in the 350 mg/m^3 dose group in late lactation in the F1a generation. Body weights of pups were reduced in both the 350 and 117 mg methyl bromide/m^3 dose groups of the F1a, F2a and F2b generations, though no consistent changes were observed in the F1b generation.

No anomalies were noted in the treated progeny that were attributed to methyl bromide exposure.

Gross pathological examination of parent animals from both generations and randomly selected F1b and F2b progeny did not reveal any treatment-related lesions. A statistically significant decrease in the mean brain weight in the F0 males and an increased

liver to body weight ratio in both sexes were found in the upper concentration group. In the F1 generation, both male and female brain weights were decreased at 350 mg methyl bromide/m^3.

Statistical analyses of the F1b progeny final body weight and organ weight data revealed no significant differences. Statistical reductions were found in the final body weight data obtained for the F2b males (350 mg methyl bromide/m^3) and F2b females (117 and 350 mg methyl bromide/m^3) compared with untreated control progeny. Analysis of F2b progeny organ weight data revealed significant decreases, compared with controls, for the female brain, heart, kidney, and liver weights (350 mg methyl bromide/m^3) and female liver weight (117 mg methyl bromide/m^3). In these two upper concentration groups, the females brain to body weight ratio was increased and the liver to brain ratio, decreased. Microscopic examination of the reproductive organs and abnormal tissues did not reveal any treatment-related lesions.

8.5.2 Teratogenicity

Female Wistar rats were exposed for 7 h/day, 5 days/week for 3 weeks to methyl bromide concentrations of 78 or 272 mg/m^3. After this time, they were mated. There was a total of 7 different exposure groups (Table 48). Female rats whose vaginal smears showed evidence of sperm were exposed for 7 h daily from day 1 (=day of finding sperm in vaginal lavage) to 19 of gestation. The day before term (gestation day 21), they were sacrificed and necropsied. The results showed no effects of the exposure on the female rats, nor were embryotoxic or other teratogenic effects found (Sikov et al., 1981).

In a further series of studies by Sikov et al. (1981), groups of 24 female New Zealand white rabbits were exposed for 7 h daily to 78 or 272 mg methyl bromide/m^3 (20 or 70 ppm) from the day of artificial insemination. The 78 mg/m^3 group was exposed up to day 24 of gestation; because of toxic effects, exposure had to be stopped on day 15 for the 272 mg/m^3 group, in which all but one pregnant rabbit died. The remaining rabbits from the control and 78 mg/m^3 exposure group were sacrificed on the 30th day of gestation. The low exposure group showed no fetotoxic or teratogenic effects. An evaluation of the fetotoxicity or teratogenic results from the high dose

group was not possible because of the high mortality rate in the pregnant rabbits (Hardin et al., 1981; Sikov et al., 1981).

In a preliminary teratology study (Breslin et al., 1990), pregnant New Zealand White rabbits were exposed via inhalation for 6 h/day to 0, 39, 117, 195, 272, or 545 mg methyl bromide/m^3 (0, 10, 30, 50, 70, or 140 ppm). Toxicity was observed in rabbits exposed to 545 mg methyl bromide/m^3 and these were sacrificed before the end of the study. No apparent embryotoxic effects were observed at any exposure level (Breslin et al., 1990).

A subsequent study by the same investigators was conducted in two parts. In Part I, groups of 26 inseminated New Zealand White rabbits were exposed via inhalation to 0, 78, 156, or 311 mg methyl bromide/m^3 (0, 20, 40, or 80 ppm) on days 7-19 of gestation. In Part II, groups of 17 inseminated rabbits were exposed for 6 h/day to 0 or 311 mg methyl bromide/m^3 (0 or 80 ppm) on days 7-19 of gestation. An additional group of 16 females, inseminated by a single male, acted as controls. On day 28 of gestation, all surviving animals were necropsied. Maternal liver, kidney, lung, brain weights, gravid uterine weights, and the number of corpora lutea, implantations, resorptions, and live/dead fetuses were noted. The fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations.

Rabbits exposed to 311 mg methyl bromide/m^3 showed moderate to severe maternal toxicity. Decreased body weight and/or body weight gain were noted. Clinical alterations included lethargy, right-sided head tilt, ataxia, and lateral recumbency. The last three signs were associated with significant histopathological lesions of the brain (multifocal areas of inflammation of the meninges and/or bilaterally symmetrical necrosis or spongiosis in the midbrain) in the above-mentioned probe study with 545 mg methyl bromide/m^3. At an exposure level of 311 mg methyl bromide/m^3, developmental effects were observed consisting of decreased fetal weights, an increase in the incidence of fused sternebrae, and an increase in the incidence of malformations [18/23] (mostly missing gallbladder or missing caudal lobe of the lung).

No adverse maternal, embryonal, or fetal effects were observed in rabbits exposed to 78 or 156 mg methyl bromide/m^3 (Breslin et al., 1990).

Methyl bromide at 0, 0.5, 5, 25, or 50 mg/kg body weight was administered in peanut oil, by gavage, to pregnant rats on days 5-20 of gestation (Peters et al., 1982). Signs of maternal toxicity were evident in the two highest dose groups. Total resorption of embryos was observed in the highest dose group and was considered to be the result of the poor health of the pregnant rats and not a primary toxic effect. In the control and 25 mg/kg groups, no effects on the skeleton or internal organs were reported. In this study, methyl bromide was not considered teratogenic and adverse effects on prenatal development only occurred when maternal toxicity was present.

8.6 Mutagenicity and related end-points

Table 50 summarizes the results of tests for the genotoxic activity of methyl bromide.

8.6.1 DNA damage

DNA adducts have been demonstrated in F344 rats, following oral or inhalation administration ^{14}C-methyl bromide. The adducts were isolated from liver, lung, stomach, and forestomach and identified as 3-methylguanine, 7-methylguanine, and O^6-methylguanine. Following exposure by either route, the levels of adducts were higher in female than in male rats and the guanine adducts were particularly prominent in the stomach and forestomach (Gansewendt et al., 1991).

Alkylation of guanine-N-7 in the DNA of liver and spleen was observed after treatment of male CBA mice with ^{14}C-labelled methyl bromide (4.9-5.0 mCi/mmol) by inhalation (340 mCi/kg body weight for 4 h) or i.p. injection (4.4 μmol/kg body weight) (Djalali-Behzad et al., 1981). They noted that the extent of DNA alkylation in the liver and spleen *in vivo* was 200 and 20 times lower, respectively, than expected from the extent of the alkylation of haemoglobin and from the relative reactivities of DNA and haemoglobin towards methyl bromide *in vitro*.

Table 50. Mutagenicity tests with methyl bromide

Test	Test system	Dose level, concentration	Metabolic activation presence/ absence	Response	Reference
Reverse mutation	*Salmonella typhimurium* TA 100, TA 98, TA 1535, TA 1537, TA 1538	0.02-0.2% (in desiccators) 2 h	+/-	positive, TA 100	Simmon et al. (1977)
Reverse mutation	*Salmonella typhimurium* TA 100, 1535 TA 98, 1537, 1538	500-5000 mg/m^3, 2 days	+/-	positive, TA 100, TA 1535	Moriya et al. (1983)
	Escherichia coli WP 2 hcr			positive	
Reverse mutation	*Salmonella typhimurium* TA 100 TA 98	500-50 000 mg/m^3 (plate), 5 days	+/-	positive at 1900 mg/m^3 negative	Kramers et al. (1985a)
SOS-umu (modified Ames test)	*Salmonella typhimurium* TA 1535/ pSK 1002	1.5 litre/min for 30 min		positive	Ong et al. (1987)
Forward mutations streptomycin resistance	*Klebsiella pneumoniae* ur$^-$ pro$^-$	950-19 000 mg/m^3, 20 h		positive at 4750 mg/m^3	Kramers et al. (1985a)
Forward mutation	*Escherichia coli* Sd 4	0.5-6 mmol/litre, 1 h		1 mutation/10^8 surviving bacteria/mmol•h	Djalali-Behzad et al. (1981)

Table 50 (continued)

Test	Test system	Dose level, concentration	Metabolic activation presence/absence	Response	Reference
Forward mutation	L5178Y mouse	0.03-30 mg/litre, 24 h		positive	Kramers et al. (1985a)
Sex-linked recessive lethal	*Drosophila melanogaster*	78 or 272 mg/m^3, 5 h		negative	McGregor (1981)
Sex-linked recessive	*Drosophila melanogaster*	750 mg/m^3 (6 h) 375 mg/m^3 (5 × 6 h) 200 mg/m^3 (15 × 6 h)		negative positive positive	Kramers et al. (1985a,b)
Sister chromatid exchanges (SCE)	Phytohaemagglutinin-stimulated human whole blood	4.3%		increased SCE frequency from 10-16.84/cell after 100-second exposures	Tucker et al. (1985)
SCE	cultured human lymphocytes	10^{-4}-10^{-6} mol/litre	+/-	positive	Garry et al. (1990)
SCE	bone marrow cells of exposed B6C3F$_1$ mice	47-778 mg/m^3 6 h/day; 5 days/week; 14 days and 12 weeks		dose response observed at 14 days only; higher in females than males	NTP (1992)
		same dose range and exposure		negative	

Table 50 (continued)

Test	Test system	Dose level, concentration	Metabolic activation presence/ absence	Response	Reference
Unscheduled DNA synthesis	human diploid fibroblasts (human embryonic intestinal cells)	up to 70% 3 h	+/-	negative	McGregor (1981)
Unscheduled DNA synthesis	SPF male Wistar rats, primary liver	10-30 mg/litre		negative	Kramers et al. (1985a)
Cell transformation	Syrian hamster embryo cells	3890-31 120 mg/m^3 2-20 h in sealed chambers		negative	Hatch et al. (1983)
Chromosomal aberrations	male and female CD (ex Sprague-Dawley) rat bone marrow cells	78 or 272 mg/m^3 single 7 h or 7 h/day; 5 days		negative	McGregor (1981)

Table 50 (continued)

Test	Test system	Dose level, concentration	Metabolic activation presence/ absence	Response	Reference
Micronucleus	male and female BDF1 mice	600-1712 mg/m^3 6 h/day; 5 days/ week; 14 days		polychromatic erythrocytes with micronuclei in the bone marrow increased 10-fold in males (778 mg/m^3) and 6-fold in females (600 mg/m^3); in peripheral blood increased 32-fold in males (778 mg/m^3) and 3-fold in females (600 mg/m^3)	Ikawa et al. (1986)
Micronucleus	male and female F344 rats	600-1712 mg/m^3 6 h/day; 5 days/ week; 14 days		polychromatic erythrocytes with micronuclei in the bone marrow increased 10-fold in males and 3-fold in females at 1314 mg/m^3	Ikawa et al. (1986)

Table 50 (continued)

Test	Test system	Dose level, concentration	Metabolic activation presence/ absence	Response	Reference
Micronucleus	in peripheral erythrocytes of B6C3F$_1$ mice	47-778 mg/m^3 6 h/day; 5 days/ week; 14 days		elevated (only at 14 days) responses over entire dose range with greatest response at 389 and 778 mg/m^3 in females; males less responsive	NTP (1992)
		same dose range and exposure routine; 13 weeks		negative	
Dominant lethal	rats, male CD (Sprague-Dawley)	78 or 272 mg/m^3 7 h/day; 5 days		negative	McGregor (1981)

Starratt & Bond (1988a) found that methylation of DNA in maize and wheat took place during fumigation using ^{14}C-labelled methyl bromide (48 mg/litre for 72 h). They identified 7-methylguanine and 1-methyladenine as major products and lesser amounts of 3-methylcytosine and 3-methyladenine and 7-methyladenine; 0.5-1% of the guanine residues in the DNA were methylated. Methylation of solid samples of calf thymus DNA and salmon testes DNA gave similar results, except that the quantity of 1-methyladenine exceeded that of 7-methylguanine (Starratt & Bond, 1988b).

In contrast, a different pattern of methylated bases was found when solutions of DNA were treated with ^{14}C-labelled methyl bromide. Here, predominantly 7-methylguanine with a small amount of 3-methyladenine and only traces of 1-methyladenine and 3-methylcytosine were identified (Starratt & Bond, 1988b). The authors noted that these results agreed better with the *in vivo* studies of Djalali-Behzad et al. (1981).

An *in vitro* assay for unscheduled DNA synthesis (UDS) was carried out in human diploid fibroblasts with exposures of 3 h and concentrations up to 70% in air. No increase in UDS was found (McGregor, 1981).

As measured by autoradiography, methyl bromide (tested at 10-30 mg/litre) did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes treated in air-tight bottles (Kramers et al., 1985a).

8.6.2 Mutation

Methyl bromide has been tested in various *in vitro* and *in vivo* test systems (Table 50).

Methyl bromide was mutagenic to *Salmonella typhimurium* TA 100 when tested at concentrations of 0.02-0.2%, in desiccators, in the absence of an exogenous metabolizing system (Simmon et al., 1977).

Positive results were also obtained in strain TA 100 in a liquid assay (tested at 10-1000 mg/litre) and a plate assay (tested in closed containers at concentrations of 500-50 000 mg/m^3). Methyl bromide was mutagenic at concentrations of 1900 mg/m^3 and higher (plate tests), and concentrations of 285 mg/litre (medium) and higher

(suspension test). The activity in the plate assay was unaffected by the presence of liver homogenates from Aroclor®-induced rats (Kramers et al., 1985a).

Methyl bromide (tested at 0.5-5 g/m^3 in a closed container) was mutagenic to *S. typhimurium* TA 1535 and TA 100 and to *E. coli* WP2 *her*, in the absence of an exogenous metabolic system (Moriya et al., 1983).

An aqueous solution of methyl bromide (tested at 0.5-6 μmol/litre) induced mutations to streptomycin independence in *E. coli* Sd-4 (Djalali-Behzad et al., 1981).

Methyl bromide showed no mutagenic activity in a modified Ames test using the impingement (*in situ*) test system, but, with the SOS *umu*-test, this compound induced a significant SOS response, even with only 30 min impingement (Ong et al., 1987). The SOS function induced by genotoxic agents was detected by a colorimetric measurement of beta-galactosidase activity encoded by the *lacZ* gene, which is regulated by the Umu operon.

Mutations to streptomycin resistance were induced in the fluctuation test with *Klebsiella pneumoniae* at concentrations of 4750 mg methyl bromide/m^3 and higher (tested at 950-19 000 mg/m^3) (Kramers et al., 1985a).

In barley, a few mutations were induced after treatment of kernels with 1.4 mmol methyl bromide/litre for 24 h, in closed vessels (Ehrenberg et al., 1974).

A sex-related recessive lethal assay was carried out on *Drosophila melanogaster* (McGregor, 1981). Male strain Oregon K *Drosophila* were exposed to 78 or 272 mg methyl bromide/m^3 for 5 h and were mated on days 1,3, or 8 following exposure. The F1 progeny from these matings were then mated brother to sister, 1-4 days after emergence from pupae and the F2 generation was examined for the absence of wild-type males. At 78 mg methyl bromide/m^3, the frequencies of lethal mutations in the F2 generations from one of the stocks were elevated, but this was not thought by the authors to be compound-related as these were higher than those at the higher concentration range.

In a sex-linked recessive lethal test on *Drosophila melanogaster*, flies of the Berlin K strain were exposed to methyl bromide at

concentrations of 70-750 mg/m^3 for increasing periods; mutation frequencies were significantly increased at the highest nontoxic concentrations. At a concentration of 600 mg/m^3, all flies died within a short time during the fourth day of exposure (Kramers et al., 1985a). Prolongation of the exposure time permitted lower concentrations to be detected as mutagenic; 487 mg/m^3 for 5×6 h and 200 mg/m^3 for 15×6 h were effective exposures whereas treatment with up to 750 mg/m^3 for 6 h was not sufficient to produce significantly increased mutation frequencies. The mutagenic effect of methyl bromide was most pronounced in postmeiotic germ cell stages (Kramers et al., 1985b).

Treatment of L5178Y mouse lymphoma cells with 0.03-30 mg methyl bromide/litre, in air-tight bottles, resulted in a dose-related increase in 6-thioguanine- and bromodeoxyuridine-resistant mutants (Kramers et al., 1985a).

8.6.3 Chromosomal effects

8.6.3.1 In vitro *studies*

Exposure of human lymphocyte cultures to 4.3% methyl bromide for 100 seconds increased the frequency of sister chromatid exchanges (SCEs) from 10.0 to 16.8 per cell (Tucker et al., 1985, 1986).

Human G_0 lymphocytes were treated with methyl bromide (0-24 μg/ml) for 30 min with, and without, addition of rat liver homogenate. After culture, the prepared slides were studied and dose-related sister chromatid exchanges (SCEs) and chromosome aberrations (CAs) were found. Methyl bromide significantly induced chromosome aberrations in the presence of S-9 (Garry et al., 1990).

Inhalation of methyl bromide gas induced mitotic recombination in somatic cells (somatic wing-spot assay) of *Drosophila melanogaster* (Katz, 1985, 1987). Third instar larvae trans-dihybrid for two recessive wing-hair mutations were exposed via inhalation to methyl bromide (0-20 000 mg/m^3) for 1 h. Wings of surviving adults were scored for the presence of clones of cells possessing malformed wing-hairs. Small and large, single (indicating a variety of genetic alterations) as well as twin spots (from mitotic recombination) were found.

8.6.3.2 In vivo *studies*

The results of *in vivo* mammalian tests for chromosomal aberrations in rat bone marrow were negative (McGregor, 1981).

Micronuclei formation was studied on F-344 rats and BDF_1 mice exposed to 0, 600, 778, 1011, 1314, or 1712 mg methyl bromide/m^3 (0, 154, 200, 260, 338, or 440 ppm) for 6 h/day and 5 days/week for 14 days (Ikawa et al., 1986). In the surviving mice, polychromatic erythrocytes with micronuclei in the bone marrow increased 10-fold in males (778 mg/m^3) and 6-fold in females (600 mg/m^3) and those in peripheral blood increased 32-fold in males (778 mg/m^3) and 3-fold in females (600 mg/m^3). In rats, polychromatic erythrocytes containing micronuclei in the bone marrow increased 10-fold in males and 3-fold in females (both 1314 mg/m^3).

Increases in SCEs and micronuclei were observed in the bone marrow cells of male and female $B6C3F_1$ mice exposed via inhalation to a concentration of 778 mg methyl bromide/m^3 (200 ppm) for 14 days (6 h/day, 5 days/week), the increases were more pronounced in female mice. In contrast, no significant increases in either SCEs or micronuclei were observed in male or female mice exposed via inhalation to a concentration of 467 mg methyl bromide/m^3 (120 ppm) for 13 weeks (NTP, 1992).

8.6.4 *Cell transformation*

Transformation in Syrian hamster embryo cells by SA/adenovirus was not enhanced by exposure to 4000-16 000 mg methyl bromide/m^3 (1000-4000 ppm) for 2 or 20 h, in sealed chambers (Hatch et al., 1983).

8.7 Carcinogenicity and related end-points

8.7.1 *Gavage studies*

Danse et al. (1984) administered methyl bromide, by gavage, to groups (10 male + 10 female) of weanling Wistar rats for 90 days at doses of 0.4, 2, 10, or 50 mg/kg body weight. At the highest dose level of 50 mg/kg, squamous cell carcinomas of the forestomach developed in 13 out of 20 animals. A marked diffuse hyperplasia of the epithelium of the forestomach was seen in all animals in this

group. However, from subsequent examination of the slides from this study it was concluded that the forestomach lesions reported at 50 mg represented inflammation and hyperplasia rather than malignant lesions (Pesticide & Toxic Chemical News, 1984).

Boorman et al. (1986) administered methyl bromide in peanut oil (50 mg/kg body weight), by gavage, to groups of 15 male Wistar rats for 13 weeks (five times a week) with a 12 week recovery period; other groups were exposed for 17, 21, or 25 weeks to methyl bromide; necropsies were performed at 13, 17, 21, and 25 weeks. At week 13, inflammation, acanthosis, fibrosis, and pseudo-epitheliomatous hyperplasia in the forestomach were observed microscopically in dosed animals. At week 25, all rats had hyperplastic lesions of the forestomach that were more severe than those at 13 weeks. Evidence of malignancy, seen in one rat, was considered to be a very early carcinoma. In the stop treatment group that had received methyl bromide for 13 weeks, there was regression of the stomach lesions, but at the 12-week final sacrifice, adhesions, fibrosis, and mild acanthosis remained (Table 43).

Hubbs & Harrington (1986) reported similar results. Gross and microscopic alterations were most pronounced in the non-glandular part of the stomach of the treated rats. Histological change in the squamous epithelial portion of the stomach included ulceration and pseudoepitheliomatous hyperplasia characterized by hyperkeratosis, acanthosis, and epithelial peg formation. Fibrosis, foreign material (hair) and subacute to chronic inflammation were found in the muscularis mucosa, submucosa, and tunica muscularis of some rats. A 30-60 day recovery period was accompanied by marked, but incomplete, regression of lesions. No evidence of malignancy was seen in the stomachs of treated rats (Hubbs & Harrington, 1986).

A two-year, oral, carcinogenicity study was carried out on 60 male and 60 female F-344 rats fed on diets fumigated with methyl bromide (Mitsumori et al., 1990). Diets contained 80, 200, or 500 mg total bromide/kg, respectively, (methyl bromide concentration being < 20 mg/kg), the controls were fed commercial basal diet (containing 30 mg bromide/kg) and a diet containing 500 mg potassium bromide (KBr)/kg. No carcinogenic effects were observed (see also section 8.4.1.2).

8.7.2 Inhalation studies

In lifetime, inhalation, carcinogenicity studies (Table 49), groups of 90 male and 80 female Wistar rats were exposed to methyl bromide concentrations of up to 350 mg/m^3 for 6 h/day, 5 days/week, for up to 130 weeks (Dreef-van der Meulen et al., 1989; Reuzel et al., 1991). Methyl bromide was a mild nasal irritant at all exposure concentrations. There was no increased incidence of neoplasms.

In a 2-year inhalation study (NTP, 1992) on male and female B6C3F$_1$ mice exposed to 39, 128, or 389 mg methyl bromide/m^3 (Table 49), there was no evidence of carcinogenic activity in either male or female mice.

8.8 Special studies

8.8.1 Target organ effects

8.8.1.1 Inhalation studies

Studies on laboratory animals have shown that, following inhalation exposure, the primary target organs are the brain, kidney, nasal cavity, heart, adrenal gland, lung, liver, and testis (Irish et al., 1940; Hurtt et al., 1987; Eustis et al., 1988) and lung (Bond et al., 1985; Kato et al., 1986; Jaskot et al., 1988) (Table 48).

Extensive target organ studies have been carried out by Eustis et al. (1988) on B6C3F1 mice and F-344 rats after inhalation of 622 mg methyl bromide/m^3 for 6 h/day, 5 days/week for 6 weeks. The histopathological changes observed were as follows:

Brain: neuronal necrosis in the internal granular layer of the cerebellar folia (mice); neurosis and loss of neurons in the cerebral cortex, hippocampus, and thalamus (rats).

Kidney: nephrosis, which occurred in all treated mice, was characterized by degeneration, necrosis, and sloughing of the epithelium of convoluted tubules in the renal cortex. In rats, there was dilatation of tubules with atrophy of the epithelium, hyaline and granular casts in the tubules, and increased cytoplasmic basophilia, indicative of epithelial regeneration. There was minimal nephrosis in one female rat.

Testes: degeneration of the testes occurred frequently in exposed mice and mild bilateral atrophy was present in two. Degeneration and atrophy of seminiferous tubules of the testes was noted in several exposed rats.

Nasal cavity: exposed male mice had various levels of degeneration and atrophy of the nasal olfactory epithelium. Minimal degeneration of the olfactory epithelium was seen in only one female mouse. In male and female rats killed after three exposures to methyl bromide, there was moderate to marked degeneration of the olfactory epithelium of the ethmoturbinates and posterior dorsal nasal septum. There was no inflammatory response. In rats, killed or dying after 10 or more exposures, actual degeneration of the olfactory epithelium was minimal or mild, but there was focal or multifocal loss of olfactory sensory cells.

Heart: degeneration of the myocardium primarily occurred in treated males with minimal myocardial degeneration in two female mice. Degeneration of the myocardium occurred more frequently and with greater severity in treated than in control male and female rats. There were increased numbers of mononuclear and fusiform nuclei that may represent interstitial cells, the foci showing a relative increase in fine reticular fibres, and scattered clear vacuoles.

Adrenal gland: exposed female mice showed diminished cellularity of the x-zone of the adrenal cortex and the affected cells contained less cytoplasm and smaller, more hyperchromatic nuclei than normal cells. Minimal to mild cytoplasmic vacuolation occurred in the adrenal cortex of exposed rats.

Liver: individual cell necrosis was noted in the liver of several treated rats and was generally more severe in affected males than females. In three males and one female, an inflammatory reaction occurred. There were no data for mice.

Thymus and spleen: thymic atrophy and lymphoid depletion of the spleen was noted in mice and rats of both sexes.

8.8.2 Neurotoxicity

Irish et al. (1940) examined the effects of a wide range of inhalation exposure conditions in rats, rabbits, guinea-pigs, and monkeys, using visual inspection to assess behavioural deficits. They

observed that nearly 60% (34 out of 58) of the rabbits surviving exposure to 128 mg/m^3 (33 ppm) developed hindlimb paralysis during the 6-month exposure period. This was the lowest concentration at which definite neurobehavioural effects could be detected in the rabbit, the other species being unaffected at this concentration.

Anger et al. (1981) studied the neurobehavioural effects of long- and short-term methyl bromide inhalation exposure on Sprague-Dawley rats and New Zealand White rabbits using more sensitive tests than those available in 1940 when the study of Irish et al., was performed. Exposure to 252 mg/m^3 (65 ppm) for weeks caused significantly reduced eye blink responses and nerve conduction velocity in rabbits, but not in rats. No effect on nerve conduction velocity, open-field activity, or coordination in rats could be seen after extended exposure at 214 mg/m^3 (55 ppm) for 36 weeks. In further studies (Russo et al., 1984), rabbits did not show any neurobehavioural effects after inhalation exposure to 105 mg methyl bromide/m^3 (27 ppm) for 7.5 h per day, 4 days per week over 8 months. A separate group of rabbits exposed to 252 mg/m^3 exhibited severe neuromuscular effects followed by partial recovery, 6-8 weeks after exposure ceased.

Behavioural effects in rats following repeated exposure to methyl bromide at concentrations of 778 or 1167 mg/m^3 (200 or 300 ppm) for 3 weeks were investigated by Ikeda et al. (1980). Relatively prolonged (12 days) motor incoordination (rotarod) was observed.

Conditioned taste aversion induced by inhalation exposure to methyl bromide in rats has been reported (Miyagawa, 1982). Rats kept under a water restriction schedule for 7 days, were permitted access to 0.3% (w/v) sodium saccharin, and were exposed to 0, 97, 195, or 389 mg methyl bromide/m^3 (0, 25, 50, or 100 ppm) for 4 h. Three days after exposure, saccharin preference tests were carried out, revealing dose-dependent saccharin aversion in the exposure group (Miyagawa, 1982).

Male Swiss-Webster mice exposed to methyl bromide concentrations up to 3500 mg/m^3 showed no effects on single-task passive avoidance but had significantly lower rotarod performance (Alexeeff et al., 1985).

Effects of methyl bromide on locomotor activity were observed in five groups of three rats after exposure to 245, 486, 731, or

972 mg/m^3 (63, 125, 188, or 250 ppm) for 8 h. The locomotor activity was measured in an activity cage before, and immediately after, the exposure, shown as an average count per hour in 12-h blocks (day -2 (before exposure) and day 1) or 4-h blocks (day 0). In the 245 mg/m^3 group, the activity was the same as that in the control group. The activity was decreased by 731 mg/m^3 and inhibited strongly by 972 mg methyl bromide/m^3 for up to 6 h after exposure (Honma et al., 1985).

The effects of methyl bromide exposure on the thiopental-induced reduction of righting reflex of rats was investigated. Three groups of eight rats were exposed to 0, 245, or 486 mg/m^3 (63 or 125 ppm) and then were injected i.p. with 60 mg thiopental/kg to induce a loss of righting reflex. The time of loss of righting reflex was measured and group means were calculated. In the control group, two out of eight rats lost the righting reflex, while in the 245 and 486 mg methyl bromide/m^3-exposure groups, the loss of righting reflex was observed in all rats and was considerably more prolonged (Honma et al., 1985).

Kato et al. (1986) described neurological signs in rats, such as paralysis and ataxia, after exposure to 1167 or 1556 mg methyl bromide/m^3, for 4 h/day over 6 weeks (section 8.4).

The acute effects of methyl bromide on electroencephalographic activity and on sleep-wakefulness and circadian rhythms have been investigated in rats (Tanaka et al., 1988). Slowing of the EEG frequency in the wakefulness (W) stage and spike-wave activity appeared at a single subcutaneous dose of 135 mg methyl bromide/kg body weight. These abnormal EEG activities did not occur at lower dose levels. Administration of methyl bromide at doses of 45, 15, or 5 mg/kg produced dose-related changes in amounts of W, non-REM sleep, and REM sleep and in their circadian rhythms. Pretreatment with glutathione effectively lessened the detrimental effects of methyl bromide on sleep-wakefulness and its circadian rhythms and increased the LD_{50} (Tanaka et al., 1988).

