TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO
EPA/600/8-88/022		PB88-179478/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
Health Effects Assessment for Bromomethane	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22

15 SUPPLEMENTARY NOTES

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
Public	Unclassified	
	20. SECURITY CLASS *(This page)* Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

T - NO
H - NO

EPA/600/8-88/022
June, 1987

HEALTH EFFECTS ASSESSMENT FOR BROMOMETHANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with bromomethane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to June, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-051. NTIS PB81-117624.

U.S. EPA. 1982. Errata for Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1986a. Health and Environmental Effects Profile for Methyl Bromide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for bromomethane. Online. (Verification date 09/29/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

RfD_{SO} (1 mg/day) and RfD_O (0.1 mg/day) values for bromomethane were based on a NOEL of 2 mg/kg 5 days/weeks in a 13-week gavage study using rats (Danse et al., 1984). Hyperplasia of the forestomach, anemia and atalectosis of the lung occurred at higher levels. The RfD_O is consistent with an RfD derived in another recent U.S. EPA (1986a) analysis.

RfD_{SI} (5 mg/day) and RfD_I (0.5 mg/day) values were based on a NOEL of 7.6 mg/kg/day associated with exposure to 65 mg/m^3 in rabbits (Irish et al., 1940). Rabbits appeared to be the most sensitive of several species tested. A CS of 27.9 was based on paralysis in rabbits at 130 mg/m^3 in the same study (Irish et al., 1940; U.S. EPA, 1986a).

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
FEL	Frank-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term-effect level
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of bromomethane are presented in Table 1-1. Synonyms for bromomethane are methyl bromide, monobromomethane, Terabol® and Embafume®.

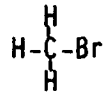
In the troposphere, the main route of bromomethane degradation is reaction with hydroxyl radicals (Robbins, 1976), and the estimated residence time of bromomethane as a result of this reaction is ~1 year (Howard and Evenson, 1976). Based on the tropospheric lifetime of bromomethane, ~3% of this compound can be expected to reach the stratosphere where it can undergo direct photolysis (Dilling, 1982; Robbins, 1976).

Volatilization of bromomethane from water is likely to be the dominant removal mechanism from aquatic systems. The average half-life for the loss of bromomethane from a surface drainage ditch (0.8 m deep) under environmental conditions at 11°C was 6.6 hours Wegman et al. (1981). Other volatilization half-lives listed in Table 1-1 were estimated using a calculated re-aeration rate ratio and typical oxyten re-aeration rates from typical water bodies. Hydrolysis may be a significant removal process in water at pH 7 since the hydrolytic half-life at 20-25°C is ~20-38 days (Ehrenberg et al., 1974; Mabey and Mill, 1978).

Brown and Rolston (1980) used soil column tests with a variety of soils to conclude that most bromomethane used in soil fumigation enters the atmosphere, although a small amount of bromomethane is chemically transformed into bromine ions. The half-life of bromomethane in soil listed in Table 1-1 is based on its volatilization half-life derived from a soil chemical screening model. There is a potential for leaching of this chemical into groundwater, as indicated by significant leaching in fumigated greenhouse soils (Wegman et al., 1981; Vanachter et al., 1981).

