Fact Sheet Date: March 12, 1998

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: Bromomethane (methyl bromide) **CAS REGISTRY NUMBER:** 74-83-9

AMBIENT WATER QUALITY VALUE: 5 ug/L

BASIS: Surface Water: Principal Organic Contaminant Classes

Groundwater: Former Reference to 10 NYCRR Subpart 5-1 Principal Organic Contaminant (POC) General Maximum Contaminant Level (MCL)

SUMMARY OF INFORMATION

Methyl bromide (CH_3Br) or bromomethane (MW 94.94) is used primarily as a fumigant in soil to control fungi, nematodes and weeds (65%) and in the space fumigation of food commodities and storage facilities (15%) (USEPA, 1989).

Pharmacokinetics

Methyl bromide is absorbed and distributed quickly and readily metabolized. Jaskot et. al. (1988) exposed rats to 55 ppm ^{14}C methyl bromide by inhalation for 3 minutes. ^{14}C was detected immediately in liver, lung, kidney and other major organs up to 32 hours post exposure. By analogy with methyl chloride reactions, methyl bromide is assumed to react with sulfhydryl groups, such as glutathione to form S-methyl glutathione (Medinsky et. al. 1985). Jaskot et al. (1988) found decreases in GSH reductase and GSH-S transferase compared to controls in the liver of rats exposed by inhalation for 5 to 10 days to 30 ppm methyl bromide. Davenport et al. (1992) found GSH depletion and GST inhibition in the brain of exposed rats.

Methyl bromide interacts in vivo by methylation of some macromolecules. Iwasaki (1988a) measured S-methyl-cysteine as the hemoglobin adduct in blood from methyl-bromide-exposed ICR mice. Groups of mice were exposed by inhalation to 80 ppm or 180 ppm

methyl bromide for 8 hours after which methyl cysteine in blood was determined. The quantity of methyl cysteine adducts showed a linear dose-response with exposure concentration (Iwasaki, 1988b). Xu et al. (1990) found binding of methyl bromide to hemoglobin in both sexes of F344 rats after oral and inhalation exposure. Effects were greater after inhalation than oral exposure.

DNA adducts (^{14}C-labelled) were detected in the liver, lung, stomach and forestomach of male and female F344 rats exposed to ^{14}C-methyl bromide by oral or inhalation routes. The highest levels of methylated guanines, especially those of $^{14}C^{6}O$-methyl guanine were found in the stomach and forestomach of the rats, demonstrating the DNA alkylating potential of methyl bromide (Gansewendt et al., 1991). Calf thymus DNA incubated in vitro with methyl bromide produced the methylated DNA bases 1-methyladenine, 7-methylguanine, 3-methyladenine and 3-methylcytosine (Starratt and Bond, 1988) after hydrolysis and chromatographic separation.

The major routes of clearance of inhaled $^{14}C\text{-}CH_3Br$ were by exhalation of $^{14}CO_2$ (43%) and urinary excretion of a ^{14}C metabolite (21%). Sixty-six percent of the total inhaled $^{14}C\text{-}CH_3Br$ was cleared by 32 hours post-exposure (Jaskot et al. 1988, Bond et al., 1985). Elimination via feces was minor. The persistence of 25% of the original dose in the tissues and carcass 32 hours post exposure, elimination of ^{14}C as $^{14}CO_2$ and incorporation into macromobcules suggests a radiolabelled metabolite that enters the one-carbon pool (Jaskot et al., 1988). In rats given a single oral dose of ^{14}C-methyl bromide only about 3% of the label was excreted in the feces (Medinsky et al., 1984).

Epidemiology

Symptoms of acute human exposure to methyl bromide by inhalation are predominantly neurological, including myoclonus, convulsion, neuropathy and death (Dempsey et al., 1992; Uncini et al., 1990) with irritation of the skin and pulmonary edema forming the acute syndrome (ATSDR, 1992). Hustinx et al. (1993) reported on nine cases of exposure during fumigation of a greenhouse. Measurements of methyl bromide at the site revealed concentrations in excess of 200 ppm methyl bromide. All suffered headaches, nausea, dizziness, and vomiting. Two workers developed twitching of all limbs (myoclonus), seizures and coma. X-rays showed lung infiltration and pleural effusion.