The effects were studied on regional brain glutathione-*S*-transferase (GST) activity and the concentrations of glutathione (GSH), monoamines, and amino acids in F-344 rats exposed to methyl bromide (Davenport et al., 1992). Exposure to 584 mg/m^3 was for 6 h/day for five days. While no histological evidence of brain lesions was noted, there was GSH depletion and GST inhibition

in the frontal cortex, caudate nucleus, hippocampus (examined for GSH only), brain stem, and cerebellum. No significant changes were observed in the concentrations of monoamines (only measured in males), but there were increases in the concentrations of aspartic acid and glycine in the frontal cortex and of aspartic acid only in the cerebellum (only measured in males).

Honma et al. (1982) exposed groups of 5-6 SD rats to methyl bromide concentrations of 39-467 mg/m^3 for 24 h or to 4-40 mg/m^3 for 3 weeks. After sacrifice (microwave), the brain was dissected and analysed for monoamines. A reduction in the norepinephrine (NE) contents of the hypothalamus and cortex + hippocampus was found at concentrations of 390 mg/m^3 and above (24-h study) or 39 mg/m^3 (3-week study), whereas levels of dopamine (DA), serotonin (5HT), and acetylcholine (ACh), were only slightly affected by exposure. In more detailed studies, rats were exposed to 120, 240, 486, or 973 mg/m^3 for 8 h (Honma, 1987; Honma et al., 1987). Decreases in DA and NE and increases in the metabolites homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were observed in various regions of the CNS in rats exposed to 319 mg/m^3. The maximal effects were obtained 0 or 2 h after exposure with the largest changes in DA (-24%) and NE (-34%) seen in the striatum. HVA and MHPG levels were increased primarily in the frontal cortex (81%) and striatum (38%). The tyrosine hydroxylase (TH) activity in the striatum, hypothalamus, frontal cortex, midbrain, and medulla oblongata was measured in brain homogenates from rats exposed to 62-973 mg/m^3 (16-250 ppm) for 8 h (Honma et al., 1991). The rats were sacrificed serially (decapitation) between 0 and 16 h after exposure. TH was also measured *in vivo* following administration of decarboxylase inhibitor. Exposure to methyl bromide dose-dependently inhibited both TH activity *in vitro* and *in vivo*. TH activity in the hypothalamus was most sensitive to methyl bromide compared with the other brain areas. The authors suggested that methyl bromide reduces catecholaminergic neuronal activity in the brain via inhibition of TH activity.

The direct effects of methyl bromide on the rat brain have been investigated using a two-probe (right striatum and left ventricle) microdialysis method (Honma, 1992). Methyl bromide (1 μg or 0.5 μg/μlitre) dissolved in 10% ethanol/90% artificial cerebrospinal fluid was perfused through the ventricle probe at a rate of

2.5 μlitre/min and changes in 3,4-dihydroxyphenylacetic acid (DOPAC), HVA, and 5-hydroxyindoleacetic acid, a serotonin metabolite, (5HIAA) content in the striatum perfusate were measured. DOPAC and HVA increased following the initiation of ventricle perfusion but the 5HIAA content of the striatum perfusate was reduced. The increases in DOPAC and HVA persisted after perfusion and the decreased 5HIAA level returned to normal. A concentration of 0.1 μg methyl bromide/μlitre had no effects on DOPAC and HVA levels, though the 5HIAA level was reduced. These findings support the findings of an increase in DOPAC and HVA in the brain homogenate of rats exposed to methyl bromide (Honma, 1987; Honma et al., 1987) indicating that dopamine metabolites in the extracellular, and, probably, intracellular, regions of dopamine nerve terminals were increased by methyl bromide itself. The extracellular level of the 5HIAA in microdialized perfusate was reduced by intraventricularly administered methyl bromide (Honma, 1992).

Systematic neuropathological studies of their central and peripheral nervous systems were carried out on male Wistar rats exposed to methyl bromide (1128 or 1945 mg/m^3) for 6 h/day, 3 days/week for 3-8 weeks (Furuta et al. 1993). Among the rats exposed to 1945 mg methyl bromide/m^3 for 10-18 days, the following neuropathological changes were noted: axonal degeneration of myelinated fibres at the cervical level of the fasciculus gracilis and the necrosis and atrophy of neurons in the caudate-putamen, thalamus, and cingulate cortex. Rats exposed to a concentration of 1128 mg methyl bromide/m^3 for 8 weeks did not show any abnormalities.

8.8.3 Immunotoxicity

No data on the immunotoxicity of methyl bromide are available.

8.9 Factors modifying toxicity; toxicity of metabolites

Cysteine has been shown to reduce the toxicity of methyl bromide, when administered to rats, mice, and rabbits, orally or s.c., 30 min before, or s.c. within 5 min following, acute poisoning (Mizyukova & Bakhishev, 1971). Cysteine treatment prevented the

death, paralysis, paresis, and spasms that developed on the 3rd-4th days after methyl bromide inhalation in other animals.

8.10 Mechanisms of toxicity - mode of action

The mode of action of methyl bromide is still not understood. Proposed mechanisms of toxicity include the direct cytotoxic effect of the intact methyl bromide molecule or toxicity due to one of its metabolites. The bromide ion concentrations are insufficient to explain methyl bromide toxicity, but it may be related to its alkylating ability.

Honma et al. (1985) concluded that the CNS toxicity seems to be due to the methyl bromide molecule itself or the methyl moiety incorporated into the tissue and does not appear to be attributable to inorganic bromide or methyl alcohol (Honma et al., 1985). In humans showing medium or severe toxic symptoms of the CNS, methanol concentrations in the blood ranged between 200 and 3000 mg/litre (Swartz et al., 1981).

The direct cytotoxic effect of methyl bromide on HeLa cells *in vitro* has been shown, whereas bromide appeared not to cause cell damage (Nishimura et al., 1980).

Methyl bromide reacted *in vitro* with a number of SH enzymes and caused progressive and irreversible inhibition (Lewis, 1948). DNA and protein alkylation by methyl bromide have previously been discussed (section 6.3).

The role of glutathione (GSH) in reducing toxicity is also not clear. Studies on the possible role of glutathione are given in section 6.3. One hypothesis for the toxicity of methyl bromide proposes the formation of a reactive species through a methyl bromide-glutathione conjugation process, but it is more probable that glutathione acts as a detoxifying agent.

9. EFFECTS ON HUMANS

Humans can be exposed to methyl bromide via inhalation, by skin contact with the compound, or through residues in food that has been fumigated with the gas to control pests. Exposure is also possible through drinking-water from wells contaminated with leaching water.

In this section, only direct exposure to gaseous or liquid methyl bromide is considered.

Since the first case reported by Schuler in 1899, there have been hundreds of cases of methyl bromide poisoning involving fatalities, systemic poisoning, skin and eye injuries, and damage to the central nervous system (von Oettingen, 1946, 1964; Hine, 1969; Torkelson & Rowe, 1981; Weller, 1982; Alexeeff & Kilgore, 1983).

Table 51 shows acute cases up to 1983 reported throughout the world. Up to 1955, most cases were from chemical manufacture or fire extinguisher incidents. Since this date, cases of poisoning from its use as a fumigant have predominated.

9.1 Clinical findings

It is important to note that the manifestations of methyl bromide poisoning may be delayed. The latent period may vary from 2 to 48 h (Holling & Clarke, 1944).

The acute and long-term effects of methyl bromide can be divided broadly into two categories: neurological and non-neurological.

The principal non-neurological symptoms reported after acute inhalation of methyl bromide are associated with the respiratory system. Chest pain or difficulty in breathing have been reported, which is consistent with pathological findings at autopsy including pulmonary oedema, bronchopneumonia, congestion, and haemorrhage (Holling & Clarke, 1944; Hine, 1969).

In fatal poisoning, the early symptoms and signs are headache, visual disturbances, nausea and vomiting, smarting of the eyes, itching of the skin, listlessness, vertigo, and tremor. Progression is usually rapid, with the development of convulsions, often with a

Table 51. Methyl bromide poisoning incidents up to 1955 and between 1955 and 1983[a]

Resulting from:	Fatalities		Systemic Poisoning		Skin Injuries		Eye Injuries		Other or unspecified injuries	
	up to 1955	1955-1983	up to 1955	1955-1983	up to 1955	1955-1983	up to 1955	1955-1983	up to 1955	1955-1983
Chemical manufacture, filling, storage, transportation, or disposal	16	1	108	45	26	4	0[b]		0[b]	
Use or leaking fire extinguishers	24	11	38	28	10	0	0[b]		0[b]	
Uses as a fumigant	44	16	3	298	0	145	0[b]	57	0[b]	78

[a] Adapted from: Alexeeff & Kilgore (1983). Data up to 1955 were taken from von Oettingen (1955).
[b] No cases known.

Jacksonian-type of progress, fever, tachypnoea associated with signs of severe pulmonary oedema, cyanosis, pallor, and death. Several neuropsychiatric signs and symptoms, such as mental confusion, mania, muscular twitches, and slurring of speech, may precede death (Wyers, 1945; Sax et al., 1984; Gosselin et al., 1984).

The clinical picture in non-fatal poisoning is extremely variable. Fatigue, blurred or double vision, nausea, and vomiting are frequent; incoordination, tremors, convulsions, exaggeration of the patellar reflexes, and a positive Babinski's sign may develop. Nearly every type of nervous disturbance has been reported. The pulmonary symptoms are comparatively slight (Sax et al., 1984). Low-level, short-term exposures to the vapour have produced a syndrome of polyneuropathy without overt central manifestations, characterized by persistent numbness in the hands and legs, impaired superficial sensation, muscle weakness, unsteadiness of gait, and absent or hypoactive distal tendon reflexes (Kantarjian & Shaheen, 1963). Victor & Adams (1980) stated that the signs and symptoms of chronic bromide poisoning intoxication consisted of dizziness, drowsiness, irritability, emotional lability, impairment of thought or memory, and, in severe cases, delirium and mania or stupor or coma.

Locally, methyl bromide is an intense vesicant on human skin. The blisters produced by methyl bromide are enormous, but rarely deep enough to destroy the entire skin layer, even though it may produce severe burns (Watrous, 1942; Butler et al., 1945; Wyers, 1945).

Both central and peripheral neurological deficits may persist; organic brain syndrome has occurred (Greenberg, 1971; Goulon et al., 1975). Profound psychological depression can occur during prolonged convalescence (Hine, 1969). Late sequelae include bronchopneumonia after severe pulmonary lesions, renal failure, and severe weakness with, or without, evidence of paralysis.

Renal failure due to tubular necrosis may be a late sequela, but this is uncommon and usually of mild proportions (Benatt & Courtney, 1948; Prain & Smith, 1952). There have been occasional reports of jaundice, elevations of liver enzyme activity in serum, and abnormal liver function tests suggestive of mild hepatotoxicity after exposure to methyl bromide (Verberk et al., 1979). In a 6-year-old boy, signs of liver involvement in conjunction with encephalopathy

after exposure to methyl bromide vapour were at first mistaken for Reye's syndrome (Shield et al., 1977).

Recovery is frequently prolonged and there may be permanent injury, commonly characterized by sensory disturbances, weakness, disturbances of gait, irritability, and blurred vision.

The effects of methyl bromide on the nervous system, based on case histories, showed that dysfunction affected the peripheral and optic nerves, cerebellar connections, and certain spinal cord tracts (Carter, 1945). Brain stem damage was described in a man who died after 30 days of unconsciousness following methyl bromide exposure (Cavanagh, 1992; Squier et al., 1992). Serum bromide levels, 2 days after admission, were 160 mg/litre (normal 3-4 mg/litre). At post-mortem examination, the brain showed mild generalized swelling, normal ventricles, and well-defined symmetrical lesions, including loss of neurones, in the mammilary bodies and inferior colliculi. The cerebellar dentate nuclei had occasional foci of neuronal loss; other brain stem regions were normal. The spinal cord was normal, but dorsal root ganglia had scattered nodules of neuronal loss. Nerve roots and thoracic peripheral nerve showed sparse chronic inflammatory exudate and patchy axonal and myelin loss. The thyroid gland was densely infiltrated with lymphocytes, plasma cells were rare, and there was no significant fibrosis. The lungs were slightly oedematous and congested. In another case of methyl bromide poisoning, a woman remained in a coma for 4 years and 8 months before death. At post-mortem, there was necrosis of both colliculi, with gliosis in the upper brainstem, reticular formation, and moderate changes in the dentate and pontine nuclei (Goulon et al., 1975).

Various visual disturbances have been reported following acute methyl bromide poisoning. These include blurring of vision, diplopia, lacrimation from eye irritation, accommodative disturbance, and central scotomata for shades of green (Grant, 1974). Ocular findings in a case of chronic methyl bromide poisoning included persistent bilateral decrease in vision, temporal optic nerve head pallor, marked attenuation of visual evoked response amplitude with normal latencies, normal electro-retinogram but abnormal electro-oculogram, and deuteranomalous (green) defect (Chavez et al., 1985).

Electrophysiological studies have been performed on patients as part of a clinical investigation of the neurological effects of methyl bromide poisoning (Goulon et al., 1975; Verberk et al., 1979; Audry et al., 1985; Lopez et al., 1986a, b; Uncini et al., 1990; Mazzini et al., 1992; Hustinx et al., 1993). Abnormal findings included epileptiform patterns in electroencephalograms, enlarged and asymmetric somatosensory evoked potentials, and evidence of axonal neuropathy in peripheral nerves.

9.1.1 Bromide levels in body tissues and fluids

In cases of methyl bromide poisoning, methyl bromide itself has been detected in human tissue on only one occcasion. This may be due to the absence of methyl bromide or, more probably, to its very short half-life in tissues, as well as difficulties in analysis. There is an inconsistency in the data as to whether there is a correlation between bromide levels and the symptoms of methyl bromide poisoning. Some authors have suggested a direct correlation between blood bromide levels and the degree of intoxication (Rathus & Landy, 1961; Hine, 1969): 400 mg/litre (ppm) - severe disability and death in some cases; 250 mg/litre (ppm) - convulsive seizure and sometimes death; 176 mg/litre (ppm) - slight residual ataxia; 135 mg/litre (ppm) - moderate disability; 100 mg/litre (ppm) or less - recovery, but symptoms of poisoning have been reported at bromide levels as low as 28 mg/litre blood and severe symptoms at blood bromide levels of 120 mg/litre (Rathus & Landy, 1961). Brenner (1978) and Bowers & Onoreski (1990) considered that the toxic threshold level for bromide in serum in humans was 500 mg/kg, though effects were observed in patients with lower levels.

However, Weller (1982) disputed a correlation between the bromide levels in serum and the severity of poisoning. In workers in a methyl bromide manufacturing plant, no definite association was found between symptoms and urine bromine concentrations (Kishi et al., 1991). A direct association between serum bromine concentrations and the severity of neurological symptoms was not found in a poisoning incident involving greenhouse workers (Hustinx et al., 1993).

9.1.2 Dermal exposure

Dermal exposure can result from direct contact with liquid methyl bromide, e.g., from accidental splashing, or through contact with contaminated boots, clothing, bandages, or gloves (Alexeeff & Kilgore, 1983). These articles are often made of rubber, which can absorb methyl bromide (Watrous, 1942). Direct eye injury or irritation can also occur. Dermal exposure to gaseous methyl bromide can also cause poisoning.

When liquid methyl bromide is spilled on the skin, it evaporates rapidly producing a cool, but not a cold, or burning sensation (Watrous, 1942). Repeated application of the liquid caused a burning or tingling sensation in the skin, which, in more severe cases, led to a sense of numbness, followed later by aching. In the early stages, the skin appeared red and slightly swollen, with blisters and second-degree burns appearing after 2-12 h in severe cases. In less severe cases, an itching dermatitis may develop after a latent period of about seven days (Watrous, 1942).

Cases of skin burns have been reported during fumigation (Bruhin, 1942) and from methyl bromide fire extinguishers (Butler et al., 1945). Bruhin (1942) reported three cases of dermal exposure during bulk fumigation of a mill. Methyl bromide poisoning occurred due to percutaneous absorption; the men were using breathing apparatus. All three men were exposed to the same conditions, they suffered first or second degree skin burns and one died as a consequence of the exposure.

Skin lesions occurred in 6 patients who were exposed to methyl bromide during the fumigation of a castle (Zwaveling et al., 1987; Hezemans-Boer et al., 1988). They had adequate airway protection, so poisoning was by dermal exposure and not by inhalation. Exposure to high concentrations of methyl bromide (about 40 g/m^3) for 40 min led to redness and blistering of the skin. Standard protective clothing (overalls - 35% cotton/65% polyester), worn over normal clothing, PVC gloves, and working shoes did not prevent this. Redness, oedema, and blistering of the skin were limited to areas where perspiration is relatively high, i.e., armpits, groin, genitals, and the skin under the waistbelt. The authors suggested that methyl bromide absorption might be increased in this partly lipophilic (sebaceous glands), partly hydrophilic (sweat glands) environment,

perhaps leading to increased absorption through the skin as well. The skin in these parts is also thinner, favouring absorption. Plasma bromide levels were highest about 13 h after exposure (mean 9.0± 1.4 mg/litre) and fell in subsequent hours (mean 6.8±2.3 mg/litre; 25 h after exposure), suggesting absorption of methyl bromide through the skin. Since the published half-life of bromide is about 100 h, the falls in plasma levels must be due almost exclusively to the distribution of bromide in tissues. No systemic effects were noted.

9.1.3 *Inhalation*

Inhalation is the primary route of exposure. Poisoning has occurred following acute, short-, and long-term exposures. Acute cases have occurred involving spilling or leaks while handling methyl bromide or where the persons were unaware of its presence (Alexeeff & Kilgore, 1983).

In spite of stronger regulations for the safe and licensed use of methyl bromide, cases of poisoning still occur. Cases have been reported in California (Edmiston & Maddy, 1987; Maddy et al., 1990) and incidents of poisoning have been reported with occupational exposure (Cantineau et al., 1988; Herzstein & Cullen, 1990), in members of the general public (Goldman et al., 1987; Polkowski et al., 1990), and in burglars entering fumigated premises (Marraccini et al., 1983; O'Neal, 1987).

9.2 General population exposure

9.2.1 *Poisoning incidents*

Earlier poisoning incidents involving the general public were mainly from the methyl bromide in fire extinguishers. More poisoning incidents have involved unauthorized entry into fumigated buildings or persons living near fumigated buildings, greenhouses, or fields being fumigated with methyl bromide.

9.2.1.1 *Poisoning associated with fire extinguishers*

Incidents involving fire extinguishers filled with methyl bromide often involved exposure to the gas by inhalation and severe burns

when the liquid was inadvertently squirted on the feet or clothing. Butler et al. (1945) described two cases where drivers suffered burns after extinguishing a fire in an armoured car. Both recovered after 2 and 8 weeks, respectively. Twenty-two cases of methyl bromide poisoning in incidents involving fire extinguishers in ships, including 6 fatalities, were reported between 1939 and 1945 (Holling & Clarke, 1944; Clarke et al., 1945). In another incident, 8 boys, 6 of whom died, were exposed accidentally to methyl bromide from a fire extinguisher (Prain & Harvey Smith, 1952). Longley & Jones (1965) described an accident during methyl bromide filling where there was massive skin contamination. Although the victim removed the contaminated clothing and washed himself thoroughly, symptoms and signs of poisoning, commencing with severe nausea appeared within 2 h, and CNS effects 5 h after the exposure. The CNS effects persisted and 6 months later there was still some disability. There were no dermal effects apart from oedema and itching of the eyelids with subsequent peeling of the skin and no evidence of pulmonary or renal involvement.

Goulon et al. (1975) reported a detailed study of three cases where one patient died after 5 years in a stuporous state with myoclonus. Two of these were females who had slept in bedrooms containing fire extinguishers filled with methyl bromide; one of these patients died, still in coma, 4 years and 8 months later. The other case was a male lorry driver, who was found in a coma after spending a night in his lorry cab, which contained a leaking fire extinguisher; 4 years later he showed only partial recovery with persisting lack of coordination, ataxia, and dysarthria. Behrens & Dukes (1986) described the case of a scrap-dealer who was poisoned by methyl bromide from fire extinguishers in obsolete aircraft engines.

A case of poisoning and the resulting death of a man (and his dog) from methyl bromide leaking from an old corroded fire extinguisher has been reported (Cavanagh, 1992; Squier et al., 1992).

Since methyl bromide is no longer in general use for fire extinguishers, the occurrence of such cases is now extremely rare.

9.2.1.2 Poisoning associated with bulk or house fumigation

In May 1978, severe methyl bromide poisoning occurred in 4 people living above a warehouse in Japan (Ishizu et al., 1988). The warehouse, containing herbs, was accidentally fumigated with a greater quantity of methyl bromide than normal giving an estimated concentration of 38 900-58 350 mg/m^3 (10 000-15 000 ppm). Three days later, one member of the family, a girl aged 12 years, developed severe convulsions and then 2 others had severe convulsions and the fourth had marked mental confusion. The serum or plasma bromide ion levels ranged from 280 to 600 mg/litre. Clinical laboratory tests showed that GOT exceeded the normal level in 3 out of 4 cases. Moreover, the LDH activity was above the normal range in three cases and CPK activity was increased in all the cases (Ishizu et al., 1988).

In California, the most frequent cause of death from non-occupational exposure, in recent years, has been unauthorized entry into structures under fumigation with methyl bromide. Most often the entry was by burglars, transients, or intoxicated persons who broke into buildings that were covered with gas resistant sheeting, locked, and posted with warning signs. During 1982-87 there were 13 such fatalities (Maddy et al., 1990).

In Florida, where homes are fumigated to destroy termites by placing a huge coloured tent over the house, the methyl bromide being released by trained technicians, 27 non-fatal cases and four fatalities following unauthorized entry were reported between 1957 and 1982 (Marraccini et al., 1983). The intervals between exposure and death ranged between 2.5 and 36 h. Three of these deaths together with three additional hospitalizations followed burglaries of tented houses during a nine-month period.

O'Neal (1987) reported that, at one hospital in Florida, 15-25 patients a year, including fatalities, were treated for methyl bromide poisoning. Proper diagnosis and therapy were hampered by the latency period (4-48 h before onset of symptoms) and the fact that the toxic state also mimics other diseases.

Even after apartments have been cleared for habitation, deaths due to methyl bromide poisoning have been reported. The fumigant can be absorbed by furniture, water beds, and walls, and can

sequester in enclosed spaces, with subsequent desorption (Dempsey et al., 1992).

Prockop & Smith (1986) reported a case in which a house fumigator wearing a faulty protective face mask was exposed briefly on one day. This was followed by malaise, although he continued to work, and then again, ten days later, when tremor and increasing malaise resulted in admission to hospital. On the next day, he was comatose with generalized major motor convulsions, and myoclonic limb movements between convulsions. On admission, the serum bromide level was 350 mg/litre (falling to 30 mg/litre 29 days later). Five years later, the patient still exhibited dysarthria, impaired arm coordination, and disturbance of gait.

A fatal case of methyl bromide poisoning was reported after fumigation of a restaurant. Although the methyl bromide levels were checked, for some reason the apparatus showed a reading of "no detectable levels" and, without putting the ventilation system on, the premises were declared safe. A restaurant employee, who then entered the building, was found dead 2.5 h later; the post-mortem inorganic bromide level in serum was 48 mg/litre. Four other workers who were in the building for 45 min had blood bromide concentrations ranging from 40 to 51 mg/litre. Another worker who was in the restaurant for 1 h 15 min, had a blood bromide concentration of 101 mg /litre. These 5 workers had immediate symptoms of malaise and fatigue, but no chronic symptoms (Fuortes, 1992).

A 13-year-old girl accidentally exposed to excessive methyl bromide concentrations after a warehouse fumigation had early symptoms of headache, dizziness, and nausea, followed a few hours later by unconsciousness, from which she recovered three days later. At that time, myoclonic jerks developed, the intensity of which progressed and was unresponsive to treatment over a two-month period. In a two-year follow-up, treatment with clonazepam and phenobarbitol decreased the intensity of myoclonus and she was able to return to school. Electrophysiological findings suggested that the methyl bromide exposure had induced a type of cortical reflex myoclonus (Uncini et al., 1990).

9.2.1.3 Poisoning associated with soil fumigation

Goldman et al. (1987) reported four episodes of community exposure to methyl bromide and chloropicrin soil fumigation in California in 1973, 1980, and two in 1984. A total of over sixty cases were involved, and, in all episodes, either evacuation of homes or cessation of fumigation was the outcome. In one episode, a strawberry field was fumigated preplanting with a methyl bromide/chloropicrin formulation (dosage and % composition not given). Local weather conditions included a temperature of 30 °C with an inversion; 32 adults and 4 children were treated with incident-related symptoms, such as eye irritation, sore throat, headache, shortness of breath, and cough. One child was hallucinating. Fumigant-related symptoms dropped off sharply with distance, 30% within 1 km compared with 4.5% more than 2 km from the field. It should be noted that these symptoms could be attributed to either methyl bromide or chloropicrin.

A nurseryman was poisoned after glasshouses near his house had been fumigated with methyl bromide (Bishop, 1992). The symptoms were delayed. By day 3 after the fumigation, he had convulsions and became comatose. There was a long recovery period and persistence of neurological signs and symptoms.

9.2.1.4 Miscellaneous incidents

Inhalation of methyl bromide from leaking canisters caused acute methyl bromide poisoning. Two grandparents and a child showed various levels of poisoning. The man showed predominantly mental disturbances, with only mild neurological signs and no convulsions; initial euphoria and lack of concern progressed to a florid psychosis. His mental state was normal 6 months later. The woman was severely affected and remained in status epilepticus for 7 days. The boy had an upper respiratory illness 24 h before methyl bromide poisoning, which might have increased his susceptibility to the toxic agent. He developed an acute encephalopathy with fluctuating conscious state, hypotonia, araflexia, and extensor plantar responses. Before methyl bromide was identified as the cause of the illness, Reye's syndrome had been diagnosed (Shield et al., 1977).

A tractor trailer-truck overturned and a cylinder (max. capacity 680 kg) was punctured. Although people were warned of the

risk, ten were admitted to hospital. The symptoms included nausea, vomiting, breathing difficulty, headache, dizziness, burning throat, coughing, and chest tightness. The primary route of exposure was inhalation for seven patients, dermal for two, and both dermal and inhalation for one. All patients recovered without neurological sequelae (Polkowski et al., 1990).

Leakage from a compressed gas cylinder caused unconsciousness and status epilepticus in a man (Mazzini et al., 1992). After awaking, he suffered from severe myoclonic jerks and major epileptic convulsions. Six months later, he still had severe action myoclonus of the limbs. A standardized neuropsychological evaluation revealed severe cognitive impairment.

9.3 Controlled human studies

Raabe (1988) carried out an inhalation study using [^{14}C]-labelled methyl bromide up to 0.1 mg/m^3 to determine the percentage of methyl bromide absorbed by the human body from air containing ambient concentrations of the gas. The uptake was 55.4% nasal and 52.1% oral (section 6.1.1.2 and Fig. 6).

9.4 Occupational exposure

Up to 1955, the majority of methyl bromide poisoning incidents resulted from chemical manufacture and filling operations, followed by fire extinguishers and fumigation (von Oettingen, 1955). Since 1955, fumigation has become the major source of fatalities (Alexeeff & Kilgore, 1983).

9.4.1 Occupational exposure during manufacture

Incidents of methyl bromide poisoning in industry have been described by Watrous (1942) and Wyers (1945). The main incidents were dermatological cases occurring principally among those who filled the small cylinders for distribution from the larger ones. Other sources of danger were defects in the plant, such as ill-fitting joints and bursting of cylinders by an undue rise in temperature. Carelessness with handling was also a cause.

Kishi et al. (1991) carried out a questionnaire survey to determine the symptoms of workers exposed to methyl bromide in the manufacturing process. Seventy five male workers (exposure length: 1-25 years) were compared with a reference group of railway workers. The questionnaire covered acute symptoms during workshift (16 questions), and general symptoms (61 questions). Acute and general symptoms were statistically higher in frequency among the exposed workers (sign test of pairwise comparison). Methyl bromide concentrations in the air in the workers' breathing zone were measured every 6 months, and were normally less than 4 mg/m^3, but, during some accidental events, they exceeded 20 mg/m^3. The mean bromide ion concentration in the urine of men working in the manufacture of methyl bromide was 18.9 mg/litre$\pm$ 10.4 (range 3.2-54.0 mg/litre), with no correlation with the symptoms reported.

Previous studies had shown that urinary bromide concentrations were an index of relatively acute exposure, correlating with the air concentration of the working site. The concentration in the work-place air sometimes accidently exceeded 58 mg/m^3. There were some cases of sub-acute poisoning with lethargy, ataxia, and retrobulbar optic neuritis. In one incident, the mean urine concentration of 20 workers exposed to methyl bromide was 277 mg/litre. On that occasion, 14 of the 21 exposed workers had abnormally accelerated tendon reflexes, 8 had paraesthesia, and 4 showed disturbance of the convergence reflex of the eyes (Kishi et al., 1991).

