Bromochloromethane Testing Rationale

CAS 74-97-5

I. INTRODUCTION

Albemarle Corporation (Albemarle) would like to submit a test plan for bromochloromethane in the Environmental Protection Agency's High Production Volume (HPV) Challenge Program.

Albemarle is committed to making existing test data publicly available for this chemical and to develop any additional screening level data needed on health and environmental effects, fate, and physicochemical properties. In order to minimize the use of animals in the testing of chemicals, Albemarle has conducted a thorough literature search for all available data, published and unpublished for bromochloromethane (BCM). It also has performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable analogy for BCM and the related chemical dibromomethane (DBM, CAS 74-95-3) and used structure-activity relationship modeling as appropriate. This document describes the data available for bromochloromethane and its dihalogenated methane analog dibromomethane (DBM). Data on both chemicals are included to provide justification for the proposed analogy. Robust summary documents have been prepared and are included for each of these chemicals in this submission. Finally, the rationale for proposed testing is described. No testing of whole animals is proposed in this test plan.

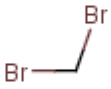
II. DEVELOPMENT OF THE DIHALOMETHANE ANALOGY

Structurally, BCM and DBM are brominated analogs of dihalogenated methanes. The halogen substituents are bromine and chlorine. Figure 1 gives the names, CAS numbers, and structures of the substances.

Figure 1. Dihalogenated Methanes Included in the HPV Program

a. bromochloromethane (BCM) CAS 74-97-5

b. dibromomethane (DBM) CAS 74-95-3



Both of these substances are clear, colorless chemicals at room temperatures. They are not flammable, and are co-manufactured in the same processes. Primary uses for both have been as chemical intermediates, and in fire extinguishing applications. Similarities of physico/chemical properties, toxicity and metabolism are described in the testing rationale sections.

III. MANUFACTURING, USE AND EXPOSURE INFORMATION

Bromochloromethane is manufactured by reacting dichloromethane with anhydrous aluminum bromide (treatment with bromine and aluminum) or by reaction with hydrogen bromide in the presence of an aluminum halide catalyst, followed by water washing and distillation (Stenger, V.A., 1978). Dibromomethane is manufactured alongside bromochloromethane production.

The largest category of current use for these chemicals is as chemical intermediates in the synthesis of a variety of organic chemicals. Because the majority of the current production volume is converted to other chemicals (i.e., is used as a chemical intermediate), human and environmental exposure to the original chemicals is limited.

Historically, bromochloromethane was used as a fire-extinguisher fluid in aircraft and in portable extinguishers (Stenger, V.A., 1978). These are no longer applications for BCM because of regulation based on it's calculated ozone-depleting potential. The US Environmental Protection Agency found that BCM was an unacceptable replacement for ozone-depleting substances in various industry sectors, including fire suppression, under the Significant New Alternatives Program (US EPA, 1999). The areas for which BCM is considered unacceptable include total flooding applications in fire suppression and explosion protection systems, as replacement for CFC113, methyl chloroform and HCFC141b in metals cleaning, electronics cleaning and precision cleaning, in aerosols as a solvent as a substitute for CFC113, methyl chloroform and HCFC 141b, and in adhesives, coatings and inks as a carrier solvent. EPA, in accordance with the Montreal Protocol on Substances that Deplete the Ozone Layer, implemented regulations listing it as a substance subject to production and consumption controls under the Clean Air Act in July, 2003 (US EPA, 2003). The regulations listed BCM as a new group (Group VIII) under Class I substances that deplete the ozone layer, with an ozone depletion potential of 0.12. This established a full ban on production and import of BCM unless the production or import is for destruction or transformation. There are provisions for exemptions for essential uses, laboratory and analytical uses.

Dibromomethane is used in organic synthesis and as a solvent for fats, waxes and resins, in gage fluids, and as a heavy liquid in solid separations. A previous use was also as an ingredient of fire extinguishing fluids.

Because of use as chemical intermediates, the potential for exposure to bromochloromethane and dibromomethane exists primarily in the workplaces of the manufacturers and their customers. Bromochloromethane has an occupational exposure limit of 200 ppm as an 8-hour time weighted average (OSHA Permissible Exposure Limit and ACGIH Time Weighted Average). The manufacturers use and recommend both personal protective equipment and engineering controls. Splash-proof chemical safety goggles, full-faceshields, or full-face respirators are recommended to protect against eye contact. Local exhaust ventilation is recommended to minimize inhalation exposure. Organic vapor cartridge respirators are recommended for use if there is a potential for exposure to vapors or mists. In case of a spill or leak, appropriate protection, which may include a respirator with supplied air, is required. Appropriate gloves, aprons, and chemical resistant clothing are used to prevent dermal contact.