TABLE 1-1

Selected Physical and Chemical Properties and Environmental Fate of Bromomethane

Property	Value	Reference
CAS number	74-83-9	
Chemical class:	brominated aliphatic hydrocarbon	
Molecular weight:	94.95	
Chemical structure:		
Melting point:	-93.7°C	Stenger, 1978
Boiling point:	3.56°C	Stenger, 1978
Vapor pressure:	1420 mm Hg	Stenger, 1978
Water solubility:	17,500 mg/ℓ at 20°C	Stenger, 1978
Log octanol/water partition coefficient:	1.19	Hansch and Leo, 1985
or		
Bioconcentration factor:	3-5 (calculated)	Lyman et al., 1982
Soil adsorption coefficient:	1.0 loamy sandy 10.0 loam 9.5 peaty clay soil	Daelmans and Siebering, 1977
Half-lives:		
Air	0.5-1.0 year (estimated)	Davis et al., 1976 Makide and Rowland, 1981; Singh et al., 1981
Water	6.6. hours (0.8 m deep) 1 day (river), estimated 3.9 days (lake,) estimated 5 days (pond), estimated	Wegman et al., 1981 Mabey et al., 1981 Mabey et al., 1981 Mabey et al., 1981
Soil	0.2 days (when applied 1 cm deep), estimated 0.5 days (when applied 10 cm deep), estimated	Jury et al., 1984 Jury et al., 1984

2. ABSORPTION

2.1. ORAL

Approximately 97% of a single oral dose of 250 μmol/kg of ^{14}C-bromomethane administered in corn oil was absorbed from the gastrointestinal tract of rats (Medinsky et al., 1984). By 72 hours after a single oral dose, <3% of the administered ^{14}C-bromomethane had been recovered from the feces. Rapid absorption is implied by the excretion of ~67% of the administered radioactivity (~29% in the expired air and ~38% in the urine) within the first 20 hours after dosing.

2.2. INHALATION

Medinsky et al. (1985) exposed rats for 6 hours to atmospheric concentrations of ^{14}C-bromomethane of 50, 300, 5700 or 10,400 nmol/ℓ (4.7, 28, 541 or 987 mg/m^3) in a head-only exposure chamber. Respiratory volumes were measured and, when combined with measured concentrations, permitted accurate estimation of the quantity of ^{14}C-bromomethane inhaled. The rats were killed immediately following exposure and the amount of radioactivity retained in the carcass was measured. From the data, the authors determined that the percentages of inhaled ^{14}C-bromomethane absorbed at 50, 300, 5700 and 10,400 nmol/ℓ were 48, 48, 38 and 27%, respectively. The authors estimated a first-order rate constant for inhalation absorption for bromomethane of 1.6 kg/hour for concentrations up to 6000 nmol/ℓ. They suggested that saturation of a metabolic pathway for the elimination of bromomethane may have been responsible for the apparent reduction in absorption (exposed as percent of inhaled "dose") at the highest concentration in this experiment. Expressed as μmol/kg body weight equivalent amounts of ^{14}C-bromomethane were absorbed at 5700 and 10,400 nmol/ℓ.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Treatment of groups of 10 male and 10 female Wistar rats by gavage with 0, 0.4, 2, 10 or 50 mg/kg of bromomethane 5 days/week for 13 weeks resulted in severe hyperplasia of the stratified squamous epithelium in the forestomachs of high-dose male and female rats and slight epithelial hyperplasia in the forestomachs of male and female rats treated with 10 mg/kg (Danse et al., 1984). Although Danse et al. (1984) reported that 6/10 females and 7/10 males treated with 50 mg/kg/day had carcinoma of the forestomach, the NTP scientists who reevaluated the histological slides from this study concluded that there were inflammatory and hyperplastic lesions, but no neoplastic lesions. In addition to the forestomach histopathology, decreased food consumption and body weight gain and anemia were observed in the male rats and slight pulmonary atelectasis was observed in both male and female rats treated with 50 mg/kg/day. No neurotoxic effects or liver histopathological alterations were observed at any dose level tested. Renal histopathology was not evaluated. Adverse effects were not observed in rats treated with 0.4 or 2.0 mg/kg/day.

Groups of four beagle dogs (sex unspecified) were fed bromomethane fumigated food for 1 year that provided intakes of 41.6, 89.1 or 178.2 mg/kg/day of bromomethane, assuming all the bromide identified in the diet was present as methyl bromide (Rosenblum et al., 1960). Three dogs/sex served as controls. At the highest dose, the dogs became lethargic, occasionally had diarrhea and excessive salivation, and had significantly increased body weights. The gain in body weight was the result of frank obesity that the authors attributed to compound-induced polyphagin. Although no effects were observed on hematological values, urinalysis, blood chemistry or mortality

rates after 1 year of treatment, mild hepatic and renal inflamation were reported in dogs exposed to the highest dietary level of bromomethane.