No data were found on the effects of oral exposure in humans (ATSDR, 1992).

Clinical manifestations of chronic methyl bromide poisoning seem to overlap to some extent with those of acute toxicity, such as peripheral neuropathy. The main chronic symptoms are nervous system disorders, that is headaches, dizziness, unsteadiness in walking and symptoms of peripheral neuropathy such as "creepy" feelings and paresthesia. Also included are sensory disorders, such as eye and nose symptoms; psychiatric symptoms, such as sleeping difficulties, impaired memory and concentration difficulties; and cardiorespiratory symptoms (Kishi et al., 1991; Anger et al. 1986).

Kishi et al. (1991) studied a group of 56 workers employed in a manufacturing process making methyl bromide and workers previously exposed to methyl bromide in the same plant but not now engaged in methyl bromide manufacture. Duration of exposure was 1 to 25 years. Breathing zone mean concentrations of methyl bromide for the previous 10 years were under 1 ppm. Maximum concentrations sometimes exceeded 5 ppm, however. The control group was chosen from age-matched workers of the Japan National Railway, reportedly never exposed to chemicals. Compared to controls, methyl bromide workers had statistically higher irritation symptoms such as runny nose or itching and burning of the hands. The exposed group was characterized by statistically greater incidence of symptoms of fatigue, dizziness, nightmares, numbness or tingling in the fingers or soles of the feet and dry and rough hands.

Acute Toxicity

Oral LD_{50} values reported for exposure to methyl bromide have varied from 60 mg/kg body weight for rabbits to 214 mg/kg body weight for rats (USEPA, 1989). Significant decreases in body, lung and liver weight, abnormal clinical signs and increased mortality were observed in mice exposed to 1200 ppm (1 hr. LC_{50}) (Alexeeff et al. 1985). Acute inhalation exposure of animals to methyl bromide can result in marked lung irritation (edema, hemorrhagic lesions), which may lead to respiratory impairment (Greenberg, 1971).

In mice and rats exposed to 160 ppm methyl bromide by inhalation for 2-6 weeks, primary target organs were brain, kidney, nasal cavity, heart, adrenal gland, liver and testis. Neuronal necrosis occurred in the cerebral cortex, hippocampus and thalamus in rats. In mice, necrosis occurred in the cerebellum (Eustis et al., 1988). Decreases in levels of neurotransmitters occurred in the brain of rats after acute exposure (Honma, 1987). Also evident were degeneration of the olefactory epithelium, myocardial degeneration and testicular degeneration of mice and rats exposed to 160 ppm for 2-6 weeks. Nephrosis occurred in all mice (Eustis et al., 1988).

At 66 ppm 7.5 hr/d, 5 d/wk, rats and guinea pigs showed essentially no response up to 6 months. However, rabbits and monkeys developed paralysis with less than 68 exposures (Irish et al., 1940).

Chronic Toxicity

The effects of long-term exposure of animals to methyl bromide have been studied in three long-term assays including two routes, oral and inhalation.

Reuzel et al. (1991) examined the toxicity of methyl bromide in male and female Wistar rats exposed by inhalation to 0, 3, 30 or 90 ppm methyl bromide 6 hr/d, 5 days a week for 29 months. Body weights in the 90 ppm group in both males and females were lower than those of controls throughout the study. Toxic effects were seen in the kidney, brain, heart, olefactory epithelium, esophagus and forestomach. The incidence of cartilaginous

metaplasia was significally increased in males of the 90 ppm group and in females of the 3 ppm group. On the basis of hyperkeratosis of the esophagus and cartilaginous metaplasia of the heart, a NOEL of 30 ppm is appropriate for the male rats. A LOAEL of 3 ppm for females can be based on the response of cartilaginous metaplasia. A decrease in absolute brain weights may correspond to neurological effects seen in other studies.