IV. TEST PLAN RATIONALE

There is a large amount of screening level test data available for dibromomethane from literature references and more current data produced for dibromomethane under the TSCA Section 4 Test Rule for HPV Unsponsored Chemicals issued on March 16, 2006 (71 FR 13708). These data allow the use of analogy and estimation to predict effects where data are missing for bromochloromethane. The robust summary documents enclosed for each chemical summarize the available studies. The critical studies to fulfill required HPV Challenge endpoints were chosen according to several factors, including documentation and detail, when the study was conducted, and access to a detailed publication or report. Overall, existing data or calculated values have been identified for all of the HPV Challenge screening level endpoints.

a. Physical Properties

The physical properties for both the chemicals are summarized in Table 1 below. Both the compounds are liquids at room temperature, with relative densities ranging from 1.93 to 2.5 gm/cu cm at 20°C. The boiling points range from 68 to 94.1 °C. The vapor pressures at 25°C range from 35.3 (DBM, measured, O'Connor, 2007) to 142 mm Hg (BCM, estimated). The water solubility estimates for BCM range from 5.3 to 16 gm/l with a comparable measured value for DBM of 9.0 grams per liter at 20 °C. The range of the log of the octanol-water partition coefficients (log P or log Kow) is from 1.41 to 1.68. These data are sufficient to describe the physical properties of this category, and no further testing is proposed.

Table 1: Physical Properties

Property	Bromochloromethane	Dibromomethane
Molecular Weight	129.38	173.86
Melting Point (°C)	-70 to -87.95 °C	< -20.0 °C (exp)
Boiling Point (°C)	68 °C	94.1 °C (367 K) (exp)
Density g/cc at 20'C	1.9344 @ 20°C	2.4969 @ 20°C
Vapor Pressure	142 mm Hg @ 25°C	35.3 mm Hg @25°C (exp)
Log P	1.41 (est)	1.68 @ 22.5 °C (exp)
Water Solubility	5.3 to 16 g/l @ 20°C	9.0 g/l @ 20 °C (exp)

exp = experimental est = estimated

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b. Metabolism

Metabolism of bromochloromethane and dibromomethane is similar. Biotransformation of dihalomethanes leads to dehalogenation with an endproduct of carbon monoxide (described in Cassarett and Doull, 1986). These processes have been determined by in vitro and in vivo experimentation.

The process of metabolism has been shown in vitro to produce carbon monoxide and inorganic bromide by microsomal enzymes of liver, lungs and kidneys, but not of the brain, or spleen. The oxidation appears to be catalyzed by a cytochrome P-450 dependent system. (cited in US EPA, 1990)

Administration of dibromomethane to rats in vivo resulted in increased levels of carboxyhemoglobin, indicative of metabolism to carbon monoxide and inorganic bromide (as cited in US EPA, 1990). Similarly, carboxyhemoglobin levels were increased in rats injected with bromochloromethane intraperitioneally (Kubic, 1974 as cited in HA, 1989), with a maximum saturation of 5% carboxyhemoglobin after 4 hours. Svirbely et al (1947) reported release of inorganic bromide in dogs, rats and rabbits exposed to 1000 ppm BCM by inhalation for 7 hours per day, 5 days per week for 14 days. Blood bromide levels were shown to increase in various species after inhalation exposure by other researchers (Torkelson, 1960, McDougal, 1985, Anderson, 1980, Gargas, 1982)

c. Environmental Fate

In general, halobromomethanes do not absorb light in the environmental UV spectrum (> 290 nm). Thus, direct photolysis would have only a minor effect on the atmospheric lifetime of bromochloromethane. Indirect photolysis via reaction with hydroxyl radicals can be estimated. The rate constant for reaction of vapor-phase chlorobromomethane with photochemically produced hydroxyl radicals has been estimated to be 0.93 to 1.11 x 10^{-13} cu cm/molecule-sec @ 25°C (Orkin et al, 1997 and DeMore, 1996 as cited in Hazardous Substances Database, HSDB). This corresponds to an atmospheric half-life of 145 days at an atmospheric concentration of 5 x 10^{+5} hydroxyl radicals per cu cm (Syracuse Research Corporation as cited by HSDB). Similarly, calculation of the rate constant using AOP v. 1.92 from EPISUITE (v. 4.0) yields a value of $0.099e^{-12}$ cu cm/molecule-sec giving a half-life estimate of 107.63 days.

If released into water, hydrolysis is not expected to be a significant process as the hydrolysis half-life of BCM under environmental conditions at 25 °C has been estimated at 44 years. (Mill, T, 1982 as cited in HSDB). Half-life estimate by the same authors for dibromomethane is 183 years. (Mabey and Mill, 1978 as cited in US EPA, 1990). Half-lives for both chemicals calculated with HYDROWIN v. 2.00 (EPISUITE v. 4.0) also were in years. However, these modeling programs may underestimate neutral hydrolysis under environmental conditions. An experimental hydrolysis study of dibromomethane determined half-lives at various pH values to range from 50 to 122 days. (Fackler, 1989)

Modeling of biodegradation using BIOWIN v. 4.10 (EPISUITE v. 4.0) predicts that neither bromochloromethane nor dibromomethane meet the definition of ready biodegradation. However, biodegradation could be a factor in the ultimate environmental fate of BCM. Screening studies have shown degradation in settled domestic wastewater inoculum under aerobic conditions, and in standard tests with activated sludge innoculum. One report indicated 100% of BCM was degraded after the initial seven-day incubation period and in each subsequent subculture with static incubation of 5 and 10 mg/l BCM in the Bunch and Chambers static culture flask biodegradability screening test (Tabak, 1981 as cited in HA, 1989). This would indicate significant biodegradation and rapid adaptation. Anaerobic microbial degradation with soil bacteria has also been reported (Kobayshi, 1982.)