3.1.2. Inhalation. As summarized in Table 3-1, groups of rats, guinea pigs, rabbits and monkeys were exposed to bromomethane at 0, 65, 130, 250, 420 or 850 mg/m^3, 7.5 hours/day, 5 days/week for up to 6 months (Irish et al., 1940).

The exposure level of 850 mg/m^3 was acutely toxic to both rats and guinea pigs. Rats and the one monkey exposed to 420 mg/m^3 had convulsions. Although no convulsions were reported in the guinea pigs, 4/11 guinea pigs exposed to 420 mg/m^3 died during treatment.

The exposure level of 250 mg/m^3 had no effect in rats and guinea pigs. In contrast, almost all (38/42) of the rabbits and half (3/6) of the monkeys showed signs of paralysis when exposed to 250 mg/m^3. Although no adverse effects were seen in monkeys exposed to 130 mg/m^3, this concentration caused paralysis in all the rabbits that survived long enough for the effect to develop. Fifteen of the 58 rabbits exposed to 130 mg/m^3 died suddenly from a severe lung infection, perhaps exacerbated by methyl bromide inhalation. Adverse changes in lung histology were reported in the rabbits that were paralyzed. An exposure level of 65 mg/m^3 is a NOAEL for rats, guinea pigs, rabbits and monkeys and the highest NOAEL tested for rabbits. These data suggest a steep dose-response curve, and not a great difference in the concentration associated with a NOAEL and a FEL.

More recently, Russo et al. (1984) exposed six adult male New Zealand White rabbits to 27 ppm (105 mg/m^3) of bromomethane by inhalation, 7.5 hours/day, 4 days/week during an 8-month period for a total duration of 900 hours. Two rabbits served as controls. No effects on the mean latency rates of the sciatic and ulnar nerves or on eyeblink amplitudes were

TABLE 3-1

Summary of Experimental Design in the Study of Irish et al. (1940)

Exposure Level		Number of Animals			
(mg/ℓ)	(mg/m^3)	Rats	Guinea pigs	Rabbits	Monkeys
0	0	15	6 males; 6 females	6	2
0.065	65	0	0	6	0
0.13	130	8 males; 8 females	5 males; 6 females	58	4
0.25	250	10 males; 12 females	14 males; 10 females	42	6
0.42	420	30	11	0	1 female
0.85	850	20	16	0	0

observed. Exposed rabbits gained less weight than controls, but this difference was reported to be unrelated to treatment. Comparing their results with the results of Irish et al. (1940) who reported paralysis in rabbits exposed to (130 mg/m^3), Russo et al. (1984) conjectured that thier failure to find neurobehavior impaired in rabbits exposed to concentrations of 27 ppm (105 mg/m^3) may have been due to the differences in the strain of the rabbits, to the possibility that the range of 27-33 ppm of methyl bromide defines the threshold level for the incidence of neurobehavioral impairment or, more likely, to imprecise monitoring procedures that resulted in variations of concentrations, which influenced the effects of exposure, since Irish et al. (1940) did not report the details of their analytical procedures.

NTP (1986) indicates that a subchronic inhalation study in rats and mice is currently in progress in preparation for a chronic toxicity-carcinogenicity experiment.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the systemic toxicity of bromomethane after chronic oral exposure could not be located in the available literature.

3.2.2. Inhalation. As indicated in Section 4.2.2., there are two chronic inhalation bioassays currently in progress, one on mice (NTP, 1986) and one on rats (U.S. EPA, 1985a; Danse et al., 1984).