9.4.2 *Occupational exposure due to methyl bromide fumigation*

In many countries, the use of methyl bromide is restricted to trained and licensed personnel.

Occupational exposure to methyl bromide can occur during the manufacturing, filling, and packaging processes, as well as during its use as a fumigant. As described in section 3.2.2, methyl bromide is used mainly for soil fumigation as well as for the fumigation of buildings and commodities, to prevent pest infestation. The various occupations involved are given in section 5.3.

Methyl bromide was used as a fumigant in the USA by an estimated 105 000 workers between 1972 and 1974 (NIOSH, 1984) and 75 000 workers in 1980 (Anger et al., 1981).

9.4.2.1 Incidents involving bulk fumigation

A poisoning incident in a mill where three fumigators were poisoned through dermal exposure to gaseous methyl bromide has been described in section 9.1.2 (Bruhin, 1942).

Johnstone (1945) and Ingram (1951) reported incidents in data-processing factories where over 200 employees were taken ill, with over 50 cases of frank methyl bromide poisoning, including two workers suspected of insanity. All 34 packers, described by Johnstone (1945), had visual disturbances and there was a high incidence of speech difficulties, mental confusion, hallucinations, and paraesthesia. Four workers claimed permanent and six temporary disabilities. The main factor in these poisonings was that the workers ignored the necessary precautionary measures (Johnstone, 1945). Kantarjian & Shaheen (1963) described 8 cases of polyneuropathy in date factory workers who suffered repeated exposure to the vapour due to faulty working techniques over a period of three months. Within 6 months all had recovered. Only 8 out of 14 employees developed symptoms, suggesting a variation in susceptibility in different individuals.

Seven workers employed in the bulk fumigation of houses were poisoned by methyl bromide (Rathus & Landy (1961). The cause was the insufficient absorption properties of the canisters in their respirators. Three of the men were burned on the area of the face covered by the respirators.

Drawneek et al. (1964) described a case of irreversible brain damage in a methyl bromide fumigator. Seven other workers, without any recognisable illness, were found to have serum bromide levels of over 50 mg/litre, at which level mild euphoria may develop and lead to carelessness in the handling of methyl bromide, and, therefore, to possible acute exposure.

Hine (1969) reported two acute and eight chronic cases of fumigation-related poisoning in California from 1957 to 1966. Four of the patients died. The most common symptoms were malaise, weakness, and dyspnoea. The deaths were preceded by convulsions and coma. All cases could be traced to a failure in preventative procedures.

A few hours after exposure, during the fumigation of cocoa beans, a dock worker developed status epilepticus, coma, and pulmonary oedema (Greenberg, 1971).

Ten cases of methyl bromide poisoning occurred in the hold of a ship whilst a rice cargo was being fumigated in port (Brodniewicz, 1967). The accident was the result of several circumstances: sealing of the crew's quarters was forgotten, some of the crew remained on the ship during, and after, fumigation, and the port fumigating team lacked experience and proper qualifications. One victim died following convulsions, acute pulmonary oedema, and heart failure. In the other cases, the main complaints were dizziness and nausea.

In a fatal case of methyl bromide poisoning of a ship's boy who slept in the crew's quarters, the levels of methyl bromide measured after fumigation had not exceeded 40 mg/m^3, but the boy was poisoned by a high concentration of the gas leaking from the fumigated commodity, because of large temperature differences (Weller, 1982).

An employee habitually not wearing a mask in a fumigating plant spraying fruits and vegetables was initially treated for psychosis, as the early symptoms of methyl bromide poisoning are similar (Zatuchni & Hong, 1981).

Cases of dermal exposure occurring during the fumigation of a castle have been reported (Zwaveling et al., 1987; Hezemans-Boer et al., 1988). Details are given in section 9.1.2.

Systemic and neuro-ophthalmic manifestations of methyl bromide poisoning including increased serum bromide level (66 mg/litre), paraesthesia and burning dysesthesia on hands and feet, and visual impairment, were described in an assistant fumigator who had been exposed acutely, twice, during the year previous to examination (Chavez et al., 1985).

9.4.2.2 *Incidents involving soil fumigation*

(*a*) *Field workers*

Table 52 shows occupational poisoning incidents, reported in California, due to methyl bromide exposure in the years 1950, 1986, and 1987, and analysed according to work activity (Edmiston & Maddy, 1987; Maddy et al., 1990).

Seven deaths through occupational exposure were reported in California between 1951 and 1965. The distribution of cases was: 1952 (1), 1956 (2), 1958 (1), 1959 (2), and 1965 (1) (Maddy et al., 1990).

Methyl bromide poisoning of four field workers occurred during the removal of soil fumigation sheets under cool weather conditions (Herzstein & Cullen, 1990). Ten days after injection of methyl bromide into the soil, the polyethylene sheets covering the soil were removed. The 4 field workers developed fatigue and light-headedness and 3 had progressive respiratory, gastrointestinal, and neurological symptoms. The acute systemic symptoms improved over several days, but neuropsychiatric symptoms that developed later persisted for several weeks. The 2% chloropicrin was not enough to warn the workers of the presence of methyl bromide.

Table 52. Summary of occupational cases of methyl bromide poisoning in California as reported by physicians, listed according to work activity and type of illness/injury [a]

Year	Work activity	Systemic	Eye	Skin	Eye/ skin	Total cases
1950	all occupational exposures	3	0	0	0	3
1986	chamber fumigator	2	0	1	0	3
1987	chamber fumigator	2	0	0	0	2
1986	field fumigator	0	1	5	0	6
1987	field fumigator	1	1	4	0	6
1987[b]	field fumigator	6	2	1	0	9
1986	"tarp" cover fumigator	4	0	1	1	6
1987	"tarp" cover fumigator	1	0	1	0	2
1987[b]	"tarp" cover fumigator	1	0	0	0	1
1986	coincidental exposure	0	1	0	0	1
1987	coincidental exposure	4	0	0	0	4
1987[b]	coincidental exposure	2	0	0	0	2
1987	emergency response	2	1	0	0	3
1987[b]	personnel	1	0	0	1	1

[a] 1950 and 1987 figures taken from Maddy et al. (1990); 1986 figures taken from Edmiston & Maddy (1987)
[b] A methyl bromide/chloropicrin formulation was used.

(*b*) *Greenhouse workers*

Methyl bromide has been used extensively in the USA since the 1950s, and, in Western Europe, since the 1960s, in the fumigation of soils in greenhouses. This can be hazardous to the health of the workers because of the enclosed area in which methyl bromide is applied (Roosels et al., 1981). Poisoning incidents have occurred in operators and other people entering fumigated areas. An analysis of eight severe cases was made by Van den Oever et al. (1978). The signs and symptoms followed the usual pattern. Nearly all incidents were associated with professional fumigation workers using the injection method.

In a case of acute occupational methyl bromide intoxication, a 27-year-old man, using methyl bromide in a greenhouse, suffered continuous epileptic convulsions for 3 weeks, followed by repeated generalized convulsions. Myoclony of the face and the fingers accompanied by a complete motor deficiency persisted; there was also bilateral deafness (Cantineau et al., 1988).

In an accident involving nine greenhouse workers (2 women, 7 men; aged 21-40 years), exposed to an inadvertent spread of methyl bromide during fumigation, two patients needed intensive care for several weeks because of severe reactive myoclonus and tonic-clonic generalized convulsions (Hustinx et al., 1993).

9.4.3 *Studies measuring the levels of bromide ion in biological fluids and tissues*

There have been a number of studies to investigate whether there is a correlation between methyl bromide exposure levels and bromide ion concentrations, but the results are conflicting.

9.4.3.1 *Manufacturing*

Ohmori & Hirata (1982), using radioactivation analysis, reported mean bromine concentrations in serum (66 μg/g) and hair (11 μg/g) from 14 methyl bromide workers, and mean bromine concentrations in serum (40 μg/g) and hair (4 μg/g) in controls. A worker suspected of methyl bromide poisoning had a level of 412 μg/g serum, 13 days after exposure.

Average bromide ion concentrations detected in 36 urine samples of workers exposed to methyl bromide were 13.3±7.7 mg/litre compared with 7.1±2.1 mg/litre in a non-exposed group (Koga et al., 1991). The atmospheric methyl bromide concentrations of exposed workers were monitored with passive samplers during their work shifts (8 h). No significant correlation was found between these methyl bromide readings and the bromide ion concentrations in urine.

9.4.3.2 *Fumigation*

Routine monitoring of bromide levels in the blood of a group of fumigators, undertaking both bulk and soil fumigation, was carried out in England between 1971 and 1979 (Cornwell, 1979). It was found that the plasma bromide levels between January and the end of the year were correlated with the number of gas applications, irrespective of the type of fumigation work undertaken (Fig. 10).

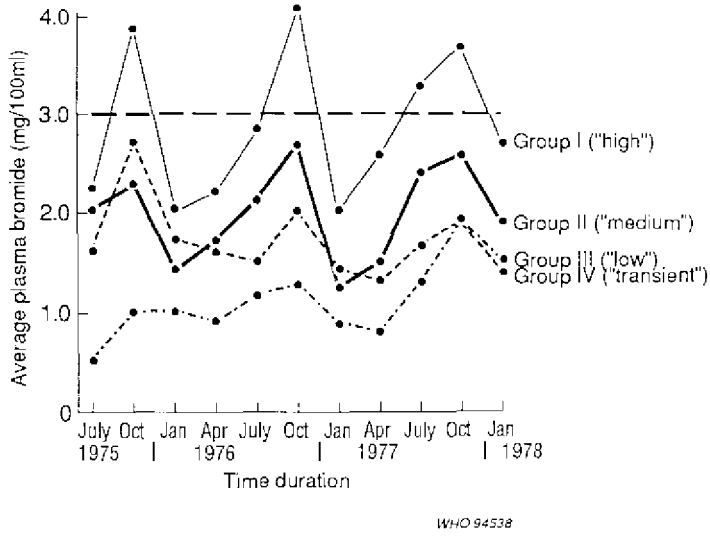


Fig. 10. Changes in the average plasma bromide levels of four groups of fumigators. From: Cornwell (1979).

The plasma bromide level was thought to rise as a result of repeated exposure to low concentrations of methyl bromide with small amounts accumulating in the body faster than the rate of elimination. During the Christmas period, when all the men took a break at the same time, the plasma bromide levels were substantially reduced. Results from October 1974 to January 1978 indicated that average plasma levels increased from 15 mg/litre in January to 25 mg/litre in October. Some fumigators carried out disproportionally more treatments of stacks, containers, and lighters, and reached plasma bromide levels of 30-60 mg/litre. A relationship between plasma bromide levels and the number of fumigation applications was found (Fig. 11).

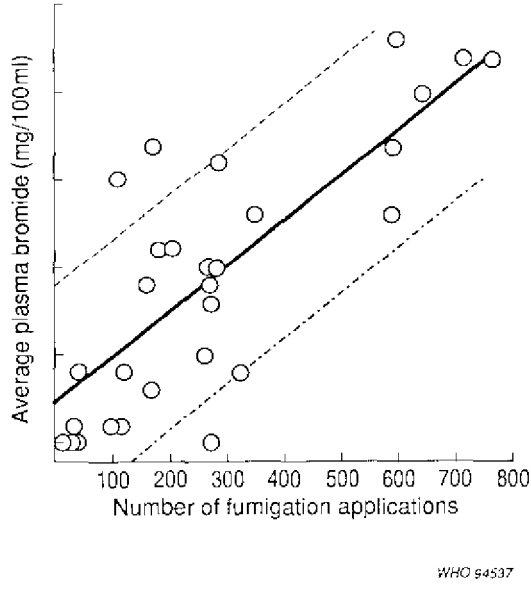


Fig. 11. Relationship (with 95% confidence limits) between the number of gas applications by fumigators and their average plasma bromide level. Modified from Cornwell (1979).

Blood bromide levels, EEGs, and transaminases were measured in 33 methyl bromide workers engaged in soil disinfection inside greenhouses. Blood bromide varied between 4 and 23 mg/litre (Verberk et al., 1979).

In a study of the bromide ion concentration in the plasma of 39 methyl bromide workers, a mean level of 6.9 mg/litre was measured compared with controls (100 workers) who had a mean of 3.7 mg/litre (Yamano et al., 1987).

Tanaka et al. (1991) measured ambient methyl bromide concentrations and urinary bromine concentrations at various plant quarantine fumigation sites in Japan. The geometric mean for exposed workers was 9.0 ± 1.85 mg/litre while the arithmetic mean for a matched control population was 6.3 ± 2.5 mg/litre. The authors found a statistically significant positive correlation between the ambient methyl bromide concentrations collected with a personal sampling device and the urinary concentrations.

9.4.4 *Haemoglobin adducts as a biological index to methyl bromide exposure*

Iwasaki et al. (1989) determined the haemoglobin adduct (haemoglobin MeCys) in methyl bromide manufacturing workers, and examined its effectiveness as a biological index of exposure to methyl bromide. Methyl bromide reacts with cysteine to form *S*-methylcysteine (MeCys) in haemoglobin (Djalali-Behzad et al., 1981). It was suggested that determination of MeCys in haemoglobin could detect previous methyl bromide exposure levels so low that they were not detected by a special medical check-up (Iwasaki et al., 1989). Haemoglobin adducts have a life span of about 2 months, so workers only intermittently exposed to methyl bromide would also be detected in such a survey. Previous studies by the same authors showed individual differences in mice in the levels of MeCys within each dose and time series group (Iwasaki, 1988a,b). These individual differences may be caused by the differential susceptibility of haemoglobin in red blood cells or individual differences in methyl bromide metabolism. These differences were found to be minor in the human study (Iwasaki et al., 1989).

Results from animal studies (Xu et al., 1990) supported the suggestion of Iwasaki et al. (1989) that the Hb adduct of methyl

bromide might be a useful parameter in the biological exposure monitoring of methyl bromide workers.

9.4.5 Neurobehavioural and other studies

Anger et al. (1986) carried out a neurobehavioural study on soil fumigators who were exposed to 9 mg methyl bromide/m^3 over an 8-h day and structural fumigators who were exposed to 0-9 mg/m^3 for 1.5 h per day. The fumigators, who reported a significantly higher prevalence of 18 symptoms, consistent with methyl bromide toxicity, than the controls, did not perform so well on 23 out of 27 behavioural tests, and were significantly lower on one test of finger sensitivity and one of cognitive performance.

EEGs and transaminases were measured in 33 methyl bromide workers engaged in soil disinfection inside greenhouses in the Netherlands. Symptoms of methyl bromide intoxication were determined by means of a specially designed questionnaire. A general neurological examination was performed. No differences compared with controls were found, with the exception of slight electroencephalographic changes in 10 workers involving diffuse increase of beta and theta activity. Workers with abnormal EEGs had higher blood bromide levels (geometric mean 10.9 mg/litre compared with a mean of 8.2 mg/litre in the other workers; the difference was statistically significant ($P < 0.05$) (Verberk et al., 1979).

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Human exposure

Human exposure to methyl bromide occurs predominantly as an occupational hazard, particularly during soil or bulk fumigation, but also during manufacture. Individuals in the vicinity of fumigated fields or buildings may also be exposed. Methyl bromide has widespread use for fumigating post-harvest foods, such as cereals, spices, dried-fruits, and nuts, as well as fresh fruits and vegetables. The determination of levels of methyl bromide and inorganic bromide in the fumigated food is important for the assessment of possible risks for human and animal health. Methyl bromide levels in food commodities usually decrease rapidly after aeration, but may be detected for some weeks after treatment. Fumigation with methyl bromide results in increased levels of inorganic bromide in food commodities and, equally, in produce grown on fumigated soils. Fumigant dosage standards should be adhered to, so that the bromide levels do not exceed the recommended limits.

The major health concern is from acute exposure.

Delayed onset of symptoms may occur. Fatal poisoning has resulted from exposures to relatively high concentrations (from 33 000 mg/m^3 or 8600 ppm onwards) of methyl bromide vapours. Non-fatal poisoning has resulted from exposure to concentrations as low as 390-1950 mg/m^3 (100-500 ppm). Organs affected by exposure include the nervous system, lung, nasal mucosa, kidney, eye, and skin. There are no epidemiological data on reproductive toxicity and carcinogenicity in humans. There are no data on any human health effects of methyl bromide residues in food or drinking-water.

10.1.1 Relevant animal studies

Methyl bromide is very toxic for all animal species by all routes of administration studied. Deaths from exposure follow a steep dose-response curve. LC_{50} (1-h) values for mice and rats are 4680 and 7300 mg/m^3, respectively.

Deaths and neurotoxicity occur within hours or days after a single inhalation exposure at high concentrations. Studies on mice

show that more prolonged exposure at low concentrations (6 h/day; 389 mg/m^3) may also produce neurotoxicity or deaths, appearing with a delayed onset of several months.

Absorption and distribution to various tissues is rapid, as is elimination. The metabolic pathways and mode of action are unknown.

The principal toxic effects associated with lethality occur in the brain and kidney. Histopathology of the brain shows necrosis of granular cells of the cerebellum in mice and rats and neuronal necrosis in the cerebral cortex, hippocampus, and thalamus, in rats. The lowest doses at which these lesions were observed were 250 mg/m^3, 6 h/day, for 2 years, in mice, and, 622 mg/m^3, 6 h/day, for 5 weeks, in rats. In the kidney, necrosis of the convoluted tubule epithelium occurs at doses of 599 mg/m^3, 6 h/day, for 2 weeks, in mice, and 1712 mg/m^3, 6 h/day, for 2 weeks, in rats. Other effects are observed in the heart (degeneration of focal necrosis), nose (necrosis of olfactory epithelium), testis (degeneration of seminiferous tubules), and other organs. In non-lethal exposure, nasal irritation and neurotoxicity (including histopathological lesions) are the major toxic effects.

No teratogenic effects have been observed in rats or rabbits. Embryotoxicity occurred in rats and rabbits only at doses that were also maternally toxic. In a rat multigeneration study, there were reductions in the fertility index in the second generation, when the animals were exposed to 117 or 350 mg/m^3 (30 or 90 ppm) for 6 h/day, but effects were not observed following exposure to 12 mg/m^3 (3 ppm) for 6 h/day.

Methyl bromide was mutagenic in several *in vivo* and *in vitro* assays.

Long-term inhalation studies on rats and mice did not reveal any evidence of carcinogenicity. Lesions originally interpreted as carcinomas of the forestomach in rats, following gavage administration, were shown in a subsequent study to regress after termination of treatment, and were considered not relevant for human risk assessment.

10.2 Environment

Methyl bromide is predominantly a naturally occurring compound. Oceans are believed to be a major natural source of methyl bromide. Another source(s) may exist in the tropics, which is yet to be explained. Anthropogenic sources from fumigation and, to a much lesser extent, motor vehicles (from the combustion of organic bromine additives in leaded petrol) add to these. Present data indicate that the globally averaged atmospheric abundance of methyl bromide is between 9 and 13 pptv, equivalent to a total atmospheric loading of 150-220 thousand tonnes. If the atmospheric lifetime is two years (assuming only atmospheric removal processes are significant), anthropogenic sources of methyl bromide represent about 25% ($\pm$10%) of the total emissions. The world production of methyl bromide in 1990 was 69 000 tonnes, having increased at a rate of 6% per year from 1984 to 1990. About 50% of the methyl bromide produced is released into the atmosphere during, or after, use. Although methyl bromide reacts with the hydroxyl radical in the troposphere, some methyl bromide is transferred by upward diffusion to the stratosphere, where it photolyses. Active bromine species react with ozone in the lower stratosphere and are partly responsible for the depletion of the ozone layer. It is estimated that anthropogenic releases of methyl bromide cause about 3% of the present total stratospheric ozone loss.

Methyl bromide is used for soil fumigation (about 77%), for quarantine, commodity fumigation (12%), for structural fumigation (5%), and for chemical intermediates (6%).

In soil, methyl bromide is degraded by hydrolysis and microbial activity. The remainder (about 50%) eventually dissipates into the atmosphere. The degradation product, principally as inorganic bromide, remains as a residue in soil.

Methyl bromide has herbicidal properties. In the vicinity of greenhouses and fumigated structures, phytotoxic effects may occur. Visible damage to the leaves of lettuce (a sensitive test plant) was noticed at 400 mg/m^3.

Soil fumigation using methyl bromide (with 2% chloropicrin) affects both target and non-target organisms: various soil microflora and fauna are adversely affected, at least temporarily, by fumigation. High mortality of non-target insects has been noticed from fumigation

under plastic sheeting. Methyl bromide could be detected in different soil types up to 3 weeks after the treatments, the highest levels being found in the upper layers (0-40 cm) of the soil.

Methyl bromide is highly toxic for aquatic organisms, though it is generally of no risk to the aquatic environment. The lowest EC_{50} or LC_{50} values reported are 2.8 mg/litre for algae, 1.7 mg/litre for daphnids, and 0.3 mg/litre for fish. NOEC levels, derived from long-term studies, as low as 0.06 mg/litre have been reported for daphnids and fish. Toxic concentrations are not expected to be reached under normal circumstances, because most of the methyl bromide applied on soil is degraded or lost, due to evaporation, before it reaches surface water via run-off. Only in very special situations (leaching of greenhouse soils to reduce inorganic bromide residues), can levels of methyl bromide in the mg/litre range occur in water. Concentrations of up to 9.3 mg methyl bromide/litre were measured in drainage water.

Similarly, relatively high levels of bromide (up to 72 mg/litre) that could adversely affect aquatic organisms were measured in drainage water from greenhouses. Long-term exposure to bromide ion resulted in an EC_{50} value of 27 mg bromide/litre for daphnia and the lowest NOEC for different fish species was 25 mg bromide/litre.

11. RECOMMENDATIONS FOR THE PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT

11.1 Human health protection

In most countries, methyl bromide is strictly regulated for application as a fumigant for soil, commodities, and structural purposes. Adherence to good practices and guidelines should ensure no adverse effects on persons exposed occupationally. Considerable care should be taken by manufacturers in the production process of methyl bromide and by suppliers in its transfer and use.

Methyl bromide does not pose a significant risk for the general population. It is, however, a very toxic substance and precautions have to be taken: exposure of the general public should be avoided through adequate precautions in fumigated buildings, greenhouses, and stores used for commodity fumigation. Fumigated premises should be clearly marked, in order to prevent accidental exposure of individuals.

11.2 Environmental protection

Emission of methyl bromide from anthropogenic sources should be reduced as far as possible. It is, therefore, desirable to reduce emissions from soil, commodity, and structural fumigation. Improvements should be sought in these areas:

(1) improved injection methods;

(2) better barrier films;

(3) better measurement of the efficacy of methyl bromide, with the goal of lower dosage rates where possible.

For commodity and, possibly, for structural fumigation, techniques should be developed to:

(1) seal fumigation chambers more tightly;

(2) capture and recycle fumigation gas.

11.3 Recommendations for further research

There is a need for:

- study of the metabolism and toxic mechanisms of methyl bromide;
- a postnatal behavioural study;
- a human epidemiological study including exposure assessment;
- development of a treatment protocol for cases of human poisoning.

Effects of methyl bromide on the depletion of the ozone layer are not yet entirely understood, indicating a need for:

- studies quantifying the distribution sources of methyl bromide and other organic bromine compounds.

There is also a need for:

- a study of the impact of sea spray on the formation of organic bromine compounds;
- a study on the degradation products of methyl bromide in the troposphere;
- further study of the rate constant for the reaction with OH^-;
- studies on soil fumigation with the aim of reducing emissions while keeping efficacy.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

12.1 FAO/WHO

The toxicology of methyl bromide was evaluated by the FAO/WHO Joint Meeting on Pesticide Residues in 1965 and 1966 (FAO/ WHO, 1965 a,b; WHO, 1967, a,b). In 1965, no acceptable daily intake (ADI) was allocated, but, in 1966, an ADI of 1 mg/kg body weight, as bromide ion, was established. In 1988, the JMPR evaluated the toxicology of the bromide ion (FAO/WHO 1988a,b) and concluded that the level causing no toxicological effect was:

Rat: 240 ppm, equivalent to 12 mg bromide/kg body weight per day

Human: 9 mg bromide/kg body weight per day

The acceptable daily intake (ADI) of 1 mg/kg body weight was confirmed.

12.2 IARC

The carcinogenic risks for humans were evaluated by an International Agency for Research on Cancer ad hoc expert group in 1986. The evaluation was updated in 1987 and it was concluded that there was inadequate evidence for carcinogenicity to humans and limited evidence for carcinogenicity to animals; the overall evaluation of carcinogenicity to humans was "not classifiable" [group 3] (IARC, 1986, 1987).

12.3 UNEP

In 1992, the United Nations Environment Programme evaluated methyl bromide on behalf of the Contracting Parties to the Montreal Protocol (UNEP, 1992). The executive summary of the evaluation reads:

> "The report covers the current understanding of the impact of methyl bromide on the ozone layer and on the uses of, and alternatives to, methyl bromide."

It was requested by the United Nations Environment Programme on behalf of the Parties to the Montreal Protocol. The report includes information presented and discussed at the International Methyl Bromide Science Workshop held in Washington, DC, on 2-3 June 1992, and at the International Workshop on Alternatives and Substitutes to Methyl Bromide held in Washington, DC, on 16-18 June 1992.

The current state of scientific knowledge concerning bromine compounds in the atmosphere is considerably less developed than the corresponding understanding of chlorine compounds. In addition, the evaluation of the alternatives and substitutes to methyl bromide as a fumigant is in an earlier stage than that for chlorofluorocarbons (CFCs), methylchloroform, carbon tetrachloride, and halons.

Methyl bromide is used as a fumigant for soils, commodities, and structures. It is currently vital for the economic viability of certain agricultural production (especially strawberries, tomatoes, peppers, tobacco, eggplants, nursery stock, vines, and turf) and for the quarantine treatment of certain products in international trade. Many developing countries are particularly dependent on the export of products currently fumigated using methyl bromide, before shipment and at ports of entry.

Total annual production and sales of methyl bromide for fumigation have increased from about 42 000 tonnes to about 63 000 tonnes between 1984 and 1990. Combining the approximate methyl bromide use-pattern data with the currently estimated fraction that escapes to the atmosphere from each use (soils: 80% of use, 50 % emitted; commodities: 15 % of use, <80 % emitted; and structural: 5 % of use, 80% emitted) indicates that about half of the methyl bromide used as a fumigant is emitted into the atmosphere. Based on current understanding, this implies an anthropogenic emission from fumigation applications of about 30 thousand tonnes in 1990, which represents 25 ± 10 % of the total (natural and anthropogenic) emissions.

Ozone destruction by bromine is more efficient on a per molecule basis than destruction by chlorine by a factor of 30-60. Therefore, 1 part per trillion by volume (pptv) of bromine is equivalent to 0.03-0.06 parts per billion by volume (ppbv) of stratospheric chlorine.

The current best estimate of the steady-state value of the Ozone Depletion Potential (ODP) for methyl bromide is 0.7. Because of the short atmospheric lifetime of methyl bromide, its relative impact on ozone is expected to be much greater over the next decade (when chlorine abundances and ozone losses are predicted to reach their maximum) than is indicated by its steady-state ODP.

There are significant uncertainties in the atmospheric budget and ODP of methyl bromide, especially the quantification of possible oceanic and terrestrial surface removal processes and the rate of formation of unreactive bromine in the stratosphere.

Model calculations suggest that anthropogenic emissions of methyl bromide used for fumigation applications could have accounted for about one-twentieth to one-tenth of the current observed global ozone loss of 4-6% and could grow to about one-sixth of the predicted ozone loss by the year 2000, if methyl bromide emissions continue to increase at the present rate of about 5-6% per year.

The anthropogenic contribution to the current atmospheric abundance of methyl bromide from fumigation applications is about 3 pptv, which is equivalent to 0.09-0.18 ppbv of stratospheric chlorine. An advance of the CFC and carbon tetrachloride phaseout schedule by three years would reduce the peak chlorine loading by 0.18 ppbv.

Therefore, elimination of methyl bromide used as a fumigant could provide an ozone-layer protection equivalent to that of an advance of the CFC and carbon tetrachloride phaseout schedule by about 1.5-3 years.

There is no single alternative to methyl bromide in the broad spectrum of applications for which it is currently used. There are, however, many alternative chemicals and procedures for specific applications. The introduction of some chemical alternatives may require government approval, which could be a lengthy process.

Rough estimates indicate that a significant fraction (from as low as 30% to as high as 90%), albeit uncertain, of methyl bromide used for soil fumigation could be replaced by chemical substitutes during the 1990s; that a substantial proportion of emissions from fumigation chambers could be captured and recycled or destroyed; that a small fraction (1-2%) of methyl bromide emissions could be eliminated by

better procedures during tank filling; and that significant reductions in emissions could be made using other alternatives or techniques, alone, or in combination. However, there are some applications for which there are limited or no alternatives, including some agricultural situations that have developed a dependence on methyl bromide, quarantine treatments, and some structural fumigation uses.