In an inhalation study, mice were exposed to 0, 10, 33 or 100 ppm methyl bromide 6 hr/d 5 d/wk for 103 weeks. Clinical signs indicative of neurotoxicity including leg tremors, abnormal posture, tachypnea and hind leg paralysis were evident in 100 ppm exposed mice and persisted although exposure was halted at 20 weeks due to excessive mortality. Degenerative changes in the cerebellum and cerebrum as well as myocardial degeneration occurred in males and females at 100 ppm. An increase of sternal dysplasia and olefactory epithelial necrosis at 100 ppm was seen. The NOAEL for this study is 33 ppm for males and females (NTP, 1992).

Mitsumori et al. (1990) fed male and female rats for 104 weeks a diet fumigated with methyl bromide. The diets contained 80, 200 or 500 ppm total bromine plus a basal diet for controls. The mean intake of total bromine was 2.67, 6.77, 16.9 mg/kg bodyweight in males and 3.23, 8.29, 20.2 mg/kg bodyweight in females. No effects on behavior or mortality were seen or significant changes in weights of organs. No proliferative lesions of the stomach like those in Danse (1984) were seen. The mean bodyweight in males and females exposed to 500 ppm was significantly lower. The authors cited a maximum NOAEL of 200 ppm bromine (6.77 mg/kg bodyweight).

Rats given daily oral doses of 0, 0.4, 2, 10 or 50 mg/kg methyl bromide by gavage (5 d/wk for 90 days) developed severe hyperplasia of the stratified squamous epithelium in the forestomach at a dose of 50 mg/kg/day and slight epithelial hyperplasia at a dose of 10 mg/kg/d (Danse, 1984). At the 50 mg/kg/d dose level, decreased food consumption, bodyweight gain and anemia were observed in male rats, as well as decreased hemosiderosis and increased hematpoeisis in the spleen. No adverse effects were observed at 0.4 or 2 mg/kg. The NOAEL is 2 mg/kg.

Genotoxicity

Methyl bromide has produced positive results in a number of mutagenicity test systems, both in vitro and in vivo (ATSDR, 1992). The DNA alkylating potential of methyl bromide has been established in mouse liver and spleen cells and rat hemoglobin (Gansewendt et al. 1990, 1991; Djalali-Behzad et al. 1981).

The ability of methyl bromide to cause gene mutations has been seen in E.coli strains Sd-4 and WP2hcr, S. typhimurium TA100 and TA1535, and Klebsiella (Djalali-Behzad et al., 1981; Moriya et al. 1983, Kramers et al., 1985, as cited in ATSDR, 1992) as well as in the mouse and Drosophila melanogaster (sex-linked recessive lethal) (Kramers et al., 1985).

In mammalian systems, sister chromatid exchange in human lymphocytes (Tucker et al.,

1986) and micronuclei induction in rat and mouse bone marrow have been seen (Ikawa et al. 1986). Sperm abnormalities have been seen in mice exposed to 10, 40 and 120 ppm and rats exposed to 30, 60, and 120 ppm methyl bromide by inhalation in 13-week National Toxicology Program studies on male reproductive endpoints (Morrissey et al., 1988) as a result of exposure to methyl bromide.

Carcinogenicity

Evidence for carcinogenic effects of exposure to methyl bromide in humans has not been found.

Assays in rats and mice indicate no carcinogenic activity relative to controls. Reuzel et al. (1991) in a well-designed study examined the toxicity and carcinogenicity of methyl bromide in male and female Wistar rats exposed by inhalation to 0, 3, 30 or 90 ppm methyl bromide 6 hr/d, 5 d/wk for 29 months. Body weights in the 90 ppm group in both males and females were lower than those of the controls throughout the study. Toxic effects were seen in the kidney, heart, brain, olefactory epithelium, esophagus and forestomach. No differences in site, type and incidence of tumors were found between the groups at any of the interim kills. There was a lower incidence of total tumors in the 90 ppm group than in the controls, due to decreased mean survival time. The authors concluded that the data on site, type and incidence of tumors in exposure groups did not indicate carcinogenic activity of methyl bromide (Reuzel et al., 1991).