Because bromomethane is a gas at 4°C and atmospheric pressure, most human exposure has occurred by inhalation. Although there are studies on the effects of occupational exposure to bromomethane (Wong et al., 1984; Verberk et al., 1979), they are not useful in quantitative risk assessment because the level of bromomethane exposure was not reported. The primary

targets of bromomethane exposure in humans are the respiratory, nervous and gastrointestinal systems. The dose-response curve is quite steep, but the onset of symptoms may be delayed several hours after an acute exposure. Workers exposed to 35 ppm (140 mg/m^3) for 2 weeks developed mild systemic poisoning accompanied by nausea, vomiting, headache and skin lesions (Watrous, 1942).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data on the oral teratogenicity of bromomethane could not be located in the available literature.

3.3.2. Inhalation. The teratogenicity of inhaled bromomethane was evaluated both in New Zealand White rabbits and female Wistar rats (Hardin et al., 1981; Sikov et al., 1980). Groups of ~20 pregnant rabbits were exposed to 0, 20 or 70 ppm (0, 78 or 270 mg/m^3) for 7 hours/day, on days 1-15 of gestation. Beginning on day 9 of gestation, convulsive movements, hindleg paresis and death were observed in the high groups dams. By day 30 of gestation, all but one were dead. Despite the signs of toxicity among rabbits exposed to 70 ppm, no teratogenic or fetotoxic effects were reported in their fetuses. No evidence of maternal toxicity or fetal teratogenicity was observed in the rabbits exposed to 20 ppm. Although the number of dead and resorped fetuses in the rabbits exposed to 20 ppm of bromomethane (19) was nigher than the number of dead and resorbed fetuses in the control group (13), the number of litters with resorptions in the rabbits exposed to 20 ppm of bromomethane (6) was not significantly different from the number of litters with resorption in the controls (7).

In contrast to the rabbits, no adverse maternal or developmental effects were observed in groups of ~35 pregnant rats exposed to 0, 20 or 70 ppm (0, 78 or 270 mg/m^3) of bromomethane, 7 hours/day on gestation days 1-19

(Hardin et al., 1981; Sikov et al., 1980). In addition, groups of ~35 rats were exposed to 20 or 70 ppm (78 or 270 mg/m^3) of bromomethane for 7 hours/day, 5 days/week for 3 weeks before mating. No maternal toxicity, no teratogenicity and no fetal toxicity were reported in the rats at any exposure level.

3.4. TOXICANT INTERACTIONS

Pertinent data regarding the interaction of bromomethane with other chemicals inhaled or ingested could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the human carcinogenicity of bromomethane after oral exposure could not be located in the available literature.

4.1.1. Inhalation. A study of workers potentially exposed to organic and inorganic brominated chemicals indicated that the incidence of death from testicular cancer was significantly higher (2/665) in workers exposed to organic bromides than would be predicted based on the standardized mortality ratio (0.11/655) (Wong et al., 1984). Bromomethane was the only common potential exposure for the two men, but they may also have been exposed to other chemicals. Exposures were not quantitated. No significant increase in the incidence of any other type of tumor was observed in this study (Wong et al., 1984).

4.2. BIOASSAYS

4.2.1. Oral. Bioassays on the carcinogenicity of oral exposure to bromomethane could not be located in the available literature. In addition, no bioassay on the carcinogenicity of bromomethane associated with oral exposure have been located.

4.2.2. Inhalation. Although no completed bioassay on the carcinogenicity of bromomethane after inhalation exposure was located in the available literature, a chronic inhalation bioassay in mice is reported to be in progress (NTP, 1986), and a chronic inhalation bioassay on rats is reported to be in progress by the Dutch National Institute for Public Health (Danse et al., 1984; U.S. EPA, 1985a).