REFERENCES

Abdalla N & Lear B (1975) Lethal dosages of methyl bromide for four plant-parasitic nematodes and the effect of soil temperature on its nematicidal activity. Plant Dis Rep, **59**: 224-228.

Adu OO & Muthu M (1985) The relative toxicity of seven fumigants to life cycle stages of *Callosobruchus chinensis* (L). Insect Sci Appl, 6: 75-78.

Alexeeff GV & Kilgore WW (1983) Methyl bromide. In: Gunther FA & Gunther JD ed. Residue reviews. Residues of pesticides and other contaminants in the total environment, Vol. 88. Berlin, Heidelberg, New York, Springer-Verlag, pp 102-153.

Alexeeff GV, Kilgore WW, Munoz P, & Watt D (1985) Determination of acute toxic effects in mice following exposure to methyl bromide. J Toxicol Environ Health, **15**: 109-123.

Alfaro Moreno A & Vegh I (1971) [Green pepper diseases produced by *Phytophthora capsici*.] An Inst Nac Invest Agr Ser Prot Veg, **1**: 9-42 (in Spanish).

American Biogenics Corporation (1986) Two-generation reproduction study in albino rats with methyl bromide - results of both generations (Study No. 4500-1525) (Unpublished final report).

Andersen ME, Gargas ML, Jones RA, & Jenkins LJ (1980) Determination of the kinetic constants for metabolism of inhaled toxicants *in vivo* using gas uptake measurements. Toxicol Appl Pharmacol, **54**: 100-116.

Anger WK, Setzer JV, Russo JM, Brightwell WS, Wait RG, & Johnson BL (1981) Neurobehavioral effects of methyl bromide inhalation exposures. Scand J Work Environ Health, 7: 40-47.

Anger WK, Moody L, Burg J, Brightwell WS, Taylor BJ, Russo JM, Dickerson N, Setzer JV, Johnson BL, & Hicks K (1986) Neurobehavioral evaluation of soil and structural fumigators using methyl bromide and sulfuryl fluoride. Neurotoxicology, 7: 137-156.

Angerer J (1977) [A method for determination of bromide in urine with help of a ionsensitive electrode.] J Clin Chem Clin Biochem, **15**: 201-204 (in German).

Angerer J (1980) [Bromide. Determination in urine.] In: Henschler D ed. [Analytical methods for the investigation of work materials detrimental to health. Analysis in biological materials.] Weinheim, Verlag Chemie, vol 2/2, pp D1-D6, 1-9 (in German).

Angerer J (1982) [Methyl bromide. Air analysis]. In: Henschler D ed. [Analytical methods for the investigation of work materials detrimental to health. Air analysis.] Weinheim, Verlag Chemie, vol 1/2, D1-D2, 1-8 (in German).

Anthon EW, Moffit HR, Couey HM, & Smith LO (1975) Control of codling moth in harvested sweet cherries with methyl bromide and effects upon quality and taste of treated fruit. J Econ Entomol, **68**: 524-526.

Arvieu JC (1983) Some physico-chemical aspects of methyl bromide behaviour in soil. Acta Hortic, **152**: 267-275.

Arvieu JC & Cuany A (1985) Effets de la matière organique sur la bioactivité et la dégradation du bromure de méthyle dans le sol. EPPO Bull, **15**: 87-96.

Asante-Poku S, Aston WP, & Schmidt DE Jr (1974) Site of decomposition of methyl bromide in cocoa beans. J Sci Food Agric, **25**: 285-291.

Atochem (1987) Fumyl-o-gas. Fiche de données de sécurité. Paris, Groupe Elf Aquitaine, 4 pp.

Atochem (1988) BM 98 SOBROM. Fiche de données de sécurité. Paris, Groupe Elf Aquitaine, 2 pp.

Audry D, Soichot P, Giard MH, & Mauguiere F (1985) Une cause rare de myoclonies avec PES "Géants": l'intoxication par le bromure de méthyle. A propos d'une observation à prédominance unilaterale. Rev EEG Neurophysiol, **15**: 45-52.

Austin RK & Phillips DJ (1985) Use of a standard-addition bromide-selective electrode technique to determine bromide and trace its migration in peaches. J Agric Food Chem, **33**: 1165-1168.

Bachem C (1927) [Contribution to the toxicology of the alkyl halogens.] Arch Exp Pathol Pharmakol, **122**: 69-76 (in German).

Bakhishev GN (1973) [Relative toxicity of aliphatic halohydrocarbons to rats.] Farmakol Toksikol, **8**: 140-142 (in Russian).

Balander PA & Polyak MG (1962) [Toxicological characteristics of methyl bromide.] Gig i Toksikol, **60**: 412-419 (in Russian).

Basile M & Lamberti F (1981) Bromide residues in edible organs of plants grown in soil treated with methyl bromide. Meded Fac Landbouwwet Rijksuniv Gent, **46**: 337-341.

Basile M, Lamberti F, & Basile AC (1987) [Inorganic bromide concentrations in soil after fumigation with methyl bromide.] Essenze Deriv Agrum, **57**: 116-120 (in Italian).

Baumann H & Heumann KG (1987) Analysis of organobromine compounds and hydrogen bromide in motor car exhaust gases with a GC/microwave plasma system. Fresenius Z Anal Chem, **327**: 186-192.

BBA (Biologische Bundesanstalt für Land- und Forstwirtschaft) (1989) [Plant protective agent register, 1989/90, Part 5.] 37th ed. Braunschweig, Federal Institute for Agriculture and Forestry, 66 pp (in German).

Behrens RH & Dukes DCD (1986) Fatal methyl bromide poisoning. Br J Ind Med, **43**: 561-562.

Bell CH (1988) Minimum concentration levels of methyl bromide required for full efficacy against seven species of stored-product beetle at two temperatures. Pestic Sci, **24**: 97-109.

Benatt AJ & Courtney TRB (1948) Uraemia in methyl bromide poisoning: A case report. Br J Ind Med, **5**: 21-25.

Berg WW, Heidt LE, Pollock W, Sperry PD, Cicerone RJ, & Gladney ES (1984) Brominated organic species in the arctic atmosphere. Geophys Res Lett, **11**: 429-432.

Beyne M & Goett C (1934) Toxicité de certains appareils extincteurs d'incendie et précautions qu'ils comportent dans leur emploi. Arch Méd Pharm Nav, **124**: 409.

Bird GW, Rich JR, & Glover SU (1974) Increased endomycorrhizae of cotton roots in soil treated with nematicides. Phytopathology, **64**: 48-51.

Bishop CM (1992) A case of methyl bromide poisoning. J Occup Med, **42**: 107-109.

Blackburn S & Philips H (1944) Experiments on the methylation and acetylation of wool, silk fibroin, collagen and gelatin. Biochem J, **38**: 171-178.

Blackith RE & Lubatti OF (1965) Fumigation of agricultural products. XX. Prolonged storage of cereals fumigated with methyl bromide. J Sci Food Agric, **16**: 455-457.

Boczek J, Klag J, & Komorowska B (1975) Effect of methyl bromide on the embryonic development of *Acarus siro* (*Acarina, Acaridae*). J Stored Prod Res, **11**: 41-46.

Bolon B, Bonnefoi M, & Morgan KT (1990) Effect of olfactory epithelial regeneration and cage environment on the sensitivity of the rat olfactory epithelium to methyl bromide. Chem Senses, **15**: 554-555.

Bond EJ (1956) The effect of methyl bromide on the respiration of the cadelle *Tenebroides mauritanicus* L. (Coleoptera: Ostomidae). Can J Zool, **34**: 405-415.

Bond EJ (1984) Manual of fumigation for insect control. 6. Chemicals used as fumigants. Rome, Food and Agriculture Organization of the United Nations, pp 71-96 (Plant Production and Protection Paper 54).

Bond EJ & Dumas T (1987) Concentrations of methyl bromide inside flour mills and in the atmosphere around the mills during and after fumigation. Proc Entomol Soc Ont, **118**: 1-6.

Bond JA, Dutcher JS, Medinsky MA, Henderson RF, & Birnbaum LS (1985) Disposition of [^{14}C]methyl bromide in rats after inhalation. Toxicol Appl Pharmacol, **78**: 259-267.

Boorman GA, Hong HL, Jamieson CW, Yoshitomi K, & Maronpot RR (1986) Regression of methyl bromide induced forestomach lesions in the rat. Toxicol Appl Pharmacol, **86**: 131-139.

Bourbos VA & Skoudridakis MT (1991) Effect of methyl bromide and chloropicrin on the soil mycoflora in greenhouse tomato. Plant Pathol Lab, **56**: 569-575.

Bowers GN Jr & Onoreski M (1990) Hyperchloremia and the incidence of bromism in 1990. Clin Chem, **36**: 1399-1403.

Brenner I (1978) Bromism: alive in well. Am J Psychiatry, **7**: 857-858.

Breslin WJ, Zablotny CL, Bradley GF, & Lomax LG (1990) Methyl bromide inhalation teratology study in New Zealand white rabbits. Midland, Michigan, The Dow Chemical Company (Unpublished final report).

Bridges RG (1955) The fate of labelled insecticide residues in food products. III. *N*-methylation as a result of fumigating wheat with methyl bromide. J Sci Food Agric, **6**: 261-268.

Brodniewicz A (1967) Poisoning of seamen with methyl bromide due to fumigation of a Polish cargo ship in Haiphong (Vietnam). Arh Hig Rada, **18**: 241-246 (in Polish with English translation).

Brodzinsky R & Singh HB (1983) Volatile organic chemicals in the atmosphere: an assessment of available data (Contract-No. 68-02-3452). Menlo Park, California, SRI International (EPA/DF-83/005a).

Bromine and Chemicals Ltd (1990) Methylbromide soil fumigation - use and application instructions. London, Bromine and Chemicals Ltd, pp 1-36.

Brown G & Jenkinson DS (1971) Bromine in wheat grown on soil fumigated with methyl bromide. Soil Sci Plant Anal, **2**: 45-54.

Brown D & Rolston DE (1980) Transport and transformation of methyl bromide in soils. Soil Sci, **130**: 68-75.

Brown AL, Burau RG, Meyer RD, Raski DJ, Wilhelm S, & Quick J (1979) Plant uptake of bromide following soil fumigation with methyl bromide. Calif Agric, **33**: 11-13.

Bruhin J (1942) [Percutaneous poisoning with methyl bromide during pest control.] University of Zurich, Medical Faculty, 31 pp (M.D. Thesis) (in German).

BUA (1987) [BUA Chemical Report 14: Methyl bromide.] Weinheim, Advisory Committee for Environmental Priority Pollutants (BUA) of the German Chemists Association, 64 pp (in German).

Burkholder WE (1966) Toxicity of methyl bromide to *Acarus siro*, a cheese-infesting mite. J Econ Ent, **59**: 110-112.

Butler ECB, Perry KMA, & Williams JRF (1945) Methyl bromide burns. Br J Ind Med, **2**: 30-31.

CAC (1986) Guide to Codex Alimentarius recommendations on pesticide residues. Part 3. Guideline levels for pesticide residues. Rome, Food and Agriculture Organization (CAC/PR 3-1986).

Cantineau A, Thomas R, Breurec JY, Bousser J, Baert A, Bonny JS, Bouget J, Dubois C, Venisse T, & Curtes JP (1988) Acute methylbromide poisoning. J Toxicol Clin Exp, **8**: 83-87.

Canton JH, Wester PW, & Matthijssen-Spiekman, EAM (1983) Study on the toxicity of sodium bromide to different freshwater organisms. Food Chem Toxicol, **21**: 369-378.

Carter B (1945) Methyl bromide poisoning. Effects on the nervous system. Br Med J, **1**: 43-45.

Castro CE & Belser NO (1981) Photohydrolysis of methyl bromide and chloropicrin. J Agric Food Chem, **29**: 1005-1008.

Castro JA, Zerba EN, De Licastro SA, Picollo MI, Wood EJ, Ruveda MA, De Moutier Aldao EM, & Libertella R (1976) Toxicity of methyl bromide and other gaseous insecticides to *Triatoma infestans*. Acta Physiol Lat Am, **26**: 106-114.

Cavanagh JB (1992) Methyl bromide intoxication and acute energy deprivation syndromes. Neuropathol Appl Neurobiol, **18**: 573-578.

CDFA (1988) Sampling for pesticide residues in California well water: 1988 update; well inventory data base. Sacramento, California, Department of Food and Agriculture, Division of Pest Management, Environmental Protection and Worker Safety, Environmental Monitoring and Pest Management Branch, 66 pp (Report EH 88-10).

CEC (1985) Report of the Scientific Committee for Pesticides on the use of methyl bromide as a fumigant for plant culture media. Luxembourg, Commission of the European Communities, pp 15-33 (EUR 10211).

Chavez CT, Hepler RS, & Straatsma BR (1985) Methyl bromide optic atrophy. Am J Ophthalmol, **99**: 715-719.

Cheetham T (1990) Pathological alterations in embryos of the codling moth (Lepidoptera: Tortricidae) induced by methyl bromide. Ann. Entomol. Soc. Am., **83**: 59-67.

Chellman GJ, White RD, Norton RM, & Bus JS (1986) Inhibition of the acute toxicity of methyl chloride in male B6C3F1 mice by glutathione depletion. Toxicol Appl Pharmacol, **86**: 93-104.

Chen T, Kilpatrick RA, & Rich AE (1962) Stylet-bearing nematodes associated with white clovers in New Hampshire. Plant Dis Rep, **46**: 346-347.

Chisholm RD & Koblitsky L (1943) Sorption of methyl bromide by soil in a fumigation chamber. J Econ Entomol, **36**: 549-551.

Cicerone RJ, Heidt LE, & Pollock WH (1988) Measurements of atmospheric methyl bromide and bromoform. J Geophys Res, **93**: 3745-3749.

Cirilli L & Borgioli A (1986) Methyl bromide in surface drinking waters. Gas-chromatographic determination by the headspace technique. Water Res, **20**: 273-275.

Clarke CA, Roworth CG, & Holling HE (1945) Methyl bromide poisoning. Br J Ind Med, **2**: 17-23.

Cochran JW (1988) A rapid, sensitive method for the analysis of halogenated gases in water. J High Resol Chromatogr Chromatogr Commun, **11**: 663-665.

Cooper DM, Griffiths NM, Hobson-Frohock A, Land DG, & Rowell JG (1978) Fumigation of poultry food with methyl bromide: effects on egg flavour, number and weight. Br Poult Sci, **19**: 537-542.

Cornwell PB (1979) Health monitoring experience of fumigators using methylbromide. Proceedings of the Fifth British Pest Control Conference, Stratford-on-Avon, England, 26-29 September 1979. London, British Pest Control Association (Sixth Session; Paper No. 17).

Cova D, Molinari GP, & Rossini L (1986) Residues after fumigation with methyl bromide: bromide ion and methyl bromide in middlings and final cereal foodstuffs. Food Addit Contam, **3**: 235-240.

Crampton RF, Elias PS, & Gangolli SD (1971) The bromide content of human tissue. Br J Nutr, **25**: 317-322.

Daelemans A (1978) Uptake of methyl bromide by plantss and uptake of bromide from decontaminated soils. Leuwen, Belgium, Catholic University (Dissertation) (in Flemish).

Daft J (1987) Determining multifumigants in whole grains and legumes, milled and low-fat grain products, spices, citrus fruit, and beverages. J Assoc Off Anal Chem, **70**: 734-739.

Daft JL (1988) Rapid determination of fumigant and industrial chemical residues in food. J Assoc Off Anal Chem, **71**: 748-760.

Daft JL (1989) Determination of fumigants and related chemicals in fatty and nonfatty foods. J Agric Food Chem, **37**: 560-564.

Daft JL (1992) Headspace method for rapid determination of methyl bromide in assorted nut samples. J Assoc Off Anal Chem, **75**: 701-706.

Dagani MJ, Barda HJ, & Sanders DC (1985) Bromine compounds. Weinheim, Verlag Chemie, pp 405-420.

Danse LHJC, Van elsen FL, & Van der Heijden CA (1984) Methylbromide: carcinogenic effects in the rat forestomach. Toxicol Appl Pharmacol, **72**: 262-271.

Darby JF, Dieter CE, & Rau GJ (1962) Evaluation of treatments for control of soil-borne pests in celery seedbeds. Plant Dis Rep, **46**: 441-443.

Davenport CJ, Ali SF, Miller FJ, Lipe GW, Morgan KT, & Bonnefoi MS (1992) Effect of methyl bromide on regional brain glutathione, glutathione-*S*-transferases, monoamines, and amino acids in F344 rats. Toxicol Appl Pharmacol, **112**: 120-127.

Davis LN, Strange JR, Hoecker JE, Howard PH, & Santodonato J (1977) Investigation of selected potential environmental contaminants: monohalomethanes. Washington, DC, US Environmental Protection Agency (EPA-560/2-77-007).

Dawson GW, Jennings AL, Drozdowski D, & Rider E (1975/77) The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J Hazard Mater, **1**: 303-318.

De Heer H, Tuinstra LGMPH, Hamaker PH, & Van der burg AMM (1983) Use of gas-tight plastic films during fumigation of glasshouse soils with methylbromide. I. Significance of permeation and leakage for the emission into the outside air. Acta Hortic, **152**: 109-126.

Dempsey DA, Becker CE & Mihm FC (1992) Death after entering an apartment building fumigated with methyl bromide and cleared for habitation. Vet Hum Toxicol, **34**: 356.

Deutschmann S, Reichel C, & Kettschau F (1989) Metabolism of methyl bromide and methyl iodide in erythrocytes compared with methyl chloride. Naunyn-Schmiedeberg's Arch Pharmacol, **339**: R12.

Deutschmann S, Peter H, Reichel C, Bolt M, & Hallier E (1989) [Kinetics of metabolism of methyl bromide and methyl iodide in erythrocytes of humans and related species.] Verh Dtsch Gesundh Arbeitsmed, **29**: 517-519 (in German).

Devaney JA & Beerwinkle KR (1982) Control of the northern fowl mite on inanimate objects by fumigation: field studies. Poult Sci, **62**: 43-46.

Devries JW, Borge JM, Schroeder JP, Bowers RH, Larson PA, & Burns NM (1985) Headspace gas chromatographic method for determination of methyl bromide in food ingredients. J Assoc Off Anal Chem, **68**: 1112-1116.

Djalali-Behzad G, Hussain S, Ostermann-Golker S, & Segerbaeck D (1981) Estimation of genetic risks of alkylating agents. VI. Exposure of mice and bacteria to methyl bromide. Mutat Res, **84**: 1-9.

Doraiswamy S, Van Winckel A, & Van Assche C (1972) Effect *in vitro* of soil fumigants on soil microbial population in relation to degradation of tobacco mosaic virus. Meded Fac Landbouwwet Rijksuniv Gent, **37**: 492-499.

Drawneek W, O'Brien MJ, Goldsmith HJ, & Bourdillon RE (1964) Industrial methyl bromide poisoning in fumigators. Lancet, **October 17**: 855-856.

Dreef-Van der Meulen HC, Reuzel PGJ, Kuper CF, Hollanders VMH, & Feron VJ (1989) Chronic inhalation toxicity of methyl bromide in rats. Third International Symposium on Soil Disinfestation, Leuwen, Belgium, September 26-30, 1988. Acta Hortic, **255**: 313-315.

Driscoll JN, Duffy M, Pappas S, & Webb M (1987) Analysis for purgeable organics in water by capillary GC/PID-ELCD. J chromatogr sci, **25**: 369-375.

Drosihn UG, Stephan BR, & Hoffmann GM (1968) [Investigations into soil contamination with methyl bromide.] Z Pflanzenkr Pflanzenschutz, **75**: 272-287 (in German).

Dudley HC & Neal PA (1942) Methyl bromide as a fumigant for foods. Food Res, **7**: 412-429.

Dudley HC, Miller JW, Neal PA, & Sayers RR (1940) Studies on foodstuffs fumigated with methyl bromide. Public Health Rep, **55**: 2251-2282.

Duffy M, Driscoll JN, Pappas S, & Sanford W (1988) Analysis of ppb levels of organics in water by means of purge-and-trap, capillary gas chromatography and selective detectors. J Chromatogr, **441**: 73-80.

Dumas T (1982) Trapping low levels of methyl bromide in air or as residues at ambient and lower temperatures for gas chromatography. J Assoc Off Anal Chem, **65**: 913-915.

Dumas T & Bond EJ (1985) Analysis of methyl bromide at ultra low concentration levels. J Agric Food Chem, **33**: 276-278.

Duvoir M, Fabre R, & Layani F (1937). L'intoxication par le bromure de méthyle. Bull Soc Méd Paris, **53**: 1540.

Easley DM, Kleopfer RD, & Carasea AM (1981) Gas chromatographic-mass spectrometric determination of volatile organic compounds in fish. J Assoc Off Anal Chem, **64**: 653-656.

Edmiston S & Maddy KT (1987) Summary of illnesses and injuries reported in California by physicians in 1986 as potentially related to pesticides. Vet Hum Toxicol, **29**: 391-397.

Edwards CA (1962) Springtail damage to bean seedlings. Plant Pathol, **11**: 67-68.

Edwards CA & Thompson AR (1973) Pesticides and the soil fauna. In: Gunther FA & Gunter JD, ed. Residue reviews. Residues of pesticides and other contaminants in the total environment. Berlin, Heidelberg, New York, Springer-Verlag, vol 45, pp 1-79.

Ehrenberg L, Osterman-Golkar S, Singh D, & Lundqvist U (1974) On the reaction kinetics and mutagenic activity of methylating and beta-halogenoethylating gasoline additives. Radiat Bot, **15**: 185-194.

El Buzz HK, Kamel AH, El-Nahal AKM, & El-Borollosy FM (1974) Effect of diet on the susceptibility of the different developmental stages of *Corcyra cephalonica staint.* to carbon bisulphide and methyl bromide. Agric Res Rev, **52**: 21-29.

Eller PM (1985) NIOSH manual of analytical methods, 3rd ed. Cincinnati, Ohio, National Institute for Occupational Safety and Health, pp 2520/1-2520/-4 (NIOSH Publication No. 84-100).

EMBA (1988) Handling and transportation of methyl bromide. Code of practice. Brussels, European Methyl Bromide Association, pp 1-8.

Enebak SA, Palmer MA, & Blanchette RA (1988) Effect of soil-borne pathogen control methods on the production of white pine nursery seedlings. Phytopathology, **78**: 1532-1533.

Ethyl Corporation (1990a) Methyl bromide applications manual. Baton Rouge, Louisiana, Ethyl Corporation, 3 pp.

Eustis SL, Haber SB, Drew RT, & Yang RSH (1988) Toxicology and pathology of methyl bromide in F344 rats and B6C3F1 mice following repeated inhalation exposure. Fundam Appl Toxicol, **11**: 594-610.

Evans JE & Hastings L (1992) The effect of methyl bromide on measures of olfactory function. Toxicologist, **12**: 270.

Fabian P (1984) Atmosphere and environment. Berlin, Heidelberg, New York, Springer-Verlag, p 41.

Fabian P, Borchers R, Penkett SA & Prosser NJD (1981) Halocarbons in the stratosphere. Nature (Lond), **294**: 733-735.

Fairall RJ & Scudamore KA (1980) Determination of residual methyl bromide in fumigated commodities using derivative gas-liquid chromatography. Analyst, **105**: 251-256.

Fallico R & Ferrante M (1991) Exposure to inorganic bromides from greenhouse crops where methyl bromide was applied for soil fumigation. Zent.bl Hyg Umweltmed, **191**: 555-562.

FAO (1980) Pesticide residues in food. Methyl bromide. Rome, Food and Agriculture Organization of the United Nations, pp 89-97 (FAO Plant Production and Protection Paper 20 Sup).

FAO/WHO (1965a) Evaluation of the toxicity of pesticide residues in food. Report of the Second Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Group on Pesticide Residues. Rome, Food and Agriculture Organization of the United Nations; Geneva, World Health Organization (FAO Meeting Report No. PL/1965/10/1; WHO/Food Add./27.65).

FAO/WHO (1965b) Evaluation of hazards to consumers resulting from the use of fumigants in the protection of food. Rome, Food and Agriculture Organization of the United Nations; Geneva, World Health Organization (FAO Meeting Report No. PL/1965/10/2; WHO/Food Add./28.65).

FAO/WHO (1988a) Pesticide residues in food - 1988. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environmental and the WHO Expert Group on Pesticide Residues. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 92).

FAO/WHO (1988b) Pesticide residues in food - 1988 evaluations. Part II - Toxicology. Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 93/2).

Filip GM & Roth LF (1977) Stump injections with soil fumigant to eradicate *Armillariella mellea* from young-growth ponderosa pine killed by root rot. Can J For Res, **7**: 226-231.

Flick EW (1985) Industrial solvents handbook, 3rd ed. Park Ridge, New Jersey, Noyes Data Corporation, 4 pp.

Foxboro (1989) Ambient air instrumentation sheet. East Bridgewater, Maryland, The Foxboro Company.

Fransi A, Pons R, Sala A, Vallejo VR, & Bertran C (1987) Wheat and soil bromide dynamics after fumigation with methyl bromide in a mediterranean climate. Plant Soil, **98**: 417-424.

Fuortes LJ (1992) A case of fatal methyl bromide poisoning. Vet Hum Toxicol, **34**: 240-241.

Furuta A, Hyakudo T, Ohnishi A, Hori H & Tanaka E (1993) Neurotoxicity of methyl bromide - neuropathologic evaluation, preliminary study. Sangyo Ika Daigaku Zasshi, **15**: 21-27.

Gansewendt B, Foest U, Xu D, Hallier E, Bolt HM, & Peter H (1991) Formation of DNA adducts in F-344 rats after oral administration or inhalation of [^{14}C]methyl bromide. Food Chem Toxicol, **29**: 557-563.

Gargas ML & Andersen ME (1982) Metabolism of inhaled brominated hydrocarbons: validation of gas uptake results by determination of a stable metabolite. Toxicol Appl Pharmacol, **66**: 55-68.

Garman JR, Freund T, & Lawless EW (1987) Testing for groundwater contamination at hazardous waste sites. J Chromatogr Sci, **25**: 328-337.

Garry VF, Nelson RL, Griffith J, & Harkins M (1990) Preparation for human study of pesticide applicators: sister chromatid exchanges and chromosome aberrations in cultured human lymphocytes exposed to selected fumigants. Teratog Carcinog Mutagen, **10**: 21-29.

Gentile IA, Ferraris L, Crespi S, & Belligno A (1989) The degradation of methyl bromide in some natural fresh waters. Influence of temperature, pH and light. Pestic Sci, **25**: 261-272.

Gentile IA, Ferraris L, Sanguinetti M, Tiprigan M, & Fisichella G (1992) Methyl bromide in natural fresh waters: hydrolysis and volatilisation. Pestic Sci, **34**: 297-301.

Gillotay D, Simon PC & Dierickx L (1989) Temperature dependence of ultraviolet absorption cross-sections of brominated methanes an ethanes. In: Bojkov RD & Fabian P, ed. Ozone in the atmosphere. Proceedings of the Quadrennial Ozone Symposium 1988 and Tropospheric Ozone Workshop, Göttingen, Germany, 4-13 August 1988. Hampton, Virginia, Deepak Publishing, pp 706-709.

Goldman LR, Mengle D, Epstein DM, Feson D, Kelly K, & Jackson RJ (1987) Acute symptoms in persons residing near a field treated with the soil fumigants methyl bromide and chloropicrin. West J Med, **147**: 95-98.

Gosselin RE, Smith RP, Hodge HC, & Braddock JE (1984) Clinical toxicology of commercial products. Baltimore, Maryland, Williams & Wilkins Company, pp III/280-III/284.

Goulon M, Nouailhat F, Escourolle R, Zarranz-ImirizalduJJ, Grosbuis S, & Levy-Alcover MA (1975) Intoxication par le bromure de méthyle. Trois observations, dont une mortelle. Etude neuro-pathologique d'un cas de stupeur avec myoclonies, suivi pendant cinq ans. Rev. Neurol., **131**: 445-468.

Grant WM (1974) Toxicology of the eye, 2nd ed. Springfield, Virginia, Charles C. Thomas, pp 680-685.

Green M, Seiber JN, & Biermann HW (1991) in situ measurement of methyl bromide in indoor air using long-path ftir spectroscopy. In: Schiff HI, ed. Measurement of atmospheric gases. Proceedings spie - the international society for optical engineering. Los angeles, California, 2-3 January 1991 (Volume 1433). Washington, DC, The International Society for Optical Engineering, pp 270-274.

Greenberg JO (1971) The neurological effects of methyl bromide poisoning. Ind Med, **40**: 27-29.

Greve PA & Grevenstuk WBF (1976) Optimization studies on the determination of bromide residues in lettuce. Meded Fac Landbouwwet Rijksuniv Gent, **41**: 1371-1381.

Greve PA & Grevenstuk WBF (1979) Gas-liquid chromatographic determination of bromide ion in lettuce: interlaboratory studies. J Assoc Off Anal Chem, **62**: 1155-1159.