Based on estimated log Koc values (DBM 24 and BCM 29-137), the dihalogenated methanes would be expected to have moderate to rapid migration through soils and low to moderate sorption to soils, (HSDB for DBM, HA for BCM). Adsorption to sediments is predicted to be not significant (US EPA, 1985).

Neither of the dihalogenated bromomethanes is likely to bioaccumulate in aquatic organisms based on the estimated bioconcentration factors calculated from octanol-water partition coefficients. Estimated BCF values of 2.4 to 3.96 (BCM) and 2.79 to 6.15 (DBM) suggest that bioconcentration potential in aquatic organisms is low.

There are sufficient data for these dihalogenated methanes to characterize the fate of these chemicals. Neither of the dihalogenated bromomethanes meet the criteria for Persistent, Bioaccumulative and Toxic (PBT) chemicals, and no further environmental fate testing is proposed.

Table 2: Environmental Aspects

Endpoint	Bromochloromethane	Dibromomethane
Direct Photodegradation Indirect Photolysis (atmospheric half-life)	Not expected 108 to 145 days (est)	Not expected 146 days (est)
Hydrolysis	Not significant (est)	Not significant (est)
Distribution (PBT profiler)	Air: 44 % Water: 40 % Soil: 16% Sediment: 0%	Air 34% Water 36% Soil 29% Sediment 0%
Level III Fugacity (EPISUITE v. 4.0)	Air: 40.5% Water: 37.8% Soil: 21.6% Sediment: 0.104%	Air: 40.5% Water: 35.9% Soil: 30.1% Sediment: 0.0983%
Biodegradation	Not ready biodegradable	Not ready biodegradable
Log Koc	29 to 137 (est)	24 (est)
Bioaccumulation: BCF	2.4 to 3.96 (est)	2.79 to 6.15 (est)

d. Aquatic Toxicity

A fathead minnow toxicity test for bromochloromethane was summarized by the EPA as having a NOEL of 80 mg/l and an LC50 of greater than 80 mg/l. (US EPA, 1990 citing Dow studies) Experimental data for dibromomethane in fish showed a trout LC50 of 45 mg/l and NOEC of 32 mg/l (Goodband, 2007b). Acute toxicity testing of dibromomethane in invertebrates (*Daphnia magna*) gave an EC50 of 66 mg/l and a NOEC of 32 mg/l (Goodband, 2007a). Invertebrate studies were not found for bromochloromethane, but a value of 164 mg/l for an acute invertebrate LC50, 48 hours, can be estimated by using the modeling program ECOSAR v. 1.00 (EPISUITE v. 4.0). DBM testing in algae produced EC50 values for growth of 210 mg/l at 96 hours, for yield 130 mg/l at 96 hours and for biomass integral, 110 mg/l (Vryenhoef, 2007).

Regrowth tests showed that dibromomethane was algistatic in action. Estimation of acute algal EC 50 for BCM can be made by ECOSAR, yielding a value of about 61 mg/l.

As there is a sufficient screening amount of acute aquatic toxicity data available for chemicals in this category, either by testing or estimation, no further testing is proposed.

Table 3: Aquatic Toxicity

Endpoint	Bromochloromethane	Dibromomethane
Acute fish LC50, 96 hours Trout Fathead minnow	 > 80 mg/l	 45 mg/l
Acute invertebrate LC50, 48 hours	164 mg/l (ECOSAR)	66 mg/l
Acute algal, EC50, mg/l, 96 hrs Growth Yield Biomass integral	60.79 (ECOSAR	 210 mg/l 130 mg/l 110 mg/l

e. Mammalian Toxicity

The dihalogenated methanes have been tested for acute toxicity by several routes of administration. Rat oral LD50 values are generally greater than 1000 mg/kg for both chemicals. Rat inhalation LC50 values for bromochloromethane in rats have ranged from 3000 ppm to greater than 5000 ppm for 7-hour exposures. Signs observed in acute toxicity tests are related to central nervous system toxicity. Liver and kidney effects have been seen in animals after single exposures.

Table 4: Comparison of LD50 and Substituent Group of Dihalomethane Derivatives

	LD50	
First halogen group	bromo	bromo
Second halogen	bromo	chloro
Rat, oral	> 1 g/kg	> 5 to < 7 g/kg
Rat, inhalation, LC50 and exposure length		5000 ppm/ 7 hr > 38.6 mg/l / 4 hr
Mouse, oral		4.3 g/kg
Rabbit, dermal	> 4 gm/kg	> 5 gm/kg

The rabbit dermal LD50 values for the di-substituted compounds are > 4 gm/kg by single dermal applications.

These materials are irritants to the eyes, and can cause irritation to corrosion of the skin if the skin is occluded by clothing. An animal sensitization test for bromochloromethane showed some skin sensitization potential, but not sufficient to lead to classification in the EU.

No further testing is proposed for the dihalogenated methanes for acute mammalian toxicity endpoints.

f. Mammalian Repeated Dose Toxicity

Oral and inhalation repeated exposure studies have been completed on bromochloromethane and dibromomethane using various animal species.