4.3. OTHER RELEVANT DATA

Bromomethane is mutagenic to Salmonella typhimurium strains TA100 and TA1535, but not to strain TA98 and TA1537, and to Escherichia coli with and without metabolic activation (Voogd et al., 1982; Moriya et al., 1983; Kramers et al., 1985; Simmon and Tardiff, 1978; Simmon et al., 1977). Bromomethane increased the frequency of lethal recessive mutations in Drosophila melanogaster (Voogd et al., 1982; McGregor, 1981; Kramers et al., 1985). Bromomethane was mutagenic in the mouse lymphoma cell assay, but not in other assays performed on mammalian systems, such as unscheduled DNA synthesis in rat liver cells (Voogd et al., 1982; Kramers et al., 1985) or human fibroblasts (McGregor, 1981). In vivo dominant lethal chromosome abnormality and sperm abnormality assays in rats and mice were also negative (McGregor, 1981).

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the carcinogenic potential of bromomethane. Applying the criteria described in the EPA's proposed guidelines for assessment of carcinogenic risk (U.S. EPA, 1986c), bromomethane may be classified in EPA Group D: not classifiable (U.S. EPA, 1986a). This category is for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available. Bromomethane may also be classified in IARC Group 3: cannot be classified.

5. REGULATORY STANDARDS AND CRITERIA

A TLV of 5 ppm (20 mg/m³) with a STEL of 15 ppm (60 mg/m³) was recommended by the ACGIH (1980) and adopted by the ACGIH (1985) to protect against the adverse neurotoxic and pulmonary effects observed after acute exposure is designated with the skin notation indicating the potential contribution of dermal absorption. The Occupational Safety and Health Administration standard is 20 ppm (80 mg/m³) for an 8-hour TWA exposure limit (OSHA, 1985). Tolerances for bromomethane on raw agricultural commodities range from 5 ppm on pears, apples and quinces to 300 ppm on asparagus and lettuce (U.S. EPA, 1982, 1983a,b).

The inhalation NOAEL of 65 mg/m³ from the Irish et al. (1940) study in which rabbits were exposed for up to 6 months has been used to derive oral RfDs (ADIs) for bromomethane following two different methodologies. In the first derivation, U.S. EPA (1980a, 1982) derived an oral RfD of 14.5 mg/day by assuming that animal and human exposures at a given concentration are equivalent and applying an absorption factor of 0.5 and an uncertainty factor of 100.

In the second derivation (U.S. EPA, 1986b), an oral RfD of 0.0004 mg/kg/day was derived from an estimated equivalent absorbed dose with application of an uncertainty factor of 10,000.

Recently, the U.S. EPA (1986a) more appropriately identified an oral NOAEL of 2 mg/kg/day from the Danse et al. (1984) study using rats. An RfD of 0.0014 mg/kg/day of bromomethane was derived. The RfD for bromomethane remains provisional until the results of the carcinogenicity studies currently in progress (NTP, 1986) are completed.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Treatment of groups of 10 male and 10 female Wistar rats by gavage with 0, 0.4, 2, 10 or 50 mg/kg of bromomethane 5 days/week for 13 weeks resulted in severe hyperplasia of the stratified squamous epithelium in the forestomachs of male and female rats treated with 50 mg/kg/day of bromomethane, and slight epithelial hyperplasia in the forestomachs of male and female rats treated with 10 mg/kg/day of bromomethane (Danse et al., 1984). An RfD_{SO} of 0.014 mg/kg/day (1.0 mg/day for a 70 kg human) can be derived by multiplying the NOAEL of 2 mg/kg/day by 5/7 to provide continuous exposure and by dividing by an uncertainty factor of 100 to account for interspecies extrapolation and the range of sensitivity to xenobiotics within the human population.