Greve PA & Hogendoorn EA (1979) Determination of fumigant residues in grain. Meded Fac Landbouwwet Rijksuniv Gent, **44**: 877-884.

Griffiths NM, Hobson-Frohock A, Land DG, Levett JM, Cooper DM, & Rowell JG (1978) Fumigation of poultry food with methyl bromide: effects on flavour and acceptability of broiler meat. Br Poult Sci, **19**: 529-535.

Grimm GR & Alexander AR (1971) Fumigation of phytophthora in sandy soil by surface application of methyl bromide and methyl bromide-chloropicrin. Plant Dis Rep, **55**: 929-931.

Gryder-Boutet DE & Kennish JM (1988) Using headspace sampling with capillary column GC-MS to analyze trace volatile organics in water and wastewater. Am Water Works Assoc J, **80**: 52-55.

Guicherit R & Schulting FL (1985) The occurrence of organic chemicals in the atmosphere of the Netherlands. Sci Total Environ, **43**: 193-219.

Guillemin MP, Hillier RS, & Bernhard CA (1990) Occupational and environmental hygiene assessment of fumigations with methyl bromide. Ann Occup Hyg, **34**: 591-607.

Guns MF (1989) Monitoring of the groundwater bromine content and plant residues in methyl bromide fumigated glasshouses. Third International Symposium on Soil Disinfestation, Leuven, Belgium, September 26-30, 1988. Acta Hortic, **255**: 337-346.

Haber SB, Drew RT, Eustis S, & Yang RSH (1985) Methyl bromide toxicity: a target organ? Toxicologist, **5**: 130 (Abstract No. 518).

Haesanen E, Manninen PKG, Himberg K, & Väätäinen V (1990) Chlorine and bromine contents in tobacco and tobacco smoke. J Radioanal Nucl Chem, **144**: 367-372.

Hague NGM (1963) Fumigation of agricultural products. XVIII. Effect of methyl bromide on the bent grass nematode, *Anguina agrostis, steinbuch 1799, filipjev 1936*, and on the germination of bent grass, *Agrostis tenuis*. J Sci Food Agric, **14**: 577-579.

Hague NGM & Clark WC (1959) Fumigation with methyl bromide and chloropicrin to control seed-borne infestations of the stem eelworm. Meded Landbouwhogesch Opzoekingasstn Gent, **24**: 628-636.

Hallier E, Jaeger R, Deutschmann S, Bolt HM, & Peter H (1990a) Glutathione conjugation and cytochrome p-450 metabolism of methyl chloride *in vitro*. Toxic *in vitro*, **4**: 513-517.

Hallier E, Deutschmann S, Reichel C, Bolt HM, & Peter H (1990b) A comparative investigation of the metabolism of methyl bromide and methyl iodide in human erythrocytes. Int Arch Occup Environ Health, **62**: 221-225.

Hallier E, Langhof T, Dannappel D, Leutbecher M, Schröder K, Goergens HW, Müller A, & Bolt HM (1993) Polymorphism of glutathione conjugation of methyl bromide, ethylene oxide and dichloromethane in human blood: influence on the induction of sister chromatid exchanges (SCE) in lymphocytes. Arch Toxicol, **67**: 173-178.

Hamilton I, Minski MJ, Milton EI, & Cleary JJ, (1972/73) The concentration and distribution of some stable elements in healthy human tissues from the United Kingdom. An environmental study. Sci Total Environ, **1**: 341-374.

Hansch C & Leo A (1979) Substituent constants for correlation in chemistry and biology. New York, Chichester, Brisbane, Toronto, John Wiley & Sons, p 173.

Hanson PR, Wainman HE, & Chakrabarti B (1987) The effects of methyl bromide on the seed of some varieties of barley. Seed Sci Technol, **15**: 155-162.

Hardia BD, Bond GP, Sikov MR, Andrew FD, Belilies RP, & Niemeier RW (1981) Testing of selected workplace chemicals for teratogenic potential. Scand J Work Environ Health, **7**: 66-75.

Harper DB (1985) Halomethane from halide ion - a highly efficient fungal conversion of environmental significance. Nature (Lond), **315**: 55-57.

Harrison BO, Peachey JE, & Winslow RO (1963) The use of nematicides to control the spread of arabis mosaic virus by *Xiphinema diversicaudatum* (Micol.). Ann Appl Biol, **52**: 243-255.

Harry EG, Brown WB, & Goodship G (1972) The disinfecting activity of methyl bromide on various microbes and infected material under controlled conditions. J Appl Bacteriol, **35**: 485-491.

Harsch DE & Rasmussen RA (1977) Identification of methyl bromide in urban air. Anal Lett, **10**: 1041-1047.

Hartill WFT & Campbell JM (1973) Control of sclerotinia in tobacco seedbeds. Plant Dis Rep, **57**: 932-934.

Hastings L (1990) Sensory neurotoxicology: use of the olfactory system in the assessment of toxicity. Neurotoxicol Teratol, **12**: 455-459.

Hastings L, Miller M, Minnema D, & Evans J (1989) Effects of methyl bromide on rat olfactory system. Chem Senses, **14**: 708.

Hatch GG, Mamay PD, Ayer ML, Casto BC, & Nesnow S (1983) Chemical enhancement of viral transformation in Syrian hamster embryo cells by gaseous and volatile chlorinated methanes and ethanes. Cancer Res, **43**: 1945-1950.

Heimann H (1944) Poisoning as result of industrial exposure to methyl bromide. NY State Ind Bull, **23**: 103-105.

Henschler D (1990) Chemicals harmful to health: toxicological-medical establishment of MAK-values, 16th ed. Weinheim, VCH Verlagsgesellschaft mbH.

Heungens A & Roos A (1982) L'influence du dazomet et du bromure de méthyle sur la faune et la flore de la litière de pin. Rev Agric, **35**(2): 2005-2050.

Heurtebise M & Ross WJ (1971) Application of 80m Br to the semi-automated analysis of bromine in biological fluids. J Radioanal Chem, **8**: 5-12.

Heuser SG & Scudamore KA (1968) Fumigant residues in wheat and flour: solvent extraction and gas-chromatographic determination of free methyl bromide and ethylene oxide. Analyst, **93**: 252-258.

Heuser SG & Scudamore KA (1970) Selective determination of ionised bromide and organic bromides in foodstuffs by gas-liquid chromatography with special reference to fumigant residues. Pestic Sci, **1**: 244-249.

Hezemans-Boer M, Toonstra J, Meulenbelt J, Zwaveling JH, Sangster B, & Van Vloten WA (1988) Skin lesions due to exposure to methyl bromide. Arch Dermatol, **124**: 917-921.

Hicken NE (1961) Termite fumigation with methyl bromide. Chem Prod, **24**: 205-207.

Hine CH (1969) Methyl bromide poisoning - a review of ten cases. J Occup Med, **11**: 1-10.

Hitchcock BE (1968) Progress of earth pearl studies in Queensland. Proc Int Soc Sugar-Cane Technol, **13**: 1382-1388.

Ho JSY (1989) A sequential analysis for volatile organics in water by purge-and-trap capillary column gas chromatography with photoionization and electrolytic conductivity detectors in series. J Chromatogr Sci, **27**: 91-98.

Hoffman GM & Malkomes HP (1974) Bromide residues in vegetable crops after soil fumigation with methyl bromide. Agric Environ, **1**: 321-328.

Hole BD (1981) Variation in tolerance of seven species of stored product coleoptera to methyl bromide and phosphine in strains from twenty-nine countries. Bull Entomol Res, **71**: 299-306.

Holling HE & Clarke CA (1944) Methyl bromide intoxication. J R Navy Med Serv, **30**: 218-224.

Hommel G (1984) [Handbook of dangerous goods (Explanatory leaflet 127).] Berlin, Heidelberg, New York, Springer-Verlag (in German).

Honma T (1987) Alteration of catecholamine metabolism in rat brain produced by inhalation exposure to methyl bromide. Jpn J Ind Health, **29**: 218-219.

Honma T (1992) Brain microdialysis study of the effects of hazardous chemicals on the central nervous system. 1. Changes in monoamine metabolites induced by cerebral methyl hromide administration measured by two-probe microdialysis (TPMD) method. Ind Health, **30**: 47-60.

Honma T, Sudo A, Miyagawa M, & Sato M (1982) Significant changes in monoamines in rat brain induced by exposure to methyl bromide. Neurobehav Toxicol Teratol, **4**: 521-524.

Honma T, Sudo A, Miyagawa M, Sato M, & Hasegawa H (1983) Changes in free amino acid contents of rat brain induced by exposure to methyl bromide. Toxicol Lett, **15**: 317-321.

Honma T, Miyagawa M, Sato M, & Hasegawa H (1985) Neurotoxicity and metabolism of methyl bromide in rats. Toxicol Appl Pharmacol, **81**: 183-191.

Honma T, Muneyuki M, & Sato M (1987) Methyl bromide alters catecholamine and metabolite concentrations in rat brain. Neurotoxicol Teratol, **9**: 369-375.

Honma T, Miyagawa M, & Sato M (1991) Inhibition of tyrosine hydroxylase activity by methyl bromide exposure. Neurotoxicol Teratol, **13**: 1-4.

Hubbs AF & Harrington DD (1986) Further evaluation of the potential gastric carcinogenic effects of subchronic methyl bromide administration. In: Proceedings of the 36th Meeting of the American College of Veterinary Pathology and the Annual Meeting of the American Society for Veterinary and Clinical Pathology, Denver, Colorado, December 1985. Denver, Colorado, American Society for Veterinary and Clinical Pathology, p 92.

Hurtt ME & Working PK (1988) Evaluation of spermatogenesis and sperm quality in the rat following acute inhalation exposure to methyl bromide. Fundam Appl Toxicol, **10**: 490-498.

Hurtt ME, Morgan KT, & Working PK (1987) Histopathology of acute toxic responses in selected tissues from rats exposed by inhalation to methyl bromide. Fundam Appl Toxicol, **9**: 352-365.

Hurtt ME, Thomas DA, Working PK, Monticello TM, & Morgan KT (1988) Degeneration and regeneration of the olfactory epithelium following inhalation exposure to methyl bromide: pathology, cell kinetics, and olfactory function. Toxicol Appl Pharmacol, **94**: 311-328.

Hustinx WNM, Van de Laar RTH, Van Huffelen AC, Vrey JC, Meulenbelt J, & Savelkoul TJF (1993) Systemic effects of inhalation methyl bromide poisoning: a study of nine cases occupationally exposed due to inadvertent spread during fumigation. Br J Ind Med, **50**: 155-159.

Hyman MR & Wood PM (1984) Bromocarbon oxidations by *Nitrosomonas europaea*. In: Crawford RL & Hanson RS ed. Microbial growth on C_1 compounds. Washington, DC, American Society for Microbiology, pp 49-52.

IARC (1986) Methyl bromide. In: Some halogenated hydrocarbons and pesticide exposures. Lyon, International Agency for Research on Cancer, pp 187-212 (IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 41).

IARC (1987) Overall evaluations of carcinogenicity: An updating of IARC monographs, volumes 1-42. Lyon, International Agency for Research on Cancer, p 245 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 7).

Ikawa N, Araki A, Nozaki K, & Matsushima T (1986) Micronucleus test of methyl bromide by the inhalation method. Mutat Res, **164**: 269 (Abstract).

Ikeda T, Kishi R, Yamamura K, Miyake H, & Sato M (1980) Behavioural effects in rats following repeated exposure to methyl bromide. Toxicol Lett, **6**: 317-321.

Ingram FR (1951) Methyl bromide fumigation control in the date-packing industry. Arch Ind Hyg Occup Med, **4**: 193-198.

Inouye T, Inouye N, Asatani M, & Mitsuhata K (1967) Cucumber green mottle mosaic virus in Japan. III. Inactivation of cucumber green mottle mosaic virus in infected plant tissue buried in soil treated with methyl bromide. Nogaku Kenkyu, **51**: 199-207.

Irish DD, Adams EM, Spencer HC, & Rowe VK (1940) The response attending exposure of laboratory animals to vapors of methyl bromide. J Ind Hyg Toxicol, **22**: 218-230.

Irish DD, Adams EM, Spencer HC, & Rowe VK (1941) Chemical changes of methyl bromide in the animal body in relation to its physiological effects. J Ind Hyg Toxicol, **23**: 408-411.

Isa AL, Fam EZ, Kamel AH, & Awadallah WH (1970) On the effect of certain fumigants on the overwintering corn borers larvae. Agric Res Rev, **48**: 43-47.

Ishizu S, Kato N, Morinobu S, Nagao N, Yamano Y, & Ito I (1988) [Cases of severe methyl bromide poisoning residing above a warehouse.] Jpn J Ind Health, **30**: 54-60 (in Japanese with English abstract).

Ito KA, Seeger ML, & Lee WH (1972) Destruction of *Byssochlamys fulva* asci by low concentrations of gaseous methyl bromide and by aqueous solutions of chlorine, an iodophor, and peracetic acid. J Appl Bacteriol, **35**: 479-483.

Iwasaki K (1988a) Determination of *S*-methylcysteine in mouse hemoglobin following exposure to methyl bromide. Ind Health, **26**: 187-190.

Iwasaki K (1988b) Individual differences in the formation of hemoglobin adducts following exposure to methyl bromide. Ind Health, **26**: 257-262.

Iwasaki K, Ito I, & Kagawa J (1989) Biological exposure monitoring of methyl bromide workers by determination of hemoglobin adducts. Ind Health, **27**: 181-183.

Japanese Ministry of Labour (1992) Toxicology and carcinogenesis studies of methyl bromide in F344 rats and BDF mice (inhalation studies). Tokyo, Industrial Safety and Health Association, Japanese Bioassay Laboratory, 197 pp (Unpublished report).

Jaskot RH, Grose EC, Most BM, Menache MG, Williams TB, & Roycroft JH (1988) The distribution and toxicological effects of inhaled methyl bromide in the rat. J Am Coll Toxicol, **7**: 631-642.

Jayanty RKM (1989) Evaluation of sampling and analytical methods for monitoring toxic organics in air. Atmos Environ, **3**: 777-782.

JEA (Japanese Environmental Agency) (1981) Chemicals in the environment. Tokyo, Japanese Environmental Agency, Office of Health Studies, Environmental Health Department, pp 92-93.

Johnstone RT (1945) Methyl bromide intoxication of a large group of workers. Ind Med, **14**: 495-497.

Jones L (1968) effect of methyl bromide treatments on several species of conifer seed. J For, **8**: 858-860.

Joshi GP (1974) Toxicity of certain chemicals on *Oryzaephilus mercator* F. (Coleoptra: Cucujidae). Appl Entomol Zool, **9**: 280-281.

Kallio H & Shibamoto T (1988) Direct capillary trapping and gas chromatographic analysis of bromomethane and other highly volatile air pollutants. J Chromatogr, **454**: 392-397.

Kantarjian AD & Shaheen AS (1963) Methyl bromide poisoning with nervous system manifestations resembling polyneuropathy. Neurology, **13**: 1054-1058.

Kato N, Morinobu S, & Ishizu S (1986) Subacute inhalation experiment for methyl bromide in rats. Ind Health, **24**: 87-103.

Katz AJ (1985) Genotoxicity of methyl bromide in somatic cells of *Drosophila* larvae. Environ Mutagen, **7**: 13 (Abstract).

Katz AJ (1987) Inhalation of methyl bromide gas induces mitotic recombination in somatic cells of *Drosophila melanogaster*. Mutat Res, **192**: 131-135.

Kelley WD & Rodriguez-Kabana R (1979) Effects of sodium azide and methyl bromide on soil bacterial populations, enzymic activities and other biological variables. Pestic Sci, **10**: 207-215.

Kempton RJ & Maw GA (1974) Soil fumigation with methyl bromide: the phytotoxicity of inorganic bromide to carnation plants. Ann Appl Biol, **76**: 217-229.

Kenaga EE (1961) Time, temperature and dosage relationships of several insecticidal fumigants. J Econ Entomol, **54**: 537-542.

Khalil MAK & Rasmussen RA (1985) The trend of bromodifluoromethane (CBrClF2) and the concentration of other bromine containing gases at the South Pole. Antarct J US, **21**: 206-207.

Khalil MAK, Rasmussen RA, & Gunawardena R (1993) Atmospheric methyl bromide: Trends and global mass balance. J Geophys Res, **98**: 2887-2896.

Khanna SC & Yadav TD (1987) Effect of methyl bromide fumigation on the germinability of wheat seed. Seed Res, **15**: 183-186.

Kiewnick L (1968) Occurrence and control of *sclerotium rolfsii*. Meded Fac Landbouwwet Rijksuniv Gent, **33**: 987-995.

King JR & Benschoter CA (1991) Comparative methyl bromide residues in Florida citrus: A basis for proposing quarantine treatments against caribbean fruit fly. J Agric Food Chem, **39**: 1307-1309.

King JR, Benschoter CA, & Burditt AK, Jr (1981) Residues of methyl bromide in fumigated grapefruit determined by a rapid, headspace assay. J Agric Food Chem, **29**: 1003-1005.

Kishi R, Ishizu I, Ito I, Katoh N, Miyake H, & Harabuch I (1988) Health research of methyl bromide manufacturing workers. Part 1. Symptoms of long-term exposure. Occupational health in the chemical industry. XXII ICOH (International Commission on Occupational Health) Congress, Sydney, New South Wales, Australia, 27 September-2 October 1987. Copenhagen, World Health Organization Regional Office for Europe, pp 120-134.

Kishi R, Itoh I, Ishizu S, Harabuchi I, & Miyake H (1991) Symptoms among workers with long-term exposure to methyl bromide. An epidemiological study. Jpn J Ind Health, **33**: 241-250.

Kisser W (1967) [The detection and quantitative determination of brominated urea derivatives in toxicology.] Arch Toxicol, **22**: 404-409 (in German).

Kissler JJ, Lider JV, Raahe RD, Raski DJ, Schmitt RV, & Hurlimann JH (1973) Soil fumigation for control of nematodes and oak root fungus in vineyard replants. Plant Dis Rep, **57**: 115-119.

Klein L (1989) Methyl bromide strip fumigation - problems encountered and ways to combat them. Third International Symposium on Soil Disinfestation, Leuven, Belgium, September 26-30, 1988. Acta Hortic, **255**: 213-225.

Knight HD & Costner GC (1977) Bromide intoxication of horses, goats, and cattle. J Am Vet Med Assoc, **171**: 446-448.

Knight HD & Reina-Guerra M (1977) Intoxication of cattle with sodium bromide-contaminated feed. Am J Vet Res, **38**: 407-409.

Koga M, Hara K, Hori H, Kodama Y, & Okubo T (1991) [Determination of bromide ion concentration in urine using a head-space gas chromatography and an ion chromatography. Biological monitoring for methyl bromide exposure.] J Univ Occup Environ Health, **13**: 19-24 (in Japanese with English summary).

Kolbezen MJ & Abu-El-Haj FJ (1972) Fumigation with methyl bromide. II. Equipment and methods for sampling and analysing deep field soil atmospheres. Pestic Sci, **3**: 73-80.

Kramers PGN, Voogd CE, Knaap AGAC, & Van der Heijden CA (1985a) Mutagenicity of methyl bromide in a series of short-term tests. Mutat Res, **155**: 41-47.

Kramers PGN, Bissumbhar B, & Mout HCA (1985b) Studies with gaseous mutagens in *Drosophila melanogaster*. In: Waters MD, Sandhu SS, Lewtas J, Claxton L, Straus G, & Nesnow S, ed. Short-term bioassays in the analysis of complex environmental mixtures IV., New York, London, Plenum Press, pp 65-73.

Krost KJ, Pellizzari ED, Walburn SG, & Hubbard SA (1982) Collection and analysis of hazardous organic emissions. Anal Chem, **54**: 810-817.

Latta R & Cowgill H (1941) Methyl bromide fumigation of greenhouse plants at U.S. Plant Introduction Garden, Glenn Dale, Md. (Abstract S.8189, Bureau of Entomology and Plant Quarantine). Washington, DC, US Department of Agriculture (E-526).

Laug EP (1941) Bromide residues in foodstuffs. Volatile and nonvolatile residues following experimental exposure to methyl bromide. Ind Eng Chem, **33**: 803-805.

Leesch JG, Gillenwater HB, & Woodward JO (1974) Methyl bromide fumigation of shelled peanuts in bulk containers. J Econ Entomol, **67**: 769-771.

Lefevre C, Ferrari P, Günier JP, & Muller J (1989) Sampling and analysis of airborne methylbromide. Chromatographia, **27**: 37-43.

Leichnitz K (1985) [Dräger-tubes methyl bromide 3/a. Detector-tubes pocket book 6.] Lübeck, Dragerwerk (in German).

Lepschy J, Stark H, & Sub A (1979) [Behaviour of methyl bromide (Terabol) in soil.] Gartenbauwissenschaften, **44**: 84-89 (in German).

Lewis SE (1948) Inhibition of SH proteins by methyl bromide. Nature (Lond), **161**: 692-693.

Linenberg A, Davis R, & Robinson D (1991) Hazardous waste site measurements of low levels of chlorinated hydrocarbons using a portable gas chromatography. Hazard Mater Control, **4**: 42-46.

Long PL, Brown WB, & Goodship G (1972) Effect of methyl bromide on coccidial oocysts determined under controlled conditions. Vet Rec, **90**: 562-566.

Longley EO & Jones AT (1965) Methyl bromide poisoning in man. Ind Med Surg, **34**: 499-502.

Lopez VC, Fernandez JAM, Yanez LP, & Vazquez MS (1986a) [Methyl bromide poisoning: I. Some historical, clinical, legal and neuropsychiatric aspects.] Arch Neurobiol, **49**: 279-290 (in Spanish).

Lopez CV, Fernandez MJA, Yanez PL, & Vazquez SM (1986b) [Methyl bromide poisoning. II. Contribution of 2 cases.] Arch Neurobiol, **49**: 311-328 (in Spanish).

Lopez-Avila V, Wood R, Flanagan M, & Scott R (1987) Determination of volatile priority pollutants in water by purge and trap and capillary column gas chromatography/mass spectrometry. J Chromatogr Sci, **25**: 286-291.

Love JL, Winchester RV, & Keating DL (1979) Fumigant and contact insecticide residues on dried fruits, cereals, nuts, and spices imported into New Zealand. N Z J Sci, **22**: 95-98.

Lovelock JE (1975) Natural halocarbons in the air and in the sea. Nature (Lond), **256**: 193-194.

Lynn GE, Shrader SA, Hammer OH, & Lassiter CA (1963) Occurrence of bromides in the milk of cows fed sodium bromide and grain fumigated with methyl bromide. J Agric Food Chem, 11: 87-91.

Mabey W & Mill T (1978) Critical review of organic compounds in water under environmental conditions. J Phys Chem Ref Data, 7: 383-415.

McGregor DB (1981) Tier II mutagenic screening of 13 NIOSH priority compounds, Report No. 32 - Individual compound report: methyl bromide. Cincinnati, Ohio, National Institute of Occupational Safety and Health, 190 pp (PB83-130211).

Mackay D & Shiu WK (1981) A critical review of Henry's Law Constants for chemicals of environmental interest. J Phys Chem Ref Data, **10**: 1175-1199.

Maddy KT, Edmiston S, & Richmond D (1990) Illness, injuries, and deaths from pesticide exposures in California 1949-1988. In: Gunter FA ed. Reviews of environmental contamination and toxicology. Berlin, Heidelberg, New York, Springer-Verlag, vol 14, pp 57-123.

MAFF (1990) Report of the working party on pesticide residues: 1988-89. Supplement to issue No. 8 (1990) of the pesticides register. London, Ministry of Agriculture, Fisheries and Food, Health and Safety Executive, 11 pp.

MAFF (1989) Report of the working party on pesticide residues: 1985-88. The twenty-fifth report of the steering group on food surveillance. London, Ministry of Agriculture, Fisheries and Food, 3 pp (Food Surveillance Paper No. 25).

Malkomes H-P (1970) [Investigations into the degradation of methyl bromide during substrate fumigation and its influence on the following crops.] Hanover, Technical University, pp 18-35 (Dissertation) (in German).

Marraccini JV, Thomas GE, Ongley JP, Pfaffenberger D, Davis JH, & Bednarczyk LR (1983) Death and injury caused by methyl bromide, an insecticide fumigant. J Forensic Sci Soc, **28**: 601-607.

Matheson gas data book (1980) The Matheson gas data book. East Rutherford, New Jersey, Matheson Gas products (A Division of Will Ross), vol 6, pp 361-363.

Matta A & Porta-Puglia A (1968) [Sensitivity to methyl bromide and vapam and secondary growth in fumigated soil of distinct functional groups of microorganisms.] Ann Fac Agrar, **4**: 261-274 (in Italian).

Maw GA & Kempton RJ (1973) Methyl bromide as a soil fumigant. Soils Fertil, **36**: 41-47.

Mazzini L, Galante M, Rezzonico M, & Kokodoko A (1992) Methylbromide intoxication: A case report. Schweiz Arch Neurol Psychiatr, **143**: 75-80.

MBSW (1992) Proceedings of the Methyl Bromide Science Workshop, Washington, DC, 2-3 June 1992. Washington, DC, Atmospheric Environmental Research, Inc., pp 90-97.

Medinsky MA, Bond JA, Dutcher JS, & Birnbaum LS (1984) Disposition of [^{14}C]methyl bromide in Fischer-344 rats after oral or intraperitoneal administration. Toxicology, **32**: 187-196.

Medinsky MA, Dutcher JS, Bond JA, Henderson RF, Mauderly JL, Snipes MB, Mewhinney JA, Cheng YS, & Birnbaum LS (1985) Uptake and excretion of [^{14}C]methyl bromide as influenced by exposure concentration. Toxicol Appl Pharmacol, **78**: 215-225.

Meister RT (1985) In: Meister RT ed. Farm chemicals handbook 85. Pesticide dictionary - Section C. Willoughby, Ohio, Meister Publishing Co., 154 pp.

Mellouki A, Talukdar RK, Schmoltner A-M, Gierczak T, Mills MJ, Solomon S, & Ravishankara AR (1992a) Atmospheric lifetimes and ozone depletition potentials of methyl bromide (CH_3Br) and dibromomethane (CH_2Br_2). Geophys Res Lett, **19**: 2059-2062.

Mellouki A, Talukdar RK, Schmoltner A-M, Gierczak T, Mills MJ, Solomon S, & Ravishankara AR (1992b) Correction to "atmospheric lifetimes and ozone depletion potentials of methylbromide (CH_3Br) and dibromomethane (CH_2Br_2)". Geophys Res Lett, **19**: 2279-2280.

Merzbach L (1928) [The pharmacology of methyl bromide and some related compounds.] Z. Ges. Exp. Med., **63**: 383-392 (in German).

Mignard E & Benet JC (1989) Diffusion of methyl bromide in soil. J Soil Sci, **40**: 151-165.

Miller DP & Haggard HW (1943) Intracellular penetration of bromide as a feature in the toxicity of alkyl bromides. J Ind Hyg Toxicol, **25**: 423-433.

Minton NA & Gillenwater HB (1973) Methyl bromide fumigation of *Pratylenchus brachyurus* in peatnut shells. J Nematol, **5**: 147-149.

Mitsumori K, Maita K, Kosaka T, Miyaoka T, & Shirasu Y (1990) Two-year oral chronic toxicity and carcinogenicity study in rats of diets fumigated with methyl bromide. Food Chem Toxicol, **28**: 109-119.

Miyagawa M (1982) Conditioned taste aversion induced by inhalation exposure to methyl bromide in rats. Toxicol Lett, **10**: 411-416.

Mizyukova IG & Bakhishev CN (1971) [Specific treatment of acute poisoning with methyl bromide.] Vrach Delo, **7**: 128-131 (in Russian with English abstract).

Moelwyn-Hughes EA (1938) The hydrolysis of the methyl halides. Proc R Soc, **A164**: 295-306.

Moje W (1960) The chemistry and nematocidal activity of organic halides. In: Metcalf RL, ed. Volume III. Advances in pest control research. New York, Intersience Publishers, pp 181-217.

Molina LT, Molina MJ, & Rowland FS (1982) Ultraviolet absorption cross sections of several brominated methanes and ethanes of atmospheric interest. J Phys Chem, **86**: 2672-2676.

Monro HAU, Dumas T, & Ruckland CT (1966) The influence of vapour pressure of different fumigants on the mortality of two stored-product insects in vacuum fumigation. J Stored Prod Res, **1**: 207-222.

Moriya M, Ohta T, Watanabe K, Miyazawa T, Kato K, & Shirasu Y (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res, **116**: 185-216.

Morrissey RE, Schwetz BA, Lamb JCIV, Ross MD, Teague JL, & Morris RW (1988) Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. Fundam Appl Toxicol, **11**: 343-358.

Mostafa SAS, Kamel AH, El-Nahal AKM, & El-Borollosy FM (1972) Toxicity of carbon bisulphide and methyl bromide to the eggs of four stored product insects. J Stored Prod Res, **8**: 193-198.