Bromochloromethane has been tested by subchronic repeated dose exposure by the inhalation route in rats, mice, guinea pigs, rabbits and dogs. Studies have ranged in length from 14 weeks to about 6 months. Dose levels ranged from 370 ppm (rats) to about 1000 ppm in all. Exposures were usually 5 to 7 hours in length, 5 days per week. Generally effects seen at 500 ppm to 1000 ppm were minor such as decreased body weights, increased relative liver and kidney weights and reversible histology in the liver and kidney. Exposure of mice to 1000 ppm caused death and marked liver injury in mice, suggesting mice were more susceptible than other species.

Dibromomethane also has repeated dose inhalation studies in rats, rabbits, dogs exposed for at least 90 days for 6-7 hours, 5 days per week. Exposure concentrations for these studies ranged up to 150 ppm in concentration.

Based on the length of studies, the multiple routes and species, as well as consistent critical effects seen for both the compounds, no further repeated exposure animal testing is proposed.

g. Genetic Toxicity

Standard bacterial mutagenicity assays (with and without metabolic activation) and chromosome aberration tests have been conducted for bromochloromethane and dibromomethane. Results of these tests have been considered positive evidence of mutagenicity. (IRIS, Bromochloromethane Carcinogenicity Assessment, as revised in 1991).

Bromochloromethane was mutagenic in Salmonella typhimurium and E. coli tests and induced sister chromatid exchange and chromosome aberrations in Chinese hamster cells in vitro (as reported in US EPA, 1990).

Dibromomethane was reported to be mutagenic in some strains of S. typhimurium (TA100 and TA 1950) and E. Coli (WU 361089 and K39) without metabolic activation and in TA 100 with metabolic activation, and weakly mutagenic in Saccharomyces cerevisiae strain D3 (as reported in US EPA, 1990). In more recent testing, DBM was considered clastogenic in a chromosome aberration test using human lymphocytes (Wright, 2007).

in vitro: **gene mutation Bacteria: Ames test**	**Positive**	**Positive**
in vitro: **chromosome aberrations Cytogenetics, CHO or CHL**	**Positive**	**Positive (human lymphocytes)**

No further testing is proposed for genetic toxicity endpoints for this group.

h. Developmental and Reproductive Screening

Although reproductive tests were not found for bromochloromethane, reproductive target organ effects were seen in some species in repeated dose studies. BCM exposure caused

decreased spermatogenesis and fibrosis in testicular tubules of guinea pigs and rabbits subchronically (114 days) exposed by inhalation to doses equivalent to 344.18 to 357.25 mg/kg and 257.23 –to 267.00 mg/kg/day respectively (Torkelson, et al. 1960)

A reproduction screening study in rats for dibromomethane by the oral route using current methodology found decreased mating performance and reduction of litter size at birth at the high dose level (500 mg/kg/day). Histopathology of reproductive organs revealed no pathology. High dose males had effects on epididymal and testes weights. No teratologic effects were noted. (Dhinsa, N.K., 2007).

	Bromochloromethane	**Dibromomethane**
Reproduction Toxicity	Male target organ effects in guinea pigs, rabbits in repeated inhalation exposure studies at doses approximately 350 and 250 mg/kg respectively	1 generation screening study: effects on reproduction at 500 mg/kg/day given orally
Developmental Toxicity		1 generation screening study: no developmental effects

As there is adequate information on the brominated homologs of halogenated methanes at the screening level for reproductive toxicity, no further testing for these endpoints is proposed.

DATA GAPS AND TEST PLAN

As mentioned previously, data existing for bromochloromethane, data from the analogous chemical dibromomethane, and estimations that can be calculated using modeling programs are adequate for screening level evaluation of bromochloromethane as a high production volume chemical. No further testing is proposed for bromochloromethane.

Summary of Data Gaps and Method of Completion

	Bromochloromethane
Photodegradation	**S**
Hydrolysis	**S**
Fugacity	**S**
Biodegradation	**S**
Acute fish	**A**
Acute invertebrate	**C, S**
Acute algal	**C, S**
Acute toxicity	**A**
Repeated dose toxicity	**A**
Genetic Toxicity	**A**
Reproductive toxicity	**C**
Developmental toxicity	**C**

A = Adequate data available
T = Testing to be done
S = Structure-activity relationship (modeling program used)
C = Use of Category Approach (read across)

Category References:

Andersen, M.E., M.L. Gargas, R.A. Jones and L. Jenkins, Jr., "Determination of the Kinetic Constants for Metabolism of Inhaled Toxicants in vivo Using Gas Uptake Measurements," Toxicol Appl Pharmacol 53(1): 100-116, 1980.

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DeMore, W.B., J Phys Chem 100: 5813-20, 1996 as cited in Hazardous Substances Database.

Dhinsa, N.K., and S. Fulcher, "Dibromomethane: Oral (Gavage) Reproduction/Developmental Toxicity Screening Test in the Rat," SPL Project Number 0466/0261, SafePharm Laboratories, UK, May, 2007

Fackler, P.H., ."Determination of the Hydrolysis Potential of Dibromomethane as a Function of pH at 25° C", Springborn Life Sciences, Inc, June 15, 1989.