6.1.2. Inhalation (RfD_{SI}). No adverse effects were observed in rabbits exposed to 65 mg/m³ of bromomethane for 7.5 hours/day, 5 days/week for 6 months (Irish et al., 1940). The next higher dose level, 250 mg/m³, resulted in paralysis and pulmonary damage in rabbits. An RfD_{SI} of 0.076 mg/kg/day (5 mg/day for a 70 kg human) is derived by multiplying the NOAEL of 65 mg/m³ by 7.5/24 and 5/7 to expand to continuous exposure and by the reference daily inhalation rate (2.0 m³/day), and dividing by the reference body weight (3.8 kg) for rabbits (U.S. EPA, 1985b) and an uncertainty factor of 100 to account for interspecies extrapolation and the range of sensitivity to xenobiotics within the human population.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). Because oral data on the chronic toxicity of bromomethane are not available, the RfD_0 of 0.0014 mg/kg/day (0.1 mg/day

for a 70 kg human) is derived from the RfD_{SO} of 0.014 mg/kg/day by dividing by an uncertainty factor of 10 to account for the use of a subchronic study to obtain an acceptable chronic intake level.

Because there are no chronic oral data on bromomethane toxicity, the CSs for oral exposure are based on anemia and atelectasis of the lungs at 50 mg/kg and epithelial hyperplasia of the forestomach at 10 mg/kg in the 13-week gavage study in rats by Danse et al. (1984).

The CSs were obtained as indicated in Table 6-1. An uncertainty factor of 10 was used to account for the use of a subchronic study to derive a chronic CS. These CSs are identified with those obtained in another recent U.S. EPA (1986a) analysis.

6.2.2. Inhalation (RfD_I). Because there are no available inhalation data on the chronic toxicity of bromomethane, the RfD_I of 0.0076 mg/kg/day (0.5 mg/day) is derived from the RfD_{SI} of 0.076 mg/kg/day by dividing by an uncertainty factor of 10 to account for the use of a subchronic study to obtain an acceptable chronic intake level.

Because there are no chronic inhalation data on bromomethane toxicity, the CSs for inhalation exposure are based on the paralysis observed in rabbits at 130 mg/m^3 and the convulsions observed in rats at 420 mg/m^3 in the 6-month study by Irish et al. (1940).

The CSs were calculated as indicated in Table 6-1. An uncertainty factor of 10 was used to account for the use of a subchronic study to derive a chronic RQ. These CSs are identified to those derived by U.S. EPA (1986a).

6.3. CARCINOGENICITY POTENTY (q_1^*)

6.3.1. Oral. Data are not sufficient for estimation of carcinogenic potential to bromomethane by oral exposure.

TABLE 6-1

Composite Scores for the Toxicity of Bromomethane by Oral and Inhalation Exposure

Route	Species/ Strain	Sex	Exposure Dosage	Human MED[a,b] (mg/day)	RV_d	Effect	RV_e	CS	Reference
Oral	rat/Wistar	M/F	10 mg/kg, 5 days/week, 13 weeks (7.1 mg/kg/day)	8.5	4.1	epithelial hyperplasia of the fore-stomach	4	16.4	Danse et al., 1984; U.S. EPA, 1986a
Oral	rat/Wistar	M/F	50 mg/kg/day, 5 days/week, 13 weeks (36 mg/kg/day)	43.1	3.0	atelectasis	7	21	Danse et al., 1984; U.S. EPA, 1986a
Inhalation	rabbit/New Zealand White	NS	130 mg/m³, 7.5 hours/day, 5 days/week, 6 months (15.3 mg/kg/day)[c]	40.6	3.1	paralysis	9	27.9	Irish et al., 1940
Inhalation	rat/NS	M/F	420 mg/m³, 7.5 hours/day, 5 days/week, 6 months (59.7 mg/kg/day)[d]	71.5	2.7	convulsions	9	24.3	Irish et al., 1940

[a]An uncertainty factor of 10 was applied to expand from subchronic to chronic exposure.

[b] The MED is obtained by multiplying the transformed dose by the cube root of the ratio of animal to human reference body weights and by the reference human body weight. The reference body weight for a rat is 0.35 kg, for a rabbit, 3.8 kg, and for a human, 70 kg (U.S. EPA, 1980b).