Mounat A & Hitier H (1959) Chemical disinfection of the soil of tobacco seed beds. Ann Inst Exp Tabac Bergerac, **3**: 287-298.

Mueller A, Jorritsma U, Hindermeier U, & Gansewendt B (1991) Human serum albumin adducts as a parameter for biomonitoring of exposure to methyl bromide. Naunyn-Schmiedeberg's Arch Pharmacol, **344**: R121.

Mueller A, Jorritsma U, & Gansewendt B (1992) Different binding of methyl bromide to blood macromolecules due to conjugator status. Naunyn-Schmiedeberg's Arch Pharmacol, **345**: R 42.

Munnecke DE & Van Gundy SD (1979) Movement of fumigants in soil, dosage responses, and differential effects. Annu Rev Phytopathol, **17**: 405-429.

Munnecke DE, Kolbezen MJ, & Stolzy LH (1969) Factors affecting field fumigation of citrus soils for control of *Armillaria mellea*. Proceedings of the First International Citrus Symposium. Lancaster, Pennsylvania, Society of the Plastics Industry, vol 3, pp 1273-1277.

Munnecke DE, Kolbezen MJ, & Wilbur WD (1978) Types and thickness of plastic films in relation to methyl bromide fumigation. Proceedings of the Agricultural Plastic Congress, San Diego, pp 482-487.

National Academy of Science (1978) Chloroform, carbou tetrachloride, and other halomethanes: an environmental assessment. Washington, DC, National Academy of Sciences, 294 pp.

NASA (1992) Chemical kinetics and photochemical data for use in stratospheric modeling. Evaluation No. 10: NASA Panel for Data Evaluation. Pasadena, California Institute of Toxicology, Jet Propulsion Laboratory, National Aeronautics and Space Administration.

NFPA (1984) Fire protection guide on hazardous materials, 9th ed. Quincy, Maryland, National Fire Protection Agency, 5 pp (NFPA No. SPP-1E).

NIOSH (1984) Monohalomethanes: methyl chloride CH_3Cl, methyl bromide CH_3Br, methyl iodide CH_3I. Curr Intell Bull, **42**: 1-22.

Nishimura M, Umeda M, Ishizu S, & Sato M (1980) Effect of methyl bromide on cultured mammalian cells. J Toxicol Sci, **5**: 321-330.

NTP (1992) Toxicology and carcinogenesis studies of methyl bromide (CAS No. 74-83-9) in B6C3F1 mice (inhalation studies). Research Triangle Park, North Carolina, National Toxicology Program, 212 pp (Technical Report Series No. 385).

Oakes JY, Bollich CN, Melville DR, Fielding MJ, & Hollis JP (1956) Soil fumigation for control of parasitic nematodes on corn at Curtis, Louisiana. Plant Dis Rep, **40**: 853-854.

Ohmori S & Hirata M (1982) [Determination of bromine contents in blood and hair of workers exposed to methyl by radioactivation analysis method bromide]. Jpn J Ind Health, **24**: 119-125 (in Japanese).

O'Neal L (1987) Acute methyl bromide toxicity. J. Emerg Nurs, **13**: 96-98.

Ong JM, Stewart J, Wen Y, & Whong W (1987) Application of SOS umu-test for the detection of genotoxic volatile chemicals and air pollutants. Environ Mutagen, **9**: 171-176.

Osborne BG, Barrett GM, Laal-Khoshab A, & Willis KH (1989) The occurrence of pesticide residues in UK home-grown and imported wheat. Pestic Sci, **27**: 103-109.

Ostrec L & Korunic Z (1989) [Some new knowledge on the applying of methylbromide in the tobacco nurseries.] Zast Bilja, **40**: 375-385 (in Yugoslavian with English abstract).

Page BD & Avon RJ (1989) Determination of methyl bromide in foods by headspace capillary gas chromatography with electron capture detection. J Assoc Off Anal Chem, **72**: 815-822.

Pauwels F (1989) Soil disinfestation in the Belgian horticulture: a practice view. Third International Symposium on Soil Disinfestation, Leuven, Belgium, September 26-30, 1988. Acta Hortic, **255**: 31-36.

Peers AMK (1985) The determination of methyl bromide in air. In: Fishbein L & O'Neill IK ed. Environmental carcinogens selected methods of analysis. Volume 7 - Some volatile halogenated hydrocarbons. Lyon, International Agency for Research on Cancer, pp 227-233 (IARC Scientific Publications No. 68).

Pellizzari ED, Zweidinger RA, & Erickson MD (1978) Environmental monitoring near industrial sites: brominated chemicals part II: appendix. Washington, DC, US Environmental Protection Agency (EPA-560/6-78-002A; US NTIS PB-286483).

Pence RJ & Morganroth J (1962) Field effects of methyl bromide on carpet beetle eggs. Pest Control, **30**: 20, 22, 24.

Penkett SA, Jones BMR, Rycroft MJ, & Simmons DA (1985) An interhemispheric comparison of the concentrations of bromine compounds in the atmosphere. Nature (Lond), **318**: 550-553.

Perrotta G (1968) [Combating 'Tracheomycosis' (tomato wilt disease) in greenhouse tomatoes.] Not Mal Piante, **78-79**: 135-140 (in Italian).

Pesticide & Toxic Chemical News (1984) No evidence of methyl bromide carcinogenicity found by NTP-panel. Pestic Toxic Chem News, **13**: 9-10.

Peters PWJ, Verhoef A, De Liefde A, Van Velsen FL, Van Soolingen J, De Geus D, Danse LHJ, & Van Logten MJ (1982) [Teratogenicity study of methyl bromide by oral administration.] Bilthoven, National Institute for Public Health and Environmental Protection (RIVM Report No. 618102 002) (in Dutch).

Piet GJ, Luijten WCMM, & Van Noort PCM (1985) 'Dynamic' head-space determination of volatile organic halogen compounds in water. In: Fishbein L & O'Neill IK, ed. Environmental carcinogens selected methods of analysis. Volume 7 - Some volatile halogenated hydrocarbons. Lyon, International Agency for Research on Cancer, pp 331-343 (IARC Scientific Publications No. 68).

Polkowski J, Crowley MS, & Moore AM (1990) Unintentional methyl bromide gas release-Florida, 1988. Morbid Mortal Wkly Rep, **38**: 880-882.

Poulet G, Pirre M, Maguin F, Ramaroson R, & Le Bras G (1992) "Role of the BrO + HO_2 reaction in the stratospheric chemistry of bromine". Geophys Res Lett, **19**: 2305-2308.

Powell DF (1975) The effect of methyl bromide fumigation on the germination of onion seed and vigor of the seedlings. Plant Pathol, **24**: 237-241.

Prain JH & Harvey Smith G (1952) A clinical-pathological report of eight cases of methyl bromide poisoning. Br J Ind Med, **9**: 44-49.

Prather MJ & Watson RT (1990) Stratospheric ozone depletion and future levels of atmospheric chlorine and bromine. Nature (Lond), **344**: 729-734.

Prather MJ, McElroy MB, & Wofsy SC (1984) Reductions in ozone at high concentrations of stratosperic halogens. Nature (Lond), **312**: 227-231.

Prishchep AG & Nikiforova EN (1969) [Bactericidal action of methyl bromide on *Escherichia coli* group bacteria.] Sci Trans Inst Vet Sanit, **32**: 279-281 (in Russian).

Prockop LD & Smith AO (1986) Seizures and action myoclonus after occupational exposure to methyl bromide. J Fla Med Assoc, **73**: 690-692.

Raabe OG (1986) Inhalation uptake of selected chemical vapors at trace levels. Final report to the California Air Resources Board Control (No. A3-132-33). Springfield, Virginia, National Technical Information Service, 290 pp (NTIS PB 86-209863).

Raabe OG (1988) Inhalation uptake of xenobiotic vapors by people (Final report August 1986-March 1988). Davis, University of California, Laboratory for Energy-related Health Research, 94 pp (ISS ARB-R-88/338; PB 88-202726).

Rasche E, Hyman MR, & Arp DJ (1990) Biodegradation of halogenated hydrocarbon fumigants by nitrifying bacteria. Appl Environ Microbiol, **56**: 2568-2571.

Raski DJ, Jones NO, Kissler JJ, & Luvisi DA (1975) Further results from deep-placement fumigation for control of nematodes in vineyards. Plant Dis Rep, **59**: 345-349.

Rasmussen RA & Khalil MAK (1984) Gaseous bromine in the arctic and arctic haze. Geophys Res Lett, **11**: 433-436.

Rathus EM & Landy PJ (1961) Methyl bromide poisoning. Br J Ind Med, **18**: 53-57.

Reeves RG, McDaniel CA, & Ford JH (1985) Organic and inorganic bromide residues in spices fumigated with methyl bromide. J Agric Food Chem, **33**: 780-783.

Reichmuth C & Noack S (1983) [Environmental effects of the fumigation of commodities.] Technol Z Getreide Mehl Backwaren, **37**: 139-144 (in German).

Reuzel PGJ, Dreef-Van der Meulen HC, Hollanders VMH, Kuper CF, Feron VJ & Van der Heijden CA (1991) Chronic inhalation toxicity and carcinogenicity study of methyl bromide in Wistar rats. Food Chem Toxicol, **29**: 31-39.

Richardson HH & Monro HAU (1962) Fumigation of jute bags with ethylene oxide and methyl bromide to eradicate potato ring rot bacteria. Appl Microbiol, **10**: 448-451.

Richardson HH & Roth H (1965) Methyl bromide, sulfuryl fluoride, and other fumigants against quarantinable *Cochlicella* and *Theba* snails. J Econ Entomol, **58**: 690-693.

Robbins DE (1976a) Photodissociation of methyl chloride and methyl bromide in the atmosphere. Geophys Res Lett, **3**: 213-216.

Robbins DE (1976b) UV absorption cross sections for methyl bromide and methyl chloride. Geophys Res Lett, **3**: 757-758.

Rogozen MB, Rich HE, Guttman MA, & Grosjean D (1987) Evaluation of potential toxic air contaminants. Phase 1. Final report (ISS SAIC-76/1035, ARB-R-88/3339. Manhattan Beach, California, Science Applications International Corporation, 582 pp (PB 88-183330/GAR)

Rolston DE & Glauz RD (1982) Comparisons of simulated with measured transport and transformation of methyl bromide gas in soils. Pestic Sci, **13**: 653-664.

Roosels D, Van den Oever R, & Lahaye D (1981) Dangerous concentrations of methyl bromide used as a fumigant in Belgian greenhouses. Int Arch Occup Environ Health, **48**: 243-250.

Rosenblum I, Stein AA, & Eisinger G (1960) Chronic ingestion by dogs of methyl bromide-fumigated food. Arch Environ Health, **1**: 316-323.

Roskill (1992) Report on the economics of bromine, 6th ed. London, Roskill Information Service, p 58.

Roth H (1973) Fumigants for quarantine control of the adult brown dog tick: laboratory studies. J Econ Entomol, **66**: 1283-1286.

Roth H & Kennedy JW (1972) Methyl bromide and aluminium phosphide as fumigants for control of adult boll weevils: laboratory studies. J Econ Entomol, **65**: 1650-1651.

Roth H & Kennedy JW (1973) *Helicella* snails infesting rosemary seeds. Methyl bromide and other fumigants for quarantine control. J Econ Entomol, **66**: 935-936.

Roth H & Richardson HH (1974) Broadbeen weevil: methyl bromide fumigation of infested faba beans. J Econ Entomol, **67**: 799-803.

Rotteveel AJW & Naber H (1987) The use of soil fumigation against yellow nutsedge. Meded Fac Landbouwwet Rijksuniv Gent, **52**: 1207-1212.

Roughan JA & Roughan PA (1984a) Pesticide residues in foodstuffs in England and Wales: Part I. Inorganic bromide ion in lettuce grown in soil fumigated with bromomethane. Pestic Sci, **15**: 431-438.

Roughan JA & Roughan PA (1984b) Pesticide residues in foodstuffs in England and Wales. Part II: Inorganic bromide ion in cucumber, tomato and self-blanching celery grown in soil fumigated with bromomethane, and the "natural" bromide ion content in a range of fresh fruit and vegetables. Pestic Sci, **15**: 630-636.

Roughan JA, Roughan PA, & Wilkins JPG (1983) Modified gas-liquid chromatographic method for determining bromide/total bromine in foodstuffs and soils. Analyst, **108**: 742-747.

Rovira AD & Ridge EH (1979) The effect of methyl bromide and chloropicrin on some chemical and biological properties of soil and on the growth and nutrition of wheat. Dev Agr Managed For Ecol, **6**: 231-250.

Roycroft JH, Jascot RH, Grose EC, & Gardner DE (1981) The effects of inhalation exposure of methyl bromide in rats. Toxicologist, **1**: 79.

Russo JM, Anger WK, Setzer JV, & Brightwell WS (1984) Neurobehavioural assessment of chronic low-level methyl-bromide exposure in the rabbit. J. Toxicol Environ Health, **14**: 247-255.

Ruth JH (1986) Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J, **47**: A/142-A/151.

Saiki E (1952) Studies on the disinfecting effect of chloropicrin, methyl bromide, prussic acid and formalin on bacteria. Nagoya J Med Sci, **15**: 270.

Saltzman BE (1983) Direct reading colorimetric indicators. In: Lioy PJ & Lioy MJY ed. Air sampling instruments for evaluation of atmospheric contaminations, 6th ed. Cincinnati, Ohio, American Conference of Governmental Industrial Hygienists, 29 pp.

Sangster J (1989) Octanol-water partition coefficients of simple organic compounds. J Phys Chem Ref Data, **18**: 1185.

Sardesai JB (1972) Response of diapausing and nondiapausing larvae of *Plodia interpunctella* to hydrogen cyanide and methyl bromide. J Econ Entomol, **65**: 1562-1565.

Sassaman JF, Jacobs MM, Chin PH, Hsia S, Pienta RJ, & Kelly JM (1986) Pesticide background statements: methyl bromide and chloropicin. In: Volume II. Fungicides and fumigants. Washington, DC, US Department of Agriculture, Forest Service (MB/C-1-156) (Agriculture Handbook No. 661).

Sato M, Miyagawa M, Honma T, & Hasegawa H (1985) Subacute effects of methyl bromide dosed by inhalation exposure to rats. Ind Health, **23**: 235-238.

Sax NI, Feiner B, Fitzgerald J, Haley TJ & Weisburger EK (1984) Dangerous properties of industrial materials, 6th ed. New York, Van Nostrand Reinhold Company, p 531.

Sayers RR, Yant WP, Thomas BGH, & Berger LB (1929) Physiological response attending exposure to vapors of methyl bromide, methyl chloride, ethyl bromide and ethyl chloride. Public Health Bull, **185**: 1-56.

Schauffler SM, Heidt LE, Pollock WH, Gilpin TM, Vedder J, Solomon S, Lueb RA, & Atlas EL (in press) Measurements of halogenated organic compounds near the tropical tropopause. Geophys Res Lett.

Scheffrahn RH, Bodalbhai L, & Su NY (1992) Residues of methyl bromide and sulfuryl fluoride in manufacturer-packaged household foods following fumigation. Bull Environ Contam Toxicol, **48**: 821-827.

Scheffrahn RH & Su NY (1992) Comparative toxicity of methyl bromide against ten nearctic termite species (Isoptera: Termopsidae, Kalotermitidae, Rhinotermitidae). J Econ Entomol, **85**: 845-847.

Schroeder KR, Hallier E, Peter H, & Bolt H (1992) Dissociation of a new glutathione S-transferase activity in human erythrocytes. Biochem Pharmacol, **43**: 1671-1674.

Scotto La Massese C & Mars S (1975) Etude préliminaire des résidus de brome dans les cultures faites dans des sols ayant reçu des applications de brome minéral KBr et organique CH_3Br. Phytiatr Phytopharm, **24**: 57-66.

Scudamore KA (1985) Multi-residue gas chromatographic method for determination of fumigant residues in cereal grains and other foods. In: Fishbein L & O'Neill IK ed. Environmental carcinogens selected methods of analysis. Volume 7 - Some volatile halogenated hydrocarbons. Lyon, International Agency for Research on Cancer, pp 351-359 (IARC Scientific Publications No. 68).

Scudamore KA (1985) Determination of methyl bromide in grain using head-space analysis. In: Fishbein L & O'Neill IK ed. Environmental carcinogens selected methods of analysis. Volume 7 - Some volatile halogenated hydrocarbons. Lyon, International Agency for Research on Cancer, pp 375-380 (IARC Scientific Publications No. 68).

Scudamore KA (1987) Fumigant residues in wheat and other cereal grains resulting from the use of 1,1,1-trichloroethane and bromomethane as a liquid fumigant mixture. Pestic Sci, **20**: 1-18.

Segers JHL, Temmink JHM, Van den Berg JHJ, & Wegman RCC (1984) Morphological changes in the gill of carp (*Cyprinus carpio* L.) exposed to acutely toxic concentrations of methyl bromide. Water Res, **18**: 1437-1441.

Sell CR & Moffitt HR (1990) Non-destructive method for estimating methyl bromide residues in apples during aeration following fumigation. Pestic Sci, **29**: 19-28.

Sell CR, Klag NG, & Burditt AK, Jr (1988) Methyl bromide residues in fresh cherries: effects of parameters in fumigation. Pestic Sci, **23**: 41-50.

Sher SA, Thomason IJ, & McCaslin RL (1958) Chisel application of methyl bromide for root-knot nematode control. Plant Dis Rep, **42**: 288-290.

Shield LK, Coleman TL, & Markesbery WR (1977) Methyl bromide intoxication: Neurologic features, including simulation of Reyes syndrome. Neurology, **27**: 959-962.

Shivanandappa T & Rajendran S (1987) Induction of glutathione *S*-transferase by fumigants in larvae of the khapra beetle, *Trogoderma granarium* (E.). Pestic Biochem Physiol, **28**: 121-126.

Siegwart Y (1987) [The implementation of food quality control in Switzerland in the year 1986.] Mitt Geb Lebensm.unters Hyg, **78**: 237-256 (in German).

Sikov MR, Cannon WC, Carr DB, Miller RA, Montgomery LF, & Phelps DW (1981) Teratologic assessment of buthylene oxide, styrene oxide and methyl bromide (Contract-No. 210-78-0025). Cincinnati, Ohio, US Department of Health and Human Services, 84 pp.

Simmon VF, Kauhanen K, & Tardiff RG (1977) Mutagenic activity of chemicals identified in drinking water. In: Scott D, Bridges BA, & Sobels FH, ed. Progress in genetic toxicology. Amsterdam, Elsevier/North-Holland Biomedical Press, pp 249-258.

Singh HB, Salas LJ, Smith SJ, & Shigeishi H (1981) Measurements of some potentially hazardous organic chemicals in urban environments. Atmos Environ, **15**: 601-612.

Singh HB, Salas LJ, & Stiles RE (1983) Methyl halides in and over the Eastern Pacific (40°N-32°S). J Geophys Res, **88**: 3684-3690.

Singh ON, Borchers R, Fabian P, Lal S, & Subbaraya BH (1988) Measurements of atmospheric BrO_x radicals in the tropical and mid-latitude atmosphere. Nature (Lond), **334**: 593-595.

Singh HB, Salas L, Viezee W, Sitton B, & Ferek R (1992) Measurement of volatile organic chemicals at selected sites in California. Atmos Environ, **26A**: 2929-2946.

Sittisuang P & Nakakita H (1985) The effect of phosphine and methyl bromide on germination of rice and corn seeds. J Pestic Sci, **10**: 461-468.

Sivasithamparam K, MacNish GC, Fang CS, & Parker CA (1987) Microflora of soil and wheat rhizosphere in a field following fumigation. Aust J Soil Res, **25**: 491-498.

Slooff W & Canton JH (1983) Comparison of the susceptibility of 11 freshwater species to 8 chemical compounds. II. (Semi)chronic toxicity tests. Aquat Toxicol, **4**: 271-282.

Smart NA (1990) Residues in foodstuffs from bromomethane soil fumigator. Adv Environ Sci Technol, **23**: 227-255.

Smirnov AM (1970) [Disinfection of combs containing beebread by gases in contagious bee diseases.] Sci Trans Inst Vet Sanit, **37**: 267-280 (in Russian).

Soremark R (1960) The biological half-life of bromide ions in human blood. Acta Physiol Scand, **50**: 119-123.

Spivakovsky CM, Yerich R, Logan JA, Wofsy SC, McElroy, & Prather MJ (1990) Tropospheric OH in a three-dimensional chemicaltracer model: An assessment based on observations of CH_3 $CC/_3$. J Geophys Res, **95**: 18,441-18,471.

Squier MV, Thompson J, & Rajgopalan B (1992) Case report: Neuropathology of methyl bromide intoxication. Neuropathol Appl Neurobiol, **18**: 579-584.

Starratt AN & Bond EJ (1981) Metabolism of methyl bromide by susceptible and resistant strains of the granary weevil, *Sitophilus granarius* (L.). Pestic Biochem Physiol, **15**: 275-281.

Starratt AN & Bond EJ (1988a) Methylation of DNA of maize and wheat grains during fumigation with methyl bromide. J Agric Food Chem, **36**: 1035-1039.

Starratt AN & Bond EJ (1988b) *In vitro* methylation of DNA by the fumigant methyl bromide. J. Environ. Health., **B23**: 513-525.

Starratt AN & Bond EJ (1990a) Residues of methyl bromide in fumigated commodities. Study submitted by Methyl Bromide Panel. London, Ontario, Research Centre, Agriculture Canada, 238 pp.

Starratt AN & Bond EJ (1990b) Methylation of food commodities during fumigation with methyl bromide. In: Studies of the magnitude and nature of pesticide residues in stored products using radiotracer techniques. London, Ontario, Research Centre, Agriculture Canada, pp 97-109.

Stein ER & Wolfenbarger DA (1989) Methyl bromide residues in fumigated mangos. J Agric Food Chem, **37**: 1507-1509.

Stenger VA (1978) Bromine compounds. In: Kirk-Othmer encyclopedia of chemical technology, 3rd ed. New York, Chichester, Brisbane, Toronto, John Wiley and Sons, vol 4, pp 243-263.

Streete PJ, Ruprah M, Ramsey JD, & Flanagan RJ (1992) Detection and identification of volatile substances by headspace capillary gas chromatography to aid the diagnosis of acute poisoning. Analyst, **117**: 1111-1127.

Strider DL (1975) Chemical control of bacterial blight of Rieger elatior begonias caused by *Xanthomonas begoniae*. Plant Dis Rep, **59**: 66-70.

Swartz RD, Millman RP, Billi JE, Bondar NP, Migdal SD, Simonian SK, Monforte JR, McDonald FD, Harness JK, & Cole KL (1981) Epidemic methanol poisoning: clinical and biochemical analysis of a recent episode. Medicine, **60**: 373-382.

Tanaka S, Arito H, Abuku S, & Imamiya S (1988) Acute effects of methyl bromide on electroencephalographic activity and sleep-wakefulness in rats. Ind Health, **26**: 101-114.

Tanaka S, Abuku SI, Seki Y, & Imamiya SI (1991) Evaluation of methyl bromide exposure on the plant quarantine fumigators by environmental and biological monitoring. Ind Health, **29**: 11-22.

Thier P & Zeumer H (1987) Manual of pesticide residue analysis. Volume 1. Bromine-containing fumigants (as total inorganic bromide). Weinheim, Verlag Chemie, pp 377-381.

Thomas DA & Morgan KT (1988) Olfactory toxicity: studies of methyl bromide. Chem Ind Inst Toxicol (CIIT) Act, **8**: 1-7.

Thomason IJ (1959) Chisel application of methyl bromide for control of root-knot nematode and fusarium wilt. Plant Dis Rep, **43**: 580-583.

Thompson RH (1966) A review of the properties and usage of methyl bromide as a fumigant. J Stored Prod Res, **1**: 353-376.

Tie X, Ko, C-Y, Mroz EJ, Cicerone RJ, Alyea FN, & Cunnold DM (1992) Three-dimensional simulation of atmospheric methyl chloroform: Effect of an ocean sink. J Geophys Res, **97**: 20,751-20,769.

Tkalich PP (1972) [Effectiveness of methyl bromide used against the hemp leaf roller.] Khim Sel'sk Khoz, **10**: 350-352 (in Russian).

Tkalich PP (1974) [Toxicological evaluation of fumigated hemp seeds.] Tr Nauch Issled Inst Lub Kul't, **35**: 97-101 (in Russian).

Torkelson TR & Rowe VK (1981) Methyl bromide. In: Patty's industrial hygiene and toxicology, 3rd rev. edn. New York, Chichester, Brisbane, Toronto, John Wiley and Sons, pp 3442-3446.

Tucker JF, Brown BW, & Goodship G (1974) Fumigation with methyl bromide of poultry foods artificially contaminated with Salmonella. Br Poult Sci, **15**: 587-595.

Tucker JD, Xu J, Stewart J, & Ong T (1985) Development of a method to detect volatile genotoxins using sister chromatid exchanges. Environ Mutagen, **7**: 48 (Abstract).

Tucker JD, Xu J, Stewart J, Baciu PC, & Ong T (1986) Detection of sister chromatid exchanges induced by volatile genotoxicants. Teratog carcinog mutagen, **6**: 14-21.

Tunney J (1972) The use of methyl bromide in disease control. Mushroom Sci, **8**: 755-762.

Turtura GC, Massa S, & Zani G (1988) Effects of methyl bromide on some bacterial groups in greenhouse soils. Ann Microbiol Enzimol, **38**: 93-98.

Uncini A, Basciani M, Di Muzio A, Antonini D, & Onofrj M (1990) Methyl bromide myoclonus: an electro physiological study. Acta Neurol Scand, **81**: 159-164.

UNEP (1992) Methyl bromide and the ozone layer: a summary of current understanding; Montreal Protocol Assessment Supplement; Synthesis report of the methyl bromide interim scientific assessment and methyl bromide interim technology and economic assessment requested by the United Nations Environment Programme on behalf of the Contracting Parties to the Montreal Protocol, June 1992. Nairobi, United Nations Environment Programme, pp 33.

Urga K (1983) Methyl bromide and phosphine residues in cereal grains and pulses. Ethiop Med, **21**: 79-83.

US EPA (1982a) Method 8010. Halogenated volatile organics, 2nd ed. Washington, DC, US Environmental Protection Agency, pp 278-289 (EPA No. SW-846; PB 87-120-291).

US EPA (1982b) Method 8240. GS/MS method for volatile organics, 2nd ed. Washington, DC, US Environmental Protection Agency, pp 433-454 (EPA No. SW-846; PB 87-120-291).

US EPA (1984a) Method 624. Guidelines establishing test procedures for the analysis of pollutants under the Clean Water Act (40 CFR 136 Purgeables). Fed Reg, **49**: 43373-43384.

US EPA (1984b) Appendix A to part 136 - Methods for organic chemical analysis of principal and industrial wastewater. Method 601. Purgeable halocarbons. Fed Reg, **49**: 43261-43271.

US EPA (1984c) Method 1624. Revision B. Guidelines establishing test procedures for the analysis of pollutants under the Clean Water Act (40 CFR 136). Volatile organic compounds by isotope dilution GC/MS. Fed Reg, **49**: 43407-43415.

US EPA (1988a) Pesticide fact handbook. Park Ridge, New Jersey, Noyes Data Corporation.

US EPA (1988b) Pesticide tolerances for inorganic bromides resulting from fumigation with methyl bromide; correction. Fed Reg, **53**: 30053-30054.

Uthman AP, Demlein PJ, Allston TD, Withiam MC, McClements MJ, & Takacs GA (1978) Photoabsorption spectra of gaseous methyl bromide, ethylene dibromide, nitrosyl bromide, thionyl chloride and sulfuryl chloride. J Phys Chem, **82**: 2252-2257.

Vanachter A (1974) Soil disinfestation in cauliflower, tomato, and witloof crops in Belgium. Agric Environ, **1**: 265-276.

Vanachter A, Feyaerts J, Van Wambeke E, & Van Assche C (1981) Bromide concentrations in water after methyl bromide soil disinfestation. II. Relation between leaching of methyl bromide fumigated greenhouse soils and bromide concentrations in the surrounding surface waters. Meded Fac Landbouwwet Rijksuniv Gent, **46**: 351-358.

Van den Oever R, Van de Mierop L, & Lahaye D (1978) [Intoxication of professionally exposed methyl bromide workers.] Belg Arch Soc Gen, **36**: 353-369 (in Flemish).

Van den Oever R, Roosels D, & Lahaye D (1982) Actual hazard of methyl bromide fumigation in soil disinfection. Br J Ind Med, **39**: 140-144.

Van Doorn IAM, Feron VJ, Van Genderen H, & Zoeteman BCJ (1989) [Report of the Netherlands Committee concerning the use of methyl bromide as a soil disinfectant in agriculture.] The Hague, Ministry of Agriculture and Fisheries, pp 3-23 (in Dutch).

Van Gundy SD, Munnecke D, Bricker J, & Minteer R (1972) Response of *Meloidogyne incognita*, *Xiphinema index*, and *Dorylaimus* species to methyl bromide fumigation. Phytopathology, **62**: 191-192.