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Goodband, T.J., and D. Mullee, "Dibromomethane: Acute Toxicity to Rainbow Trout (Oncorhynchus mykiss)" SPL Project Number 0466/0263, SafePharm Laboratories, June 22, 2007. Bromine Compounds, Ltd, and Albemarle Corporation, sponsors, 2007b.

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Mabey, W. and T. Mill, "Critical Review of Hydrolysis of Organic Compounds in Water under Environmental Conditions," J Phys Chem Ref Data, 7:383-415, 1978

McDougal, JN, GW Jepson, HJ Clewell, and M.E. Anderson, "Dermal Absorption of Dihalomethane Vapors," Toxicology and Applied Pharmacology, 79, pp 150-158, 1985.

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Svirbely, J.L., B. Highman, W.C. Alford, and W.F. von Oettingen, “The Toxicity and Narcotic Action of Mono-chloro-mono-bromomethane with Special Reference to Inorganic and Volatile Bromide in Blood, Urine, and Brain,” J. Ind. Hyg. Toxicol, 29:382-389, 1947.

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Torkelson, T.R., F. Oyen, and VK Rowe, “The Toxicity of Bromochloromethane (Methylene Chlorobromide) as Determined on Laboratory Animals,” American Industrial Hygiene Association Journal, Vol. 21, No. 4, 1960.

US EPA, “Health and Environmental Effects Profile (HEEP) for Methylene Bromide”. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, D.C., 1987.

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US EPA: Federal Register, Vol. 64, No. 81, April 28, 1999, Environmental Protection Agency, Protection of the Stratospheric Ozone: Listing of Substitutes for Ozone-Depleting Substances, Final Rule, 1999.

US EPA, Federal Register, Vol. 68, No. 138, Friday, July 18, 2003, Environmental Protection Agency, 40 CFR Part 82, Protection of Stratospheric Ozone: Phaseout of Chlorobromomethane Production and Consumption; Final Rule, 2003.

US EPA, Federal Register, Vol. 71, No. 51, Friday, March 16, 2006, Environmental Protection Agency, 40 CFR Parts 9 and 79, Testing of Certain High Production Volume Chemicals; Final Rule, p 13707-13735, 2006.

Vryenhoef, H., and D.M. Mullee, “Algal Growth Inhibition Test“, SPL Project Number: 0466/0265, SafePharm Laboratories, U.K., Bromine Compounds, Ltd, and Albemarle Corporation, sponsors, May 15, 2007.

Wright, N.P., “Chromosome Aberration Test in Human Lymphocytes In Vitro,“ SPL Project Number 0466/0262, SafePharm Laboratories, U.K., May 15, 2007.

I U C L I D

Data Set

Memo	:	BCM HPV dossier
CAS No.	:	74-97-5
EC No.	:	200-826-3
EINECS Name	:	Bromochloromethane
CAS Name	:	Bromochloromethane
Common name	:	BCM
Molecular Formula	:	C H2 Br Cl

Number of pages	:	34

1. General Information

Id 74-97-5

Date 04.28.06

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

Smiles Code	:	C(Cl)Br
Molecular formula	:	C H2 Br Cl
Molecular weight	:	129.38 (CRC Handbook of Chemistry, 1998)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	Typical for marketed substance
Substance type	:	organic
Physical status	:	Liquid
Purity	:	= > 98% w/w
Colour	:	Colorless to light yellow
Odour	:	Sweet

04.28.06

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Remark	:	CAS name: Bromochloromethane
Remark	:	Pure substrance: Methylene chlorobromide
Remark	:	Pure substrance: Monochloromonobromomethane
Remark	:	Pure substance: chloromethyl bromide
Remark	:	Pure substance: methane, chlorobromo
Remark	:	Trade name: BCM
Remark	:	Trade name: Halon 1011
Remark	:	Trade name: Chlorobrom
Remark	:	Trade name: MIL-B-4394-B

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling	:	provisionally by manufacturer/importer
Specific limits	:	No
Symbols	:	Xn
R-Phrases	:	(20) Harmful by inhalation
S-Phrases	:	(23) Do not breathe fumes/vapour

04.28.06

1.6.2 CLASSIFICATION

Classified	:	provisionally by manufacturer/importer
Class of danger	:	Harmful
R-Phrases	:	(20) Harmful by inhalation
Specific limits	:	No

04.28.06

1.6.3 PACKAGING

1.7 USE PATTERN

Remark	:	BCM was once used as a fire extinguisher fluid in aircraft and portable fire extinguishers (Stenger, VA, 1978). It is also used in chemical synthesis (Kuney, JH, 1988). Uses for BCM are restricted under actions by the US Environmental Protection Agency as detailed in the regulatory measures section.

04.28.06

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Remark	:	Bromochloromethane is prepared by reacting dichloromethane with anhydrous aluminum bromide (treatment with bromine and aluminum) or by reaction with hydrogen bromide in the presence of an aluminum halide catalyst, followed by water washing and distillation (Stenger, V.A., 1978).