Groups of $B6C3F_1$ mice of each sex were exposed to methyl bromide by inhalation at 0, 10, 33 or 100 ppm 6 hr/d 5 d/wk for 103 weeks. In mice exposed to 100 ppm, early mortality was high, exposure was discontinued and the remaining mice allowed to live to term. There was an increase in the incidence of nonneoplastic lesions in the brain, heart, bone (sternum) and nose. There was no indication of carcinogenic activity of methyl bromide in male or female $B6C3F_1$ mice exposed to 10, 33 or 100 ppm (NTP, 1992).

Methyl bromide has been reported not to have carcinogenic activity in rats after oral exposure. Squamous cell carcinomas were found in the forestomach of 13 out of 20 rats exposed by gavage to 50 mg/kg methyl bromide for 90 days by Boorman et al. (1986) and Danse et al. (1984). After discontinuation of methyl bromide administration nearly all lesions regressed, suggesting they were not malignant. Reevaluation of the histological sides led NTP scientists to conclude that the lesions were hyperplastic and not carcinomas. Mitsumori et al. (1990) exposed male and female F344 rats to diets fumigated with methyl bromide containing 80, 200 or 500 ppm total bromine residues for 104 weeks. There were no indications of carcinogenic effects in any dose group compared to controls.

DERIVATION OF VALUES

No evidence exists that methyl bromide is a carcinogen in animals, despite considerable evidence that it has genotoxic potential. A chronic toxicity endpoint is, therefore, appropriate for a water value based on human health protection. The appropriate dose

route is oral rather than inhalation and oral data are appropriate for a value based on consumption. No oral human data exists, therefore, an oral animal study will be used.

Mitsumori et al. (1990) is a long-term feeding study in rats but doses are measured in terms of total bromine that may not represent ingestion of methyl bromide. Also, there is a lack of concurrence of effects with two other oral studies.

Danse et al. (1984) is a well-quantified oral study, although the length of exposure is less than chronic. USEPA (1989) determined the NOAEL for this study to be 2 mg/kg/day (IRIS, 1992) and the Department concurs. USEPA (1989) calculated an oral reference dose equivalent to an acceptable daily intake using the NOAEL of 2 mg/kg corrected to a time-weighted average (2 x 5/7 da/wk) of 1.4 mg/kg/day, an uncertainty factor of 100 for inter- and intra-species variation and 10 for use of less than a lifetime study. The Department concurs with these derivations, that are consistent with 6 NYCRR 702.5. Based on a 70 kg adult, 2 L water consumption, and 20% relative source contribution a water quality value of 10 ug/L can be calculated (6 NYCRR 702.5).

Surface Water

Methyl bromide is a principal organic contaminant (Class 1). Regulations [6 NYCRR 702.2(b)] require that the value be the most stringent of the values derived using the procedures found in sections 702.3 through 702.7. The principal organic contaminant class value of 5 ug/L (702.3(b)) represents the most stringent value that can be derived for methyl bromide. Therefore, the ambient surface water quality value for methyl bromide is 5 ug/L.

Groundwater

The principal organic contaminant (POC) groundwater standard of 5 ug/L (6 NYCRR 703.5) applies to methyl bromide. This standard became effective on January 9, 1989 by inclusion by reference to 10 NYCRR Subpart 5-1 standards. The basis and derivation of the POC standard are described in a separate fact sheet.

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SEARCH STRATEGY

Integrated Risk Information System (IRIS) - Searched 12/92.

Registry of Toxic Effects of Chemical Substances (RTECS) - Searched 12/92.

Chemical Carcinogenesis Research Information System (CCRIS) - Searched 12/92.

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National Technical Information Service (NTIS) - Searched by New York State Library 9/93.

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