Van Gundy SD, Perez JG, Stolzy LH, & Thomason IJ (1974) A pest management approach to the control of *Pratylenchus thornei* on wheat in Mexico. J Nematol, **6**: 107-116.

Van Leeuwen CJ, Rijkeboer M, & Niebeek G (1986) Population dynamics of *Daphnia magna* and modified by chronic bromide stress. Hydrobiologia, **133**: 277-285.

Van Leeuwen FXR & Sangster B (1987) The toxicology of bromide ion. CRC Crit Rev Toxicol, **18**: 189-213.

Van Rhee JA (1977) Effects of soil pollution on earthworms. Pedobiologia, **17**: 201-208.

Van Wambeke E, Vanachter A, & Van Assche C (1974) Some factors affecting bromide residues in soil and plant. Meded Fac Landbouwwet Rijksuniv Gent, **39**: 1311-1324.

Van Wambeke E, Vanachter A, & Van Assche C (1988) Measures for improving soil fumigation. Brighton Crop Protection Conference on Pests and Diseases, Brighton, England, 21-24 November 1988. London, The British Crop Protection Council, pp 199-204.

Van Wees AMP, Rijk MAH, Rijnaars MW, & De Vos RH (1984) Chromatographic methods for the determination of inorganic bromide in vegetables. In: Frigerio A & Milon H, ed. Chromatography and mass spectrometry in nutrition science and food safety. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 19-25.

Veenendahl G & Dibbets G (1981) [Permeation of methyl bromide into different types of drinking waterpipes.] Kiwa, Inspection Institute for Water Pipeline Materials (KIWA), pp 1-35 (in Dutch with English Summary).

Verberk MM, Rooyakkers-Beemster T, De Vlieger M, & Van Vliet AGM (1979) Bromine in blood, EEG and transaminases in methyl bromide workers. Br J Ind Med, **36**: 59-62.

Victor M & Adams RD (1980) Nonbarbiturate sedative-hypnotics; psychtherapeutic, stimulant, and psychotogenic drugs. In: Isselbacher KJ, Adams RD, Braunwald E, Petersdorf RG, & Wilson, JD ed. Harrison's principles of internal medicine, 9th ed. New York, McGraw-Hill Book Company (Abstract 229).

Vincent LE & Lindgren DL (1975) Toxicity of phosphine and methyl bromide at various temperatures and exposure periods to the four metamorphic stages of *Trogoderma variabile*. J Econ Entomol, **68**: 53-56.

Vitte VI, Sorokina LV, & Subbotina SB (1970) [Residual amounts of bromides in plant food products fumigated with methyl bromide and characteristics of their biological action.] Gig Primen Toksikol Pestic Klin Otrav, **8**: 386-392 (in Russian).

Vodolagin VD (1971) Biology of the dog rose-eating weevil (*Megastigmus aculeatus*) and measures for controlling it. Sci Trans Efirnomaslich Cult Inst, **3**: 115-117.

Von Oettingen WF (1946) The toxicity and potential dangers of methyl bromide with special reference to its use in the chemical industry, in fire extinguishers and in fumigation. Washington, DC, US Government Printing Office, pp 1-41.

Von Oettingen WF (1955) The halogenated aliphatic, olefinic, cyclic, aromatic, and aliphatic-aromatic hydrocarbons including the halogenated insecticides, their toxicity and potential dangers. Washington, DC, US Public Health Service, pp 15-30 (Publication No. 414).

Von Oettingen WF (1964) Methyl bromide. The halogenated hydrocarbons of industrial and toxicological importance. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 25-55.

Watrous RM (1942) Methyl bromide-local and mild systemic effects. Ind Med, **11**: 575-579.

Wegman RCC, Greve PA, De Heer H, & Hamaker PH (1981) Methyl bromide and bromide-ion in drainage water after leaching of glasshouse soils. Water Air Soil Pollut, **16**: 3-11.

Wegman RCC, Hamaker, PH, & De Heer H (1983) Bromide-ion balance of a polder district with large-scale use of methyl bromide for soil fumigation. Food Chem Toxicol, **21**: 361-367.

Weihing JL, Schuster ML, Riesselman JH, & Cook JA (1971) Control of fusarium wilt of petunia with three soil fumigants. Plant Dis Rep, **55**: 580-582.

Weller D (1982) [Methyl bromide: Toxicology and therapy.] Frankfurt am Main, Degesch GmbH, pp 21-42 (in German).

Wells JM & Payne JA (1975) Mycoflora of pecans treated with heat, low temperatures, or methyl bromide for control of the pecan weevil. Phytopathology, **65**: 1393-1395.

Wester PW, Canton JH, & Dormans JAMA (1988) Pathological effects in freshwater fish *Poecilia reticulata* (guppy) and *Oryzias latipes* (medaka) following methyl bromide and sodium bromide exposure. Aquat Toxicol, **12**: 323-343.

Weststeijn G (1973) Soil sterilization and glasshouse disinfection to control *Fusarium oxysporum* f. *lycopersici* in tomatoes in the Netherlands. Neth J Plant Pathol, **79**: 36-40.

Whitehead AG, Fraser JE, & Storey G (1972) Chemical control of potato cyst-nematode in sandy clay soil. Ann Appl Biol, **72**: 81-88.

Whitney WK, Jantz OK, & Bulger CS (1958) Effects of methyl bromide fumigation on the viability of barley, corn, grain sorghum, oats, and wheat seeds. J Econ Entomol, **51**: 847-861.

Wilhelm E, Battino R, & Wilcock RJ (1977) Low pressure solubility of gases in liquid water. Chem Rev, **77**: 219-262.

Wilmer JWGM, Reuzel PGJ, & Dreef van der Meulen HC (1983) Subchronic (13 week) inhalation toxicity study of methyl bromide in rats. Zeist, The Netherlands, CIVO Institutes, TNO, 46 pp (CIVO Report No. V 82.378).

Windholz M (1983) The Merck index, 10th ed. Rahway, New Jersey, Merck & Co., Inc., p 865.

Winstead NN & Garriss HR (1960) Control of cabbage clubroot in North Carolina. Plant Dis Rep, **44**: 14-18.

Winteringham FPW, Harrison A, Bridges RG, & Bridges PM (1955) The fate of labelled insecticide residues in food products. II. The nature of methyl bromide residues in fumigated wheat. J Sci Food Agric, **6**: 269-275.

WMO (1992) Scientific assessment of ozone depletion, 1991. Geneva, World Meteorological Organization, 330 pp (Report No. 25).

Wofsy SC, McElroy MB, & Yung YL (1975) The chemistry of atmospheric bromide. Geophys Res Lett, **2**: 215-218.

Wohlgemuth R, Drosihn J, & El-Lakwah F (1976) [Experiments to fumigate piled expeller lying in quarantine against the Khapra beetle.] Berlin, Federal Biological Institute for Agriculture and Forestry, 29 pp (in German).

Woodrow JE, McChesney MM, & Seiber JN (1988) Determination of methyl bromide in air samples by headspace gas chromatography. Anal Chem, **60**: 509-512.

Wyers H (1945) Methyl bromide intoxication. Br J Ind Med, **2**: 24-29.

Wylie PL (1988) Comparing headspace with purge and trap for analysis of volatile priority pollutants. Am Water Works Assoc J, **80**: 65-72.

Xu D, Peter H, Hallier E, & Bolt HM (1990) Hemoglobin adducts of monohalomethanes. Ind Health, **28**: 121-123.

Yamano Y (1991) [Experimental study on methyl bromide poisoning in mice. Acute inhalation study and the effect of glutathione as an antidote.] Jpn J Ind Health, **33**: 23-30 (in Japanese).

Yamano Y, Ito I, Nagao N, & Ishizu S (1987) [A simple determination method of bromide ion in plasma of methyl bromide workers by head-space gas chromatography.] Jpn J Ind Health, **29**: 196-201 (in Japanese with English abstract).

Yeates GW, Bamforth SS, Ross DJ, Tate KR, & Sparling GP (1991) Recolonization of methyl bromide sterilized soils under four different field conditions. Biol Fertil Soils, **11**: 181-189.

Yung YL, Pinto JP, Watson RT, & Sander SP (1980) Atmospheric bromine and ozone pertubations in the lower stratosphere. J Atmos Sci, **37**: 339-353.

Zatuchni J & Hong K (1981) Methyl bromide poisoning seen initially as psychosis. Arch Neurol, **38**: 529-530.

Zwart A, Arts JHE, Ten Berge WF, & Appelman LM (1992) Alternative acute inhalation toxicity testing by determination of the concentration-time-mortality relationship: experimental comparison with standard LC_{50} testing. Regul Toxicol Pharmacol, **15**: 278-290.

Zwart A (1988) Acute inhalation study of methylbromide in rats. Zeist, The Netherlands, CIVO Institutes, TNO, 17 pp (CIVO Report-No. V88. 127/27).

Zwaveling JH, De Kort Wlam, Meulenbelt J, Hezemans-Boer M, Van Vloten WA, & Sangster B (1987) Exposure of the skin to methyl bromide: a study of six cases occupationally exposed to high concentrations during fumigation. Hum Toxicol, **6**: 491-495.

RESUME

1 Propriétés physiques et chimiques, méthodes d'analyse

A la température ambiante et sous la pression normale, le bromure de méthyle est un gaz incolore dont le point d'ébullition est d'environ 4 °C. Il est plus lourd que l'air et on peut facilement le liquéfier en-dessous du point critique. Il est inodore sauf à fortes concentrations auquel cas il dégage une odeur chloroformique. Il est ininflammable à l'air, sauf aux concentrations comprises entre 10 et 16%, mais brûle dans l'oxygène. Le bromure de méthyle n'est que légèrement soluble dans l'eau mais facilement soluble dans les autres solvants courants. Il peut pénétrer dans de nombreuses substances comme le béton, le cuir, le caoutchouc et certaines matières plastiques.

Le bromure de méthyle s'hydrolyse en méthanol et acide bromhydrique en solution aqueuse, la vitesse d'hydrolyse dépendant du pH. C'est un agent de méthylation efficace qui réagit sur les amines et les composés soufrés. La plupart des métaux sont inertes au bromure de méthyle pur et sec mais des réactions de surface peuvent avoir lieu sur le zinc, l'étain, l'aluminium et le magnésium en présence d'impuretés ou d'humidité. Des réactions explosives ont été observées avec l'aluminium et le diméthylsulfoxyde.

Le bromure de méthyle existe dans le commerce sous forme de gaz liquéfié. Les formulations destinées à la fumigation des sols contiennent de la chloropicrine (2%) ou de l'acétate d'amyle (0,3%) comme agents d'alerte. D'autres formulations peuvent contenir jusqu'à 70% de chloropicrine ainsi que d'autres fumigants ou hydrocarbures comme diluants. Pour la fumigation des marchandises, on utilise du bromure de méthyle à 100%.

Il existe des méthodes d'analyse pour le dosage du bromure de méthyle dans l'air, l'eau, le sol, les produits alimentaires et la nourriture pour animaux. Parmi les méthodes directes de dosage du bromure de méthyle dans l'air sur le terrain, on peu citer les analyseurs de gaz par conductivité thermique, les tubes de détection colorimétrique, les analyseurs à infrarouge, et les détecteurs par photo-ionisation. Pour les dosages de routine, on recommande la chromatographie en phase gazeuse avec détection par capture

d'électrons, éventuellement couplée à la spectrométrie de masse pour la confirmation au laboratoire.

Pour le dosage par chromatographie en phase gazeuse du bromure de méthyle dans l'eau, on peut utiliser diverses techniques d'injection (purge, piégeage, espace de tête par exemple). Pour le dosage en routine du bromure de méthyle dans les produits alimentaires, on recommande de procéder à une extraction par un mélange d'acétone et d'eau puis à une chromatographie en phase gazeuse sur colonne capillaire selon la technique de l'espace de tête avec détection par capture d'électrons. Etant donné que le bromure de méthyle se transforme en partie en bromure dans le sol, les denrées alimentaires et les produits biologiques, l'ouvrage étudie également les méthodes de recherche et de dosage des bromures. Parmi les méthodes utilisées pour le dosage des bromures dans diverses matrices, on peut citer les méthodes colorimétriques, la spectroscopie de rayons X, la potentiométrie, l'analyse par activation neutronique, la chromatographie en phase gazeuse ainsi que la chromatographie en phase liquide à haute performance (HLPC).

2 Sources d'exposition humaine et environnementale

On pense que les océans sont la source essentielle de bromure de méthyle. La principale source d'origine humaine en est la fumigation des sols et de l'intérieur des habitations. Les véhicules à moteur qui utilisent de l'essence au plomb émettent également une petite quantité de bromure de méthyle.

En 1990, la consommation mondiale de bromure de méthyle a dépassé 67 millions de kg soit une augmentation de 46% depuis 1984. On produit généralement le bromure de méthyle par action du méthanol sur l'acide bromhydrique et, dans certains procédés, on l'obtient à côté du tétrabromobisphénol A. Le bromure de méthyle est généralement stocké et transporté à l'état liquide sous pression dans des récipients d'acier.

Le bromure de méthyle est utilisé à environ 77% pour la fumigation des sols, à 12% pour la fumigation des marchandises et notamment des marchandises soumises à quarantaine, à 5% pour la fumigation des construction et à 6% comme intermédiaire dans l'industrie chimique.

Sous forme gazeuse, il est utilisé comme fumigant des sols, soit en plein champ, soit sous serre pour la destruction des ravageurs. Sous forme liquide, on l'applique avant la plantation, soit par injection dans le sol, soit en plaçant des jattes pleines de bromure de méthyle sous une couverture en plastique et en laissant le produit s'évaporer sur place (méthode à froid) ou par chauffage (méthode à chaud). Les méthodes autorisées varient selon le pays. Le type de matière plastique utilisé est également important.

Les doses de bromure de méthyle à appliquer dépendent également des normes légales en vigueur dans les différents pays, de l'espèce de ravageur à détruire (type, ampleur de l'infestation), de la récolte suivante, du type de sol et de la couverture plastique utilisée (durée de couverture et nature de la matière plastique). Le bromure de méthyle est généralement épandu sur le sol à des doses comprises entre 50 et 100 g/m^2.

En fumigation spatiale, le bromure de méthyle est utilisé sur les produits agricoles (par exemple fourrage, céréales, noix, etc.) ainsi que pour la destruction des termites et des rongeurs. Pour la plupart des denrées stockées dans des pièces et des silos fermés ou sous une couverture étanche au gaz, on utilise des doses de 16 à 30 g de bromure de méthyle par m^3. Après la fumigation, il faut aérer les locaux pendant un certain temps. Cette fumigation est également importante dans le cas des légumes et des fruits frais soumis à quarantaine.

Parmi les utilisations industrielles du bromure de méthyle, on l'emploie en synthèse organique, généralement en tant qu'agent de méthylation, ou comme solvant à bas point d'ébullition, par exemple pour l'extraction de l'huile de noix et de différentes graines ou celle des huiles essentielles. L'emploi du bromure de méthyle comme réfrigérant ou comme produit extincteur à usage général, n'a plus qu'un intérêt historique.

3 Transport, distribution et transformation dans l'environnement

Le bromure de méthyle est naturellement présent dans l'atmosphère et les quantités qui résultent de l'activité humaine viennent s'y ajouter. Le bromure de méthyle réagit en petites quantités sur les radicaux hydroxyles de la troposphère mais il en

passe une certaine proportion dans la stratosphère par diffusion verticale. Là, c'est la photolyse qui gagne en importance, puisqu'elle devient le mécanisme dominant d'élimination du bromure de méthyle dans la partie basse de la stratosphère. Il en résulte la formation de brome actif qui réagit sur l'ozone stratosphérique et pourrait être en partie responsable de la destruction de la couche d'ozone.

Dans le sol, le bromure de méthyle est partiellement hydrolysé en ion bromure. Après fumigation au bromure de méthyle, on peut lessiver le sol à l'eau afin d'éviter que les ions bromure formés ne soient fixés par les végétaux plantés après stérilisation du sol. Cet accroissement de la concentration en bromure peut poser des problèmes si l'on utilise pour cela des eaux de surface. Le bromure de méthyle peut diffuser à travers les canalisations d'eau potable en polyéthylène si le sol environnant a subi une fumigation avec ce produit.

Dans le sol, le bromure de méthyle peut diffuser jusqu'à une profondeur de 0,8 m selon le type de sol, la dose d'emploi, le mode d'épandage et la durée de fumigation, la couche supérieure du sol en retenant la majeure partie. Le transport du gaz s'effectue par écoulement ou diffusion moléculaire, mais il est également influencé par le présence de processus simultanés de piégeage comme une sorption ou une dissolution, et qui peuvent être irréversibles comme l'hydrolyse. La quantité de bromure de méthyle transformée en bromure dépend principalement de la teneur du sol en matières organiques. Les bromures ainsi produits sont largement solubles dans l'eau et peuvent être fixés par les plantes ou descendre plus profondément dans le sol par lessivage.

La quantité de bromure qui s'accumule dans les plantes dépend de divers facteurs comme la dose d'emploi, la durée d'exposition, le débit d'aération, les propriétés physiques et chimiques du sol, la climatologie (température et précipitations), l'espèce végétale et la nature du tissu végétal. En particulier, les légumes-feuilles comme la laitue et les épinards, peuvent fixer des quantités relativement importantes d'ions bromure sans présenter de symptômes de phytotoxicité. En revanche, d'autres plantes cultivées comme les oeillets, les plants d'agrumes, le coton, le céleri, les poivrons ou les oignons sont particulièrement sensibles à la fumigation par le bromure de méthyle.

Le bromure de méthyle et ses produits de réaction, dont on n'a considéré jusqu'ici que les bromures, peuvent pénétrer dans la chaîne alimentaire de deux manières; soit par consommation de plantes cultivées dans des serres ou dans des champs traités par fumigation avant la plantation, soit par consommation de produits alimentaires traités au bromure de méthyle pendant l'entreposage. A partir d'une certaine concentration, les bromures peuvent être dangereux pour la santé et il existe un seuil de tolérance pour le bromure présent dans les denrées alimentaires. La concentration des autres produits de réaction n'a pas été étudiée.

Dans le sol, le bromure de méthyle subit une dégradation par hydrolyse et décomposition microbienne. La constante de vitesse d'hydrolyse varie avec la température et le pH et augmente avec l'intensité de la lumière.

Le coefficient de partage octanol/eau (log P_{ow}) du bromure de méthyle est égal à 1,19, ce qui indique que sa bioaccumulation est faible.

Le bromure de méthyle qui n'est pas décomposé lors de la fumigation pénètre dans la troposphère et gagne la stratosphère par diffusion verticale. Il ne semble pas qu'il existe un important gradient de concentration vertical du bromure de méthyle dans la troposphère, mais sa concentration diminue rapidement dans la basse stratosphère où il subit une photolyse.

4 Concentrations dans l'environnement et exposition humaine

La concentration du bromure de méthyle mesurée dans l'air de zones inhabitées, varie de 40 à 100 ng/m^3 (10 à 26 pptv), les valeurs pour l'hémisphère nord étant supérieures à celles à celles que l'on trouve dans l'hémisphère sud. La plupart des valeurs vont de 9 à 15 pptv. Des différences saisonnières ont été constatées à l'occasion d'un certain nombre d'études. Dans les zones urbanisées et industrialisées, les concentrations sont beaucoup plus élevées avec des valeurs moyennes allant jusqu'à 800 ng/m^3 voire jusqu'à 4 μg de bromure de méthyle par m^3. A proximité des champs et des serres, on constate, lors de la fumigation et de l'aération, des concentrations de bromure de méthyle beaucoup plus élevées, des valeurs de 1 à 4 mg/m^3 ayant été mesurées dans une étude à des distances allant

jusqu'à 20 m d'une serre, quelques heures après l'injection du produit; quatre jours plus tard, la concentration était tombée au dixième de cette valeur.

Dans un échantillon d'eau de mer prélevé en surface, on a trouvé une concentration de bromure de méthyle de 140 ng/litre. Dans des échantillons d'eau littorales de la Mer du Nord, la concentration moyenne en ions bromure était de 18,4 mg/litre; dans les cours d'eau de l'arrière pays, cette concentration était beaucoup plus faible, sauf là où l'on pratiquait la fumigation par le bromure de méthyle ou dans les zones polluées par les rejets industriels. Dans les eaux de drainage d'une serre hollandaise, on a signalé des concentrations de 9,3 mg de bromure de méthyle par litre et de 72 mg d'ions bromure par litre. Dans les eaux rejetées par une serre belge, on a trouvé après fumigation une concentration de 280 mg de bromure par litre.

La teneur naturelle du sol en bromure dépend du type de ce sol mais elle est généralement inférieure à 10 mg/kg. La teneur en résidus de bromure dans les sols traités dépend du traitement, de la dose d'emploi, du type de sol, des précipitations, du lessivage par l'eau et de la température.

Il peut y avoir de fortes concentrations de bromure de méthyle ou d'ions bromure dans les cultures vivrières poussant sur des sols préalablement traités au bromure de méthyle ou qui ont subi une fumigation après récolte.

Plus rarement, on a constaté que les concentrations de bromure dans les légumes frais cultivés sur des sols qui avaient traité avec du bromure de méthyle, dépassaient les teneurs en résidus autorisées. Dans certains pays, il est interdit de cultiver des légumes sur des sols traités de cette manière.

On utilise largement le bromure de méthyle pour la fumigation des denrées alimentaires après récolte, par exemple les céréales et notamment le froment, les épices, les noix, les fruits secs ou frais et le tabac. La concentration en bromure de méthyle diminue en général rapidement après aération et au bout de quelques semaines on ne peut plus déceler de résidus. Certains produits comme les noix et les graines ou des aliments gras comme le fromage ont tendance à retenir le bromure de méthyle et le brome minéral.

Il peut y avoir exposition humaine au fumigant lui-même comme aux résidus d'ions bromure. Il pourrait également y avoir un risque

d'accroissement de la concentration du bromure de méthyle ou des bromures dans l'eau des puits peu profonds situés à proximité de terrains où l'on pratique la fumigation par le bromure de méthyle.

Les personnes qui vivent à proximité immédiate des champs, des serres ou des entrepôts traités au bromure de méthyle pourraient courir le risque d'une exposition au gaz. Il existe également un risque individuel pour les personnes qui pénètrent accidentellement ou délibérément dans une maison traitée contre la vermine avant que l'on ait annoncé qu'il n'y a plus de danger.

L'exposition professionnelle au bromure de méthyle est le risque le plus probable pour les travailleurs lors de la production, du remplissage des récipients et des opérations de fumigation. Seuls les fumigateurs sont désormais considérés comme constituant un groupe à haut risque étant donné que, sur les lieux de production, des mesures de sécurité très strictes sont appliquées. Ceux qui sont employés au traitement des constructions peuvent être exposés à des concentrations beaucoup plus élevées que les valeurs-seuil après 24 heures d'aération (80 à 2000 mg/m^3). Cependant, un ouvrier expérimenté utilisera un équipement protecteur approprié. Les travailleurs agricoles qui procèdent à la fumigation du sol peuvent être exposés pendant de longues durées à des doses transitoires élevées de bromure de méthyle. De par la nature même du processus, le traitement d'une serre peut exposer les travailleurs à d'importantes concentrations de bromure de méthyle (100-1200 mg/m^3). Il est vrai cependant, que pour combattre des risques inhérents aux diverses opérations de fumigation, on a établi des règles de sécurité très strictes qui impliquent notamment le port d'un équipement protecteur. Cela n'empêche pas des accidents de se produire par suite d'une exposition excessive.

5 Cinétique et métabolisme

Des études au cours desquelles on a fait inhaler du bromure de méthyle à des rats, des chiens beagle et des volontaires humains ont révélé que le produit était rapidement résorbé au niveau pulmonaire. La résorption est également rapide chez le rat après administration par voie orale.

Une fois résorbé, le bromure de méthyle ou ses métabolites se répartissent rapidement dans de nombreux tissus, notamment les

poumons, les surrénales, les reins, le foie, les fosses nasales, le cerveau, les testicules et les tissus adipeux. Lors d'une étude par inhalation sur des rats, on a constaté que la concentration tissulaire du bromure de méthyle passait par un maximum une heure après l'exposition puis diminuait rapidement, aucune trace n'étant plus décelable au bout de 48 heures. On n'a pas encore élucidé le métabolisme du bromure de méthyle inhalé mais le glutathion pourrait jouer un rôle.

Dans les tissus de plusieurs espèces, notamment l'homme, on a observé une méthylation des protéines et des lipides après exposition au bromure de méthyle par voie respiratoire. On a également mis en évidence la présence d'adduits méthylés de l'ADN après exposition de rongeurs ou de cellules de rongeurs *in vivo* ou *in vitro*.

Lors d'études d'inhalation avec du bromure de méthyle marqué par du [^{14}C], on a observé que la principale voie d'élimination du radiocarbone était l'exhalation de $^{14}CO_2$. La quantité de radiocarbone retrouvée dans le urines a été moindre. Après administration par voie orale de bromure de méthyle, on a constaté que c'était par la voie urinaire que le ^{14}C était principalement excrété.

Le système nerveux central est également est un organe cible important du bromure de méthyle. La neurotoxicité de ce composé est sans doute liée à une modification de la teneur en monoamines, en acides aminés et éventuellement en catécholamines.

6 Effets sur les êtres vivants dans leur milieu naturel

L'une des utilisations commerciales du bromure de méthyle consiste dans la destruction des nématodes, des mauvaises herbes et des champignons terricoles qui causent des maladies chez les plantes comme la fonte des semis, et divers types de pourritures et de verticillioses.

Peu d'études ont été consacrées aux effets du bromure de méthyle sur les organismes aquatiques car ce composé n'est lui-même que peu soluble dans l'eau. Les valeurs de la CL_{50} vont de 17 mg/litre pour *Cyprinus carpio* L. sur 4 heures, à 1,2 mg/litre pour *Poecilia reticulata* sur 48 heures. Aux concentrations mortelles, il est probable que la mort est causée par des lésions au niveau des branchies et de l'épithélium buccal.

Après fumigation par le bromure de méthyle, il se forme des ions bromure que l'on retrouve dans l'eau après lessivage. Ces ions bromure ont été à l'origine d'intoxications aiguës chez différents organismes dulçaquicoles à des concentrations allant de 44 à 5800 mg de Br^-/litre; la concentration sans effets observables lors d'épreuves à long terme allant de 7,8 à 250 mg de Br^-/litre. Les ions bromure ont également un effet perturbateur marqué sur la reproduction des crustacés et des poissons.

En fumigation, on peut appliquer du bromure de méthyle directement sur les semis, sur les boutures ou sur les plantes après récolte, pour les débarrasser des parasites pendant le transport et l'entreposage. Si le taux d'humidité ou la température sont trop élevés, il peut y avoir retard à la germination, voire perte de la capacité germinative.

Certains végétaux, en particulier les légumes-feuilles, sont sensibles à la fumigation par le bromure de méthyle, soit par excès de bromure dans le sol, soit indirectement en raison des effets de ce composé sur la microflore terricole. Quelquefois, le bromure de méthyle a au contraire un effet positif sur les végétaux car il peut stimuler leur croissance et améliorer le rendement des cultures.

La fumigation par le bromure de méthyle détruit non seulement les parasites visés mais également une partie de la flore, des gastéropodes, des arachnides et des protozoaires terricoles.

On l'utilise de préférence à d'autres insecticides en raison de son aptitude à pénétrer rapidement et profondément dans la masse des produits traités et dans les sols. Les doses d'emploi pour traiter les marchandises entreposées vont essentiellement de 16 à 100 g/m^3 pendant deux à trois jours, selon la température. La dose nécessaire pour la destruction des oeufs et des pupes est plus élevée que pour les insectes adultes. La tolérance varie selon les diverses espèces d'insectes, selon leurs divers stades de développement et chez une même espèce, en fonction de la souche.

On ne dispose d'aucune donnée relative aux effets directs du bromure de méthyle sur les oiseaux et les mammifères sauvages.

7 Effets sur les animaux d'expérience

Des études d'inhalation effectuées sur divers espèces de mammifères montrent que la sensibilité au bromure de méthyle varie nettement selon l'espèce et le sexe. La droite dose-mortalité présente une pente accentuée chez toutes les espèces animales étudiées.

Chez le rat et la souris, les principaux signes cliniques d'intoxication sont des manifestations neurologiques avec, à fortes concentrations, une irritation des muqueuses.

Ces manifestations neurologiques consistent notamment en fasciculations et paralysie. Divers auteurs ont également fait état à doses plus faibles, de modifications dans l'activité locomotrice, d'anomalies de la fonction nerveuse périphérique, de modifications du rythme circadien et d'aversion gustative conditionnée.

On a également décrit des altérations histo-pathologiques au niveau du cerveau, des reins, des muqueuses nasales, du coeur, des surrénales, du foie et des testicules chez des rats et des souris exposés à diverses concentrations de bromure de méthyle.

Une exposition de brève durée au bromure de méthyle provoque des lésions au niveau des cellules de soutien de l'épithélium olfactif et des cellules sensorielles matures mais la réparation et la récupération sont rapides.