04.28.06

41.8 REGULATORY MEASURES

Remark : The US Environmental Protection Agency found that BCM was an unacceptable replacement for ozone depleting substances in various industry sectors under the Significant New Alternatives Program (US EPA, 1999). The areas for which BCM was unacceptable included total flooding applications in fire suppression and explosion protection systems, as replacement for CFC113, methyl chloroform and HCFC141b in metals cleaning, electronics cleaning and precision cleaning, in aerosols as a solvent as a substitute for CFC113, methyl chloroform and HCFC 141b, and in adhesives, coatings and inks as a carrier solvent. EPA, in accordance with the Montreal Protocol on Substances that Deplete the Ozone Layer, implemented regulations listing it as a substance subject to production and consumption controls under the Clean Air Act in July, 2003 (US EPA, 2003). The regulations listed BCM as a new group (Group VIII) under class I substances that deplete the ozone layer, with an ozone depletion potential of 0.12. This established a full ban on production and import of BCM unless the production or import is for destruction or transformation. There are provisions for exemptions for essential uses, laboratory and analytical uses.

04.28.06

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : OSHA Permissible Exposure Limit: Table Z-1: 8-hr Time Weighted Average: 200 ppm (1050 mg/cu m)

04.28.06

Remark : ACGIH 8-hr Time Weighted Average (TWA): 200 ppm

04.28.06

Remark : NIOSH Recommended Exposure Limit: 10 hr Time Weighted Average: 200 ppm. Immediately Dangerous to Life or Health: 2000 ppm

04.28.06

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : = -70 °C / -87.9°C / -86.5 °C /-87.95 °C
Method : other: Literature values
Test substance : Bromochloromethane, > 98% purity

Remark : Estimate using PBT Profiler / Literature (Lide, DR., 1999)/ cited in HA, 1989 / Riddick et al, 1986 as cited in HEED, 1990.

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2.2 BOILING POINT

Value : = 68 °C / 68 °C / 67 °C
Method : Other: Literature values
Test substance : Bromochloromethane, > 98% purity

Remark : Albemarle Corporation MSDS / Literature (Lide, DR, 1999) / cited in HA, 1989

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2.3 DENSITY

Type : Density
Value : = 1.92 at 25 °C / 1.9344 g/cu cm at 20 °C
Method : other: Literature values
Test substance : Bromochloromethane, > 98% purity

Remark : Albemarle Corporation MSDS / Literature (Lide, DR, 1999)
04.28.06

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Type : Vapor Pressure
Value : 147.2 mmHg at 25 °C
Method : other: Literature values
Test substance : Bromochloromethane, > 98% purity

Remark : Riddick, J.A., 1986 cited in HEED, 1990
04.28.06

Type : Vapor Pressure
Value : = 142 mmHg at 25 °C / 141.07 mm Hg at 24.05 °C
Method : other: Literature values
Test substance : Bromochloromethane, > 98% purity

Remark : Daubert, TE, 1989 / cited in HA, 1989
04.28.06

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log Kow : 1.41
Method : Other: Literature
Test substance : Bromochloromethane, > 98% purity

Remark : Literature: Tewari, Y.B., 1982 and as cited in PBT Profiler and in HA, 1989.
04.28.06

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 5300 mg/l at 25 °C
Remark : Estimated from PBT profiler
Test substance : Bromochloromethane, > 98% purity

Solubility in : Water
Value : $1.67 \times 10^{+4}$ mg/l at 20 °C / 9,000 mg/l at 25 °C/ 16.7 g/l at 25 °C

Remark : Literature: Yalkowsky, S.H., 1992 / cited in HA, 1989 / Tewari,Y.B., 1982
04.28.06

2.6.2 SURFACE TENSION

Value 33.32 dynes/cm @ 20 °C
Remark : Literature: Dean, J.A., 1987
04.28.06

2.7 FLASH POINT

Type : Flash Point
Method : other: Literature value
Test substance : Bromochloromethane, > 98% purity

Remark : No flash point or fire points could be demonstrated by standard tests in air. BCM has a history of use in fire extinguishers.
Literature: Clayton, GD, 1994
04.28.06

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Type	**:**	Viscosity
Value	**:**	= 0.670 mN.s/sq m at 20 °C
Method	**:**	other: literature
Test substance	**:**	Bromochloromethane, > 98% purity
Remark	**:**	Literature: Dean, J.A., 1987

04.28.06

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	Photodegradation
Test substance	:	Bromochloromethane, purity > 98%
Remark	:	Direct photolysis should have only a minor effect on the atmospheric lifetime of chlorobromomethane due to its very low UV absorption at wavelengths > 290 nm (Orkin, VL et al, 1997 as cited in HSDB)
Type	:	Estimation of overall hydroxyl rate constant
Remark	:	Calculation of the rate constant for the atmospheric reaction between photochemically produced hydroxyl radicals and the test substance in the vapor phase gives an overall rate constant value of $0.0994e^{-12}$ cm3/molecule-sec. This rate constant calculates to an estimated half-life of 107.63 days. (12 hr day, $1.5e^{6}$ OH/cm^{3}; AOP Program v. 1.92 from EPISUITE v. 4.0)