[c]Based on a rabbit inhalation rate of 2 m³/day (U.S. EPA, 1985b) and dividing by the rabbit reference body weight of 3.8 kg (U.S. EPA, 1985b).

[d]Based on a rat inhalation rate of 0.22 m³day (U.S. EPA, 1980a) and a rat reference body weight of 0.35 kg (U.S. EPA, 1980b).

NS = Not specified

6.3.2. Inhalation. No evidence of carcinogenicity was observed in the inhalation studies reported in the literature (Irish et al., 1940; Russo et al., 1984). Their short duration, however, may have precluded detection of tumors. Currently, two long-term inhalation bioassays are in progress; one with mice by NTP (1986) and one with rats at the Dutch National Institute for Public Health (Danse et al., 1984; U.S. EPA, 1985a). Current data are not sufficient for estimation of carcinogenic potential by inhalation exposure.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. Cincinnati, OH. p. 265-266.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1985-1986. Cincinnati, OH. p. 23.

Brown, B.D. and D.E. Rolston. 1980. Transport and transformation of methyl bromide in soil. Soil Sci. 130(2): 68-75.

Daelemans, A. and H. Siebering. 1977. Distribution of methyl bromide over the phases in soil. Meded. Fac. Landbouwwet., Rijdsuniv. Gent. 42: 1729-1738.

Danse, L.H., F.L. van Velsen and C.A. vander Heijden. 1984. Methyl bromide: Carcinogenic effects in the rat forestomach. Toxicol. Appl. Pharmacol. 72: 262-271.

Davis, D.D., G. Machado, B. Conway, Y. Oh and R. Watson. 1976. A temperature dependent kinetics study of the reaction of OH with CH_3Cl, CH_3Cl, CH_2Cl_2, $CHCl_3$, CH_3BR. J. Chem. Phys. 65: 1268-1274.

Dilling, W.L. 1982. Atmospheric environment. Chapter 5. In: Environmental Risk Analysis for Chemicals, R.A. Conway Ed. Van Nostrand Reinhold Co., New York. p. 154-197.

Ehrenberg, L., S. Oster-Golkar, D. Singh and U. Lundquist. 1974. On the reaction kinetics and mutagenic activity of methylating and beta-halogenoethylating additives. Radiat. Bot. 15: 185-194.

Hansch, C. and A.S. Leo. 1985. Medchem Project. Pomona College, Claremont, CA.

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7: 66-75.

Howard, C.J. and K.M. Evenson. 1976. Rate constants for the reactions of hydroxyl and methane and fluorize, chlorine and bromine substituted methanes at 296°K. J. Chem. Phys. 64: 197-202.

Irish, D.D., E.M. Adams, H.C. Spencer and V.K. Rowe. 1940. The response attending exposure of laboratory animals to vapors of methyl bromide. J. Ind. Hyg. Toxicol. 22: 218-230.

Jury, W.A., W.F. Spencer and W.J. Farmer. 1984. Behavior assessment model for trace organics in soil. III. Apllication of screening model. J. Environ. Qual. 13: 573-579.

Kramers, P.G., C.E. Voogd, A.D. Knapp and C.A. Vander Heijden. 1985. Mutagenicity of methyl bromide in a series of short-term tests. Mutat. Res. 155(1-2): 41-48.

Lyman, W.J., W.F. Reehe and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. In: Environmental Behavior of Organic Compounds. McGraw-Hill, New York. p. 5-5.

Mabey, W. and T. Mill. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7: 383-415.

Mabey W.R., J.H. Smith, R.T. Podoll, et al. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014.

Makide, Y. and F.S. Rowland. 1981. Tropospheric concentrations of ethylchloroform, CH_3CCl_3, in January 1978 and estimates of the atmospheric residence times for hydrohalocarbons. Proc. Natl. Acad. Sci. U.S.A. 78(10): 5933-5937.