Les études d'inhalation de longue durée (jusqu'à deux ans) effectuées sur des rats, ont révélé la présence de lésions de la muqueuse nasale et du myocarde. Lors d'une étude à long terme analogue chez la souris, les lésions primitives ont été observées au niveau du cerveau, du coeur et de la muqueuse nasale. Aucun signe de cancérogénicité n'a été observé chez l'une ou l'autre espèce.

L'administration par voie orale de 50 mg de bromure de méthyle par kg de poids corporel à des rats pendant des périodes allant jusqu'à 25 semaines a entraîné une inflammation et une hyperplasie grave au niveau de l'épithélium de la portion cardiaque de l'estomac. Après une période de récupération, qui a suivi l'exposition au bromure de méthyle, la principale lésion observée était une fibrose de la portion cardiaque de l'estomac. Chez des rats traités quotidiennement pendant 25 semaines, on a également constaté la présence d'un cancer précoce à ce niveau.

Des souris B6C3F et des rats F344 exposés à des concentrations de bromure de méthyle allant jusqu'à 467 mg/m^3 pendant 13 semaines, ont présenté de légères anomalies morphologiques des spermatozoïdes, la durée du cycle oestral n'étant pas affectée.

Deux générations consécutives de rats CD Sprague-Dawley ont été soumis par la voie respiratoire à des concentrations de bromure de méthyle allant jusqu'à 350 mg/m^3 sans que l'on constate d'effets notables sur leur croissance, les divers processus de la reproduction ni sur leur descendance. Il y avait diminution des indices de fécondité des mâles et des femelles aux deux doses les plus élevées, chez les rats de la génération F_1 et de la génération F_{2b}.

On a étudié les effets toxiques du bromure de méthyle sur le développement de lapins blancs de Nouvelle-Zélande, exposés à 311 mg de bromure de méthyle par m^3 (6 heures/jour, du 7ième au 19ième jour de la gestation). Les effets toxiques relevés chez les mères étaient modérés à graves. Les effets sur le développement observés aux doses toxiques pour les mères, consistaient en une réduction du poids du foetus, une augmentation de la fréquence des modifications squelettiques mineures ainsi qu'en malformations (essentiellement absence de la vésicule biliaire ou du lobe inférieur du poumon). Toutefois à la dose de 272 mg/m^3, la toxicité maternelle était moins marquée et il n'y avait plus d'effets embryotoxiques.

Aucun effet nocif maternel, embryonnaire ou foetal n'a été observé chez des lapins exposés à des doses de bromure de méthyle égales à 78 ou 156 mg/m^3. Pour les lapins blancs de Nouvelle-Zélande, on a fixé à 156 mg/m^3 la dose sans effets observables pour la toxicité maternelle et les effets toxiques sur le développement.

Le bromure de méthyle s'est révélé mutagène dans plusieurs systèmes d'épreuve *in vitro* et *in vivo*. Il provoque des mutations létales récessives liées au sexe chez *Drosophila melanogaster* ainsi que des mutations dans des cellules mammaliennes en culture. Il ne provoque pas de synthèse anarchique de l'ADN (non programmée) ni de transformation cellulaire dans les cultures de cellules mammaliennes. Chez des souris à qui on avait administré du bromure de méthyle par diverses voies, on a observé une méthylation de l'ADN au niveau des cellules hépatiques et spléniques. Chez des rats et des souris, on a observé la formation de micro-noyaux dans les cellules de la moelle osseuse et les leucocytes périphériques.

On ignore le mécanisme de la toxicité du bromure de méthyle.

8 Effets sur l'homme

Il peut y avoir exposition humaine au bromure de méthyle, soit par inhalation du gaz, soit par contact avec le liquide. L'exposition peut également se produire par la voie digestive à la suite de l'ingestion d'eau de boisson contaminée par des eaux de lessivage polluées.

Une étude contrôlée sur l'homme a révélé que, après inhalation, environ 50% de la dose administrée étaient absorbés.

Le bromure de méthyle provoque des lésions au niveau du système nerveux, des poumons, des muqueuses nasales, du rein, de l'oeil et de la peau. Les effets sur le système nerveux central consistent en troubles visuels, confusion mentale, engourdissement, tremblements, et troubles de l'élocution. Une contamination topique peut entraîner une irritation et des brûlures cutanées ainsi que des lésions oculaires.

L'exposition à de fortes concentrations de bromure de méthyle provoque un oedème pulmonaire. Dans les cas d'intoxication par le bromure de méthyle, la cause immédiate de la mort est généralement une dépression du système nerveux central entraînant une paralysie respiratoire et/ou une défaillance circulatoire, précédées par des convulsions et un coma.

Lors d'intoxications aiguës ou chroniques par le bromure de méthyle, on a observé différents symptômes neuro-psychiatriques. Une exposition de brève durée à de faibles concentrations de vapeurs de bromure de méthyle peut produire un syndrome polyneuropathique sans manifestations centrales évidentes.

Parmi les séquelles tardives de l'intoxication on peut noter une broncho-pneumonie consécutive à de graves lésions pulmonaires, une insuffisance rénale avec anurie et une très importante faiblesse avec ou sans signes de paralysie. Généralement ces symptômes tendent à disparaître en quelques semaines à quelques mois. Toutefois, on a observé des déficits permanents généralement caractérisés par des troubles sensoriels, de la faiblesse, une baisse de l'acuité visuelle et des troubles de la démarche.

L'exposition au bromure de méthyle s'accompagne d'une augmentation du taux sanguin de bromure. Chez les fumigateurs, il existe une relation entre le nombre d'opérations auxquelles ils ont participé et le taux plasmatique moyen de bromure.

RESUMEN

1 Propiedades físicas y químicas y métodos analíticos

El bromuro metílico es un gas incoloro a la temperatura ambiente y a la presión atmosférica normal, con un punto de ebullición de 4 °C aproximadamente. Es más pesado que el aire y se licúa con facilidad por debajo de sus puntos críticos. Es inodoro, excepto en concentraciones altas, en las que tiene un olor parecido al cloroformo. No es inflamable en el aire, excepto en la gama de concentraciones del 10-16%, pero arde en oxígeno. El bromuro metílico es ligeramente soluble en agua, pero fácilmente soluble en otros disolventes corrientes. Puede penetrar a través de numerosas sustancias, como cemento, cuero, caucho y ciertos plásticos.

El bromuro metílico se hidroliza dando metanol y ácido bromhídrico en solución acuosa, con una velocidad de hidrólisis que depende del pH. Es un agente metilante eficaz que reacciona con las aminas y con los productos que contienen azufre. La mayoría de los metales son inertes ante el bromuro metílico seco y puro, pero se producen reacciones de superficie sobre el zinc, el estaño, el aluminio y el magnesio en presencia de impurezas o humedad. Se han señalado reacciones explosivas con el aluminio y el sulfóxido dimetílico.

El bromuro metílico se comercializa en forma de gas licuado. Las formulaciones par la fumigación del suelo contienen cloropicrina (2%) o acetato amílico (0,3%) como agentes de aviso. Otras formulaciones incluyen hasta el 70% de cloropicrina o de otros fumigantes o hidrocarburos como diluyentes inertes. Para la fumigación de mercancías se utiliza bromuro metílico al 100%.

Se han descrito métodos analíticos para la determinación del bromuro metílico en el aire, el agua, el suelo, los alimentos y los piensos. Entre los aparatos para la determinación directa del bromuro metílico en el aire, en condiciones prácticas, figuran los analizadores de gases por conductividad térmica, los tubos de detección colorimétrica, los analizadores en infrarrojos y los detectores por fotoionización. Se recomienda la cromatografía de gases (CG) con detección por captura de electrones (DCE) para las

mediciones corrientes, seguida a veces de la confirmación por espectrometría de masa (EM) en el laboratorio.

Para la determinación por CG del bromuro metílico en el agua se utilizan técnicas de purga y captura, así como de muestreo en el espacio superior. Se recomienda la extracción con acetona y agua seguida de la cromatografía capilar de gas del espacio superior con DCE para la determinación ordinaria del bromuro metílico en los alimentos. Teniendo en cuenta que una parte del bromuro metílico se convierte en bromuro en el suelo, los alimentos y los productos biológicos, se examinan también los métodos de determinación del bromuro. Entre los utilizados para esa determinación en distintas matrices figuran métodos colorimétricos, la espectroscopia de rayos X, la potenciometría, el análisis por activación neutrónica, la cromatografía de gases y la cromatografía de líquidos de alto rendimiento.

2 Fuentes de exposición humana y ambiental

Se estima que los océanos son la fuente más importante de bromuro metílico. La principal fuente antropogénica de bromuro metílico es la fumigación de suelos y locales. Los vehículos de motor que utilizan gasolina con plomo emiten una pequeña cantidad de bromuro metílico.

En 1990, el consumo mundial de bromuro metílico fue superior a 67 millones de kg, con un aumento del 46% respecto a 1984. Se fabrica corrientemente por reacción entre el metanol y el ácido bromhídrico y en algunos procedimientos es un coproducto que acompaña al tetrabromobisfenol A. El bromuro metílico se almacena y transporta habitualmente como gas licuado a presión en recipientes de acero.

El 77% aproximadamente del bromuro metílico fabricado se emplea para la fumigación del suelo, el 12% para la fumigación de cuarentena y de mercancías, el 5% para la fumigación de edificios y el 6% para obtener intermediarios químicos.

El gas se emplea como fumigante del suelo en los campos o los invernaderos en la lucha contra las plagas. Se aplica en forma de líquido antes de la plantación, por inyección en el suelo o por evaporación en recipientes colocados bajo las cubiertas de plástico, dejando que el producto se evapore *in situ* (método frío) o por

calentamiento (método caliente). Hay diferencias en los métodos utilizados en los distintos países. También es importante el tipo de cubierta de plástico empleada.

Las dosis de bromuro metílico que se han de aplicar dependen de las normas reglamentarias de los distintos países, el parásito vegetal que se ha de eliminar (tipo, amplitud de la infestación), el cultivo siguiente, el tipo de suelo y la cubierta de plástico empleada (tiempo de recubrimiento y tipo de plástico). El bromuro metílico se aplica habitualmente al suelo en concen-traciones comprendidas entre 50 y 100 g/m^2.

En la fumigación espacial se emplea el bromuro metílico para el tratamiento de productos agrícolas (por ej., alimentos, cereales, nueces, etc.) y la lucha contra las termitas y los roedores. Se emplean concentraciones de 16–30 g de bromuro metílico por m^3 para la mayor parte de los productos almacenados en naves y silos cerrados herméticamente y bajo cubiertas impermeables a los gases. La fumigación debe ir seguida de un periodo de aireación. También es importante la fumigación de hortalizas y frutas frescas en donde han de observarse reglamentos de cuarentena.

Entre los usos industriales del bromuro metílico figuran la síntesis orgánica, habitualmente como agente metilante, y el empleo como disolvente de baja temperatura de ebullición, por ejemplo, para la extracción de aceites de nueces, semillas y flores. La utilización del bromuro metílico como refrigerante y como agente general de extinción de incendios sólo tiene ahora impor-tancia histórica.

3 Transporte, distribución y transformación en el medio ambiente

El bromuro metílico se halla presente de modo natural en la atmósfera. Se suman a esa presencia las fuentes antropogénicas. Aunque una pequeña cantidad del bromuro metílico reacciona con el radical hidroxilo en la troposfera, parte del bromuro metílico pasa a la estratosfera por difusión ascendente. En esa capa adquiere importancia creciente la fotólisis del bromuro metílico, siendo el mecanismo predominante de desaparición en la estratosfera baja. El bromo activo reacciona con el ozono en la estratosfera y se cree que es en parte responsable de la destrucción de la capa de ozono.

En el suelo, el bromuro metílico se hidroliza parcialmente para dar ion bromuro. Después de la fumigación con bromuro metílico, el suelo puede ser lixiviado con agua para evitar que los iones bromuro formados sean captados por los vegetales plantados después en el suelo esterilizado. Este aumento de las concen-traciones de bromuro puede producir problemas cuando se utilizan aguas superficiales para la lixiviación. El bromuro metílico puede difundirse a través de las tuberías de polietileno de conducción de agua potable, si el suelo que las rodea ha sido fumigado con bromuro metílico.

En el suelo, el bromuro metílico puede difundirse hasta una profundidad de 0,8 m, en función del tipo de suelo, la dosis, el método de aplicación y la duración de la fumigación; la mayor concentración de bromuro metílico se alcanza en la parte superior del suelo. El transporte del gas se produce por flujo de masas y difusión molecular, pero también influyen los procesos de desaparición que se produzcan simultáneamente, como la absorción y la disolución, y los procesos de desaparición irreversible, como la hidrólisis. La cantidad de bromuro metílico convertido en bromuro depende principalmente del contenido en materias orgánicas del suelo. El bromuro producido es principalmente hidrosoluble y puede ser captado por las plantas o desplazado a niveles inferiores del suelo por lixiviación con agua.

En las plantas, la cantidad de bromuro acumulado depende de distintos factores, como la concentración, el tiempo de exposición, la tasa de aireación, las propiedades físicas y químicas del suelo, las tendencias climáticas (temperatura y pluviosidad), las especies vegetales y el tipo de tejido de las plantas. En particular las hortalizas de hoja, como la lechuga y la espinaca, pueden captar cantidades relativamente altas de ion bromuro sin síntomas fitotóxicos. Por el contrario, otros cultivos, como los claveles, los planteles de cítricos, el algodón, el apio, los pimientos y las cebollas, son especialmente sensibles a la fumigación con bromuro metílico.

El bromuro metílico y sus productos de reacción, entre los cuales sólo se ha considerado hasta ahora el bromuro, pueden entrar en la cadena alimentaria de dos modos: consumo de alimentos cultivados en invernaderos o en campos fumigados antes de la plantación o alimentación con productos fumigados con bromuro

metílico en el curso del almacenamiento. En determinadas concentraciones, el bromuro puede ser peligroso para la salud; se han indicado niveles de tolerancia para el bromuro contenido en los alimentos. No se han investigado los niveles de otros productos de reacción.

El bromuro metílico se degrada en el suelo por hidrólisis y descomposición microbiana. La constante de hidrólisis varía con la temperatura y el pH, y aumenta con la luz.

El coeficiente de partición octanol/agua (log P_{ow}) del bromuro metílico es de 1,19, lo que sugiere la existencia de una bioacumulación baja.

El bromuro metílico que no se ha degradado en el curso de la fumigación pasa a la troposfera y por difusión ascendente a la estratosfera. No parece que haya un gradiente vertical importante del bromuro metílico en la troposfera, pero las concentraciones disminuyen con rapidez en la estratosfera baja por acción de la fotólisis.

4 Niveles ambientales y exposición humana

Las concentraciones de bromuro metílico, medidas en el aire en zonas sin habitar, varían entre 40 y 100 ng/m^3 (10 a 26 pptv), siendo los valores en el hemisferio Norte superiores a los del hemisferio Sur. La mayoría de las concentraciones se hallan en la gama de 9-15 pptv. En algunos estudios se han observado diferencias estacionales. En las zonas urbanas e industriales, las concentraciones son mucho mayores, con valores medios de hasta 800 ng/m^3, llegando a veces hasta 4 μg de bromuro metílico por m^3. En el curso de la fumigación y la aireación, las concentraciones de bromuro metílico son apreciablemente más altas cerca de los campos y los invernaderos, habiéndose medido valores de 1-4 mg/m^3 en un estudio a distancias de hasta 20 m de un invernadero, algunas horas después de la inyección en el suelo; cuatro días más tarde se observó la décima parte de ese valor.

La concentración de bromuro metílico en una muestra de agua del mar de superficie fue de 140 ng/litro. En muestras de agua costera cerca del mar del Norte, el valor medio de las concentraciones de ion bromuro fue de 18,4 mg/litro; la concentración de ion bromuro en los ríos de tierra adentro fue

mucho más baja, excepto en las regiones donde se practicaba la fumigación con bromuro metílico o en las zonas de contaminación industrial. En el agua de drenaje de un invernadero de los Países Bajos se señalaron concentraciones de 9,3 mg de bromuro metílico/litro y de 72 mg de ion bromuro/litro. En el agua evacuada de un invernadero belga se registró un valor de 280 mg de bromuro/litro después de la fumigación.

El contenido de bromuro natural del suelo depende del tipo de suelo, pero suele ser inferior a 10 mg/kg. La presencia de restos de bromuro en el suelo fumigado depende del tratamiento, la dosis, el tipo de suelo, la cantidad de lluvia o de agua de lixiviación y la temperatura.

Las concentraciones de bromuro metílico o bromuro pueden ser altas en los alimentos que se han cultivado en suelos tratados previamente con bromuro metílico o que se han fumigado después de la recolección.

En hortalizas frescas cultivadas en suelos previamente fumigados con bromuro metílico se han observado excepcional-mente concentraciones de bromuro que rebasaban el nivel autori-zado de residuos. En algunos países no se permite cultivar hortalizas en los suelos tratados.

El bromuro metílico se utiliza ampliamente para la fumigación de productos alimenticios después de la recolección, como trigo y cereales, especias, nueces, frutas frescas y desecadas, y tabaco. Las concentraciones de bromuro metílico suelen descender con rapidez después de la aireación y no se detectan residuos al cabo de unas semanas. Algunos alimentos, como las nueces, las semillas y productos grasos como el queso, tienden a retener el bromuro metílico y el bromuro inorgánico.

Las personas pueden estar expuestas al fumigante y a restos de ion bromuro. También existe el riesgo de que haya bromuro metílico o un aumento del contenido de bromuro en el agua de pozos situados cerca de lugares en donde se ha fumigado bromuro metílico.

Las personas que viven cerca de campos, invernaderos o almacenes fumigados con bromuro metílico pueden estar expuestos al gas. Los seres humanos pueden también correr peligro si accidental o deliberadamente penetran en locales que han sido fumigados para erradicar plagas antes de declararlos seguros.

La exposición profesional al bromuro metílico es el riesgo más probable de los operarios en el curso de la fabricación, el llenado y la fumigación. Dadas las medidas de seguridad aplicadas estrictamente en las fábricas, sólo se considera actualmente como grupo de alto riesgo a los fumigadores. Los fumigadores que realizan el tratamiento de edificios pueden tener una exposición muy superior al valor umbral límite (VUL) después de 24 horas de aireación (80-2000 mg/m^3). Sin embargo, los operarios convenientemente capacitados utilizarán equipo protector apropiado. Los obreros que trabajan en el campo durante la fumigación del suelo pueden estar expuestos durante periodos más prolongados a dosis pasajeras de bromuro metílico. Dada la naturaleza de la fumigación de los invernaderos, los operarios pueden también encontrar concentraciones más altas (100-1200 mg/m^3). Así pues, la gestión del riesgo provocado por los distintos aspectos de la fumigación exige medidas de seguridad estrictas y el empleo de equipo protector. Pese a ello se producirán todavía casos aislados de sobreexposición accidental.

5 Cinética y metabolismo

Los estudios de inhalación efectuados en ratas, perros sabuesos y seres humanos han mostrado la absorción rápida del bromuro de metilo por los pulmones. También se absorbe con rapidez en las ratas después de la administración oral.

Tras la absorción, el bromuro metílico o sus metabolitos se distribuyen con rapidez en numerosos tejidos, comprendidos los pulmones, las glándulas suprarrenales, los riñones, el hígado, los cornetes nasales, el cerebro, los testículos y el tejido adiposo. En un estudio de inhalación efectuado en ratas, la concentración tisular de bromuro metílico alcanzó el valor máximo una hora después de la exposición, pero descendió con rapidez, no encontrándose indicios 48 horas más tarde. Todavía no se ha esclarecido el metabolismo del bromuro metílico inhalado, pero parece que interviene el glutatión.

Se ha observado la metilación de proteínas y lípidos en los tejidos de varias especies, incluidos los seres humanos, expuestos a través de la inhalación. También se han detectado aductos de ADN metilado después de la exposición *in vivo* e *in vitro* de roedores o células de roedores.

En los estudios de inhalación con bromuro metílico marcado con [^{14}C], la expiración de $^{14}CO_2$ fue la principal vía de eliminación de ^{14}C. Por la orina se eliminó una cantidad menor de ^{14}C. Tras la administración oral de bromuro metílico, la excreción urinaria fue la principal vía de eliminación del ^{14}C.

El sistema nervioso central es un importante destinatario del bromuro metílico. En la neurotoxicidad provocada por el bromuro metílico pueden intervenir modificaciones del contenido de monoaminas y aminoácidos y tal vez de catecolaminas.

6 Efectos en los seres vivos del medio ambiente

El bromuro metílico se utiliza comercialmente en la lucha contra los nematodos, las malas hierbas y los hongos transmitidos por el suelo que provocan trastornos tales como el resecamiento, la putrefacción de la copa o las raíces y el marchitado.

Se han realizado escasos estudios sobre los efectos del bromuro metílico en los seres acuáticos, pues el propio bromuro metílico sólo es ligeramente soluble en agua. Los valores de la CL_{50} van de un valor a las cuatro horas de 17 mg/litro para *Cyprinus carpio* L. a otro a las 48 horas de 1,2 mg/litro para *Poecilia reticulata*. En concentraciones letales, las lesiones de las agallas y el epitelio oral son la causa probable de la muerte.

El ion bromuro se forma a partir del bromuro metílico después de la fumigación y se halla en el agua tras la lixiviación. Se observó una toxicidad aguda por iones bromuro en distintos seres de agua dulce en concentraciones comprendidas entre 44 y 5800 mg de Br^-/litro; la concentración de efecto no observado (NOEC) en las pruebas de larga duración varió entre 7,8 y 250 mg de Br^-/litro. Los iones bromuro produjeron una marcada alteración de la reproducción de crustáceos y peces.

El bromuro metílico puede aplicarse directamente como fumigante a las semillas o los esquejes de las plantas o a los productos alimenticios después de la recolección para la desinfestación en el curso del transporte y el almacenamiento. Puede producirse el retraso de la germinación o la pérdida de la capacidad germinativa si la humedad o la temperatura son demasiado altas.

Algunos cultivos, en particular las hortalizas de hoja, son sensibles a la fumigación con bromuro metílico debido a la presencia de bromuro en exceso en el suelo o indirectamente por los efectos en la microflora del suelo. El bromuro metílico tiene a veces un efecto positivo sobre las plantas, favoreciendo su crecimiento y el rendimiento de los cultivos.

La fumigación con bromuro metílico erradica no sólo los seres vivos a los que se aplica sino también una parte de la flora del suelo, los gastrópodos, los arácnidos y los protozoos.

El bromuro metílico se utiliza a menudo de preferencia a otros insecticidas por su capacidad para penetrar con rapidez y profundidad en productos no envasados y en los suelos. Las dosis de bromuro de metilo utilizado como fumigante en almacenes se sitúan sobre todo entre 16 y 100 g/m^3 durante 2-3 días, dependiendo la dosis de la temperatura. Para matar los huevos y las pupas se necesita una dosis más alta que en el caso de los insectos adultos. Existen variaciones en la tolerancia de las distintas especies y fases de insectos y entre las distintas estirpes del mismo insecto.

No existen datos sobre los efectos directos del bromuro metílico en las aves y los mamíferos silvestres.

7 Efectos en los animales de experimentación

Los estudios de inhalación realizados en varias especies de mamíferos han mostrado que existen claras diferencias relacionadas con la especie y el sexo en lo que se refiere a la susceptibilidad al bromuro metílico. No se observó una respuesta dosis-mortalidad muy marcada en ninguna de las especies animales ensayadas.

Las manifestaciones neurológicas son los principales signos clínicos de toxicidad en las ratas y los ratones y, en concentraciones más altas, se ha observado también la irritación de las mucosas.

Entre las manifestaciones neurológicas destacan los espasmos y la parálisis. Con dosis más altas varios autores han señalado modificaciones de la actividad locomotriz, disfunción de los medios periféricos, cambios del ritmo circadiano y aversión gustativa condicionada.

Se han descrito lesiones histopatológicas en el cerebro, el riñón, la mucosa nasal, el corazón, las glándulas suprarrenales, el hígado y

los testículos de ratas y ratones expuestos a distintas concentraciones de bromuro metílico.

Las células de soporte olfativas y las sensoriales maduras sufren lesiones por la exposición a corto plazo al bromuro metílico, pero la reparación y la recuperación son rápidas.

Los estudios de inhalación de larga duración (hasta 2 años) en ratas mostraron lesiones de la mucosa nasal y el miocardio. En un estudio análogo de larga duración en ratones se observaron los efectos tóxicos primarios en el cerebro, el corazón y la mucosa nasal. En ninguna de ambas especies se registraron signos de carcinogenicidad.

La administración oral de 50 mg de bromuro metílico/kg de peso corporal a ratas durante un periodo de hasta 25 semanas produjo inflamación e hiperplasia intensa del epitelio del antro cardial. Tras un periodo de recuperación postexposición, la principal lesión observada fue la fibrosis del antro cardial. En la rata tratada diariamente durante 25 semanas se observó un carcinoma inicial del antro cardial.

Los ratones B6C3F y las ratas F344 expuestos a dosis de hasta 467 mg de bromuro metílico/m^3 durante 13 semanas mostraron cambios ligeros de la morfología del esperma sin que se afectara la duración del ciclo estral.

La exposición por inhalación a dosis de hasta 350 mg de bromuro metílico/m^3 no produjo ningún efecto digno de mención sobre el crecimiento, los procesos reproductivos y las crías de dos generaciones consecutivas de ratas CD Sprague-Dawley. Los índices de fecundidad de machos y hembras se redujeron con dos niveles máximos de concentraciones en la camada F_{2B} de la generación F_1.

En los estudios sobre la toxicología del desarrollo efectuados en conejos blancos de Nueva Zelandia, la exposición a 311 mg de bromuro metílico/m^3 (6 h/día; días 7-19 de la gestación) mostró una toxicidad materna moderada a intensa. Los efectos en el desarrollo observados con dosis tóxicas para la madre consistieron en disminución del peso del feto, aumento de la incidencia de variaciones óseas ligeras y presencia de malformaciones (principalmente ausencia de la vesícula biliar o del lóbulo caudal del pulmón). Sin embargo, con dosis de 272 mg/m^3 la toxicidad materna fue menos marcada y no se produjeron efectos embriotóxicos.

No se observaron efectos maternos, embrionarios o fetales adversos en conejos expuestos a 78 ó 156 mg de bromuro metílico/m^3. En conejos blancos de Nueva Zelandia se indicó un nivel sin efectos observados (NOEL) de 156 mg de bromuro metílico/m^3 en lo que respecta a la toxicidad materna y del desarrollo.

Se ha observado que el bromuro metílico es mutagénico en varios sistemas de ensayo *in vitro* e *in vivo*. Provoca mutaciones letales recesivas ligadas al sexo en *Drosophila melanogaster* y mutaciones en células de mamífero cultivadas. No induce la síntesis no programada del ADN ni la transformación celular en células de mamífero cultivadas. En ratones a los que se administró bromuro metílico por distintas vías se observó la metilación del ADN en el hígado y el bazo. Se indujo la formación de micronúcleos en las células de la médula ósea y de la sangre periférica de ratones y ratas.

Se desconoce el mecanismo de la toxicidad del bromuro metílico.

8 Efectos en la especie humana

La exposición humana al bromuro metílico puede producirse por inhalación del gas o por contacto con el líquido. También se produce exposición por ingestión de agua de bebida contaminada con agua de lixiviación.

Un estudio en la especie humana con testigos mostró que la captación del producto después de la exposición por inhalación es del 50% aproximadamente de la dosis administrada.

El bromuro metílico es nocivo para el sistema nervioso, los pulmones, la mucosa nasal, los riñones, los ojos y la piel. Entre los efectos en el sistema nervioso central figuran la visión enturbiada, la confusión mental, la pérdida de sensibilidad, el temblor y los defectos del habla. La exposición tópica puede provocar irritación cutánea, quemaduras y lesiones oculares.

La exposición a altas concentraciones de bromuro metílico causa edema pulmonar. La depresión del sistema nervioso central con parálisis respiratoria e insuficiencia respiratoria es a menudo la causa inmediata de la muerte, que va precedida de convulsiones y coma.

Se han observado distintos signos y síntomas neuropsiquiátricos en el curso de las intoxicaciones agudas y prolongadas producidas por bromuro metílico. Las exposiciones de corta duración a dosis bajas de vapores han producido un síndrome de polineuropatía con manifestaciones centrales patentes.

Entre las secuelas tardías figuran la bronconeumonía consecutiva a lesiones pulmonares graves, la insuficiencia renal con anuria y la debilidad extrema, con o sin signos de parálisis. Por lo general esos síntomas tienden a remitir después de un periodo de unas semanas o meses. Sin embargo, se han observado deficiencias sin recuperación, caracterizadas habitualmente por trastornos sensoriales, debilidad, alteraciones del carácter y enturbiamiento de la visión.

La exposición al bromuro metílico va acompañada de un aumento de la concentración de bromuro en la sangre. En los fumigadores se observa una relación entre el número de aplicaciones del gas y la concentración plasmática media de bromuro.

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