3.1.2 STABILITY IN WATER

Type	:	Abiotic
Method	:	Literature
Test substance	:	Bromochloromethane
Remark	:	The hydrolysis half-life of bromochloromethane has been estimated at about 44 years at 25°C and pH 7. Therefore, hydrolysis should not be environmentally significant. (Mabey, W. and T. Mill, 1978, cited in HEED, 1990) Measurement of chlorobromomethane reaction kinetics as a function of pH and temperature indicate that HS- promoted reactions exceed hydrolysis rates at HS- concentrations greater than 2-17 uM, well within ranges common in sulfate-reducing environments. Therefore abiotic reactions with bisulfide ions may be of considerable importance in sulfate-reducing environments. (Roberts, AL, 1992 cited in HEED, 1990). Other estimation of hydrolysis rates yields a rate constant of of $9.350e^{-008}$ L/molecule-sec at pH > 8 and 25 degrees C. The rate constant estimated in this modelling does not include the neutral rate constant, which could be the dominant hydrolysis rate at environmental pH values. Half-life from this rate for pH 8 is estimated at 2.349 e^{+005} years, and for pH 7 at 2.349 $e^{+005.}$ (HYDROWIN program v. 2.00, from EPISUITE, v. 4.0).

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3.1.3 STABILITY IN SOIL

Remark	:	A Koc of 21 can be estimated (assuming water solubility 16.7 g/l, and using method of Lyman). This suggests high soil mobility (Swann et al, 1983 cited in US EPA, 1990). The Koc estimates suggest that BCM is not tightly bound to soil through adsorption. It is also unlikely that BCM adsorb to sediment, thus not interfering with volatilization or biodegradation in disappearance from aquatic environment. BCM has been reported to undergo microbial degradation under anoxic conditions when cultured with soil bacteria (Kobayashi, H., 1982).
Test substance	:	Bromochloromethane, > 98% purity

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Remark : Koc = 29 to 137 (HA, 1989.) "Adsorption on particulates and subsequent precipitation in sediments in aquatic environments is not significant".

Remark Calculation of Koc using KOCWIN v. 2.00 (EPISUITE 4.0) yields values of 21.73 L/kg using molecular connectivity index methods and 16.72 L/kg when based on an experimental log Kow of 1.41.

Test substance : Bromochloromethane, > 98% purity
04.28.06

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : other: adsorption/desorption
Media : water – soil
Remark : The partition coefficient of BCM between sandy loam soil and water was reported to be 0.2497.
Reference : Mokrauer, J.E., 1989 as cited in HSDB
Test substance : Bromochloromethane, > 98% purity
04.28.06

3.3.2 DISTRIBUTION

Remark : Distribution as estimated by PBT Profiler

Water	40%
Soil	16%
Sediment	0%
Air	44%

Reference : Literature: estimated by Syracuse Research Corporation as cited in Hazardous Substance Database and as estimated using PBT Profiler.
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Remark : Level III Fugacity-Based Environmental Partitioning Modelling
The following table represents the fugacity modelling calculated using the parameters: Molecular weight 129.38, Henry's Law Constant Constant 0.00146 atm-m^3/mole (Henry database), Vapor pressure 143 mm Hg (MPBWIN program), Log Kow 1.41 (KOCWIN program) and Soil Koc 21.7 (KOCWIN MCI method).

Persistence Time: 183 hours
Reaction Time: 969 hours Percent reacted: 18.9%
Advection time: 226 hours Percent advected: 81.1%

Reference : Modelling using EPISUiTE v. 4.0

Environmental Compartment	Mass Amount (percent)	Half-life (hours)	Emissions (kg/hr)	Fugacity (ATM)	Reaction (kg/hr) (percent)	Advection (kg/hr) (percent)

Air	40.5	2,916	1000	$4.2e^{-010}$	52.9 1.76	$2.23e^{+003}$ 74.2
Water	37.8	360	1000	$1.17e^{-008}$	399 13.3	208 6.92
Soil	21.6	720	1000	$8.93e^{-008}$	114 3.81	0 0
Sediment	0.104	3,240	0	$1.05e^{-008}$	0.122 0.00405	0.0114 0.000379

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : Domestic wastewater innoculum or activated sludge innoculum
Test substance : Bromochloromethane, > 98% purity

Remark : Results of two aerobic biodegradation screening studies in aqueous media suggest that biodegradation could be relevent to aquatic fate.
In the first study, BCM at an initial concentration of 5 or 10 mg/l underwent 100% degradation within 7 days using a settled domestic wastewater innoculum and aerobic conditions. Complete degradation ensued with 3 successive subcultures. (Tabak, H.H., 1981)
In a 4 week biodegradation screening test (MITI test), using BCM at 100 ppm, and activated sludge innoculum, removal of 0-12% of BOD was reported (CITI, 1992).

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Type : Biodegradation estimation
Test substance : Bromochloromethane, > 98% purity

Remark : Estimations using BIOWIN v. 4.10 (EPISUITE 4.0) predict that bromochloromethane does not meet ready biodegradation criteria, but the time frame for primary biodegradation is days to weeks, and ultimate biodegradation timeframe is weeks.

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : ca. 2.4
Method : other: estimations
Remark : A bioconcentration factor of 2.4 can be estimated using PBT profiler using regression derived equations, and a log Kow of 1.41. This suggests the potential for bioconcentration in aquatic organisms is low (Swann, R.L., 1983)
Test substance : Bromochloromethane, > 98% purity.
04.28.06

BCF : ca. 3.96
Method : other: estimations

Remark : A bioconcentration factor of 3.96 L/kg wet weight can be estimated using BCFBAF v. 3.00 (EPISUITE v. 4.0) based on a log Kow (experimental) of 1.41. A value for BCF if 4 L/kg wet weight was also identified in the Experimental BCF-kM Database structure match. This suggests the potential for bioconcentration in aquatic organisms is low (Swann, R.L., 1983)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	Not reported
Unit	:	mg/l
NOEC	:	= 80 mg/l
LC50	:	= > 80 mg/l
Method	:	other: Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975), EPA-660/3-75-009
GLP	:	No
Test substance	:	Bromochloromethane, > 98% purity
Reliability		1
Remark	:	Dow Chemical Company Studies (1960), summarized by US EPA (in HEED, 1990)

04.28.06

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	Estimation
Remark	Estimation of acute invertebrate toxicity using the ECOSAR v. 1.00 modelling program (EPISUITE v. 4.0), based on an estimated Kow of 1.43, an experimental water solubility of 16.7 g/L and a chemical class of neutral organics gives a Daphnid 48 hour LC50 prediction of 164 .033 mg/L (ppm).

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Type	Estimation
Remark	Estimation of acute toxicity to green algae using the ECOSAR v. 1.00 modelling program (EPISUITE v. 4.0), based on an estimated Kow of 1.43, an experimental water solubility of 16.7 g/L and a chemical class of neutral organics, gives a 96 hour EC50 prediction of 60.789 mg/L (ppm).

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	In vivo
Type	:	Dermal absorption via exposure in air
Species	:	Rat
Strain		Fischer 344
Numbers of animals	:	6 males per group
Doses	:	2,500, 5,000, 20,000 or 40,000 ppm air concentrations
Route of administration	:	other: dermal exposure via air concentration
Exposure time	:	4 hours
GLP	:	No
Test substance	:	BCM: 98% by weight in air
Method	:	Body-only exposures in chambers with individual protection to prevent pulmonary uptake from test article concentrations in air
Remark	:	A 33 liter chamber was constructed with six individual compartments to house rats fitted with latex masks conected to outside airlines. Rats were fitted with right jugular cannulas for blood sampling while confined in the exposure chambers. Blood samples were taken prior to the exposure, at 0.5 hours, and hourly during exposures, except during the 1 hour exposure experiment when samples were drawn every 10 minutes. Tissue/air partition coefficients for BCM were 41.5 +/-0.9 for blood/air, 29.2 +/- 0.5 for liver/air, and 11.1 +/- 1.8 for muscle/air. Plasma bomide levels increased with increasing exposure concentrations of BCM, but not in a linear fashion. Plasma bromide levels for 2,500 ppm BCM were 0.8 mM, for 5,000 ppm, 0.9 mM, for 20,000, 3.4 mM, and for 40,000 ppm, 5.6 mM. 4 hour blood levels for the same concentrations were 6.2, 26.0, 104.4, and 224.4 ug/ml. Permeablilty constants for these values were 0.81, 0.81, 0.77 and 0.77 cm/hr.
Reference		McDougal, J.N. et al., 1985
Result	:	The Health Advisory reports that the dermal flux in this study was 0.011 to 0.164 mg/cm^3/hour. (HA, 1989)
Reliability		1

04.28.06

Method	:	Inhalation exposure
Remark	:	Kinetics of absorption of inhaled bromochloromethane in male Fisher 344 rats was shown to be a composite of a slow first order and a saturable uptake process. Km (the concentration in air at which uptake occurs at one-half the maximum rate) was calculated to be 119 ppm (630 mg/m^3) and the Vmax (the maximum rate of uptake) was calculated to be 11.4 mg/kg/hour. (Anderson, M.E. et al, 1980) In another experiment, male F344 rats were exposed to nine initial concentrations of 100 to 10,000 ppm bromochloromethane vapor for 175 to 205 minutes in a closed inhalation chamber. Chamber concentration disappearance curves indicated that absorption was biphasic, consisting of a rapid equilibrium phase completed in 70 to 110 minutes and a slow phase that was nearly linear after equilibrium. The rapid uptake phase reportedly represents the initial blood-gas equilibrium. The slow uptake phase reportedly represents metabolism and and loading into poorly perfused tissues, and was a composite of a saturable process at lower concentrations and a first order process. Kinetic constants for the saturable process were determined and included a Km of 91 ppm and a Vmax of 10.5 mg/kg/hour. (Gargas, M.L. and M.E. Anderson, 1982). Kinetics of bromochloromethane metabolism was studied by Gargas et al (1986) using 4 hour inhalation studies with male F344 rats. Gas uptake was determined during exposure to 200 to 4000 ppm test article in a closed chamber, and plasma bromide levels and carboxyhemoglobin levels were

determined following exposure to constant concentrations of 51 to 2006 ppm. The gas uptake data indicated that metabolism had both first order and saturable components. The oxidative, cytochrome P-450 mediated pathway was high affinity and low capacity with production of CO saturable at bromochloromethane concentrations greater than 200 ppm; the