McGregor, D.B. 1981. Tier II mutagenic screening of 13 NIOSH priority compounds: Individual compound report: Methyl bromide. NTIS PB83-130211. p. 190. (Cited in U.S. EPA, 1985a)

Medinsky, M.A., J.A. Bond, J.S. Dutcher and L.S. Birnbaum. 1984. Disposition of [^{14}C]methyl bromide in Fischer-344 rats after oral or intraperitoneal administration. Toxicology. 32: 187-196.

Medinsky, M.A., J.S. Dutcher, J.A. Bond, et al. 1985. Uptake and excretion of [^{14}C]methyl bromide as influenced by exposure concentration. Toxicol. Appl. Pharmacol. 78: 215-225.

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116(3-4): 185-216.

NTP (National Toxicology Program). 1986. Management Status Report. Toxicology Research and Testing Program, 09/06/86.

OSHA (Occupational Safety and Health Administration). 1985. OSHA Occupation Standards Permissible Exposure Limits. Code of Federal Regulations. (29 CFR 1910.1000)

Robbins, D.E. 1976. Photodissociation of methyl chloride and methyl bromide in the atmosphere. Geophys. Res. Lett. 3: 213-216.

Rosenblum, I., A.A. Stein and G. Eisinger. 1960. Chronic ingestion by dogs of methyl bromide-fumigated food. Arch. Environ. Health. 1: 316-323.

Russo, J.M., W.K., J.V. Setzer and W.S. Brightwell. 1984. Neurobehavioral assessment of chronic low-level methyl bromide exposure in the rabbit. J. Toxicol. Environ. Health. 14: 247-255.

Sikov, M.R., W.C. Cannon, D.B. Carr, R.A. Miller and L.F. Montgomery. 1980. Teratologic assessment of butylene oxide, styrene oxide and methyl bromide. Prepared by Battelle, Pacific Northwest Laboratory, Richland, WA, under Contract No. 210-76-0025. PHS, CDC, U.S. DHEW. [Also publ. NTIS PB 81-168510]

Simmon, V.F. and R.G. Tardiff. 1978. Mutagenic activity of halogenated compounds found in chlorinated drinking water. Water Chlorination: Environ. Impact Health Eff. Proc. Conf. 2: 417-431.

Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ. Sci. 2: 249-258.

Singh, H.B., L.J. Salas and H. Shigeishi. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos. Environ. 15: 601-612.

Stenger, V.A. 1978. Bromine compounds. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 4, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 251-252.

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Halomethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-051. NTIS PB81-117624.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 79347-79357.

U.S. EPA. 1982. Errata for Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1983a. Tolerance for pesticide chemicals in an on raw agricultural commodities inorganic bromide resulting from fumigation with methyl bromide. Federal Register. 48: 20052.

U.S. EPA. 1983b. Tolerance for pesticide chemicals in or on raw agricultural commodities, inorganic bromides resulting from fumigation with methyl bromide. Federal Register. 48: 50533-50534.

U.S. EPA. 1984. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Chemical Hazard Information Profile. Draft Report Methyl Bromide. Rev. Feb. 20, 1985. U.S. EPA, OTS, Washington, DC.

U.S. EPA. 1985b. Reference Values for Risk Assessment. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986a. Health and Environmental Effects Profile for Methyl Bromide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for bromomethane. Online. (Verification date 09/29/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986c. Guidelines for Carcingen Risk Assessment. Federal Register. 51(185): 33992-34003.

Vanachter, A., J. Feyaerts, E. Van Wambeke and C. Van Assche. 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 ground and surface waters. Meded. Fac. Landbouwwet., Rijksuniv. Gent. 46(1): 351-358. [CA 95(23):199023z]

Verberk, M.M., T. Rooyakkers-Beemster, M. DeVlieger and A.G.M. VanVliet. 1979. Bromine in blood, EEG and transaminases in methyl bromide workers. Br. J. Ind. Med. 35(1): 59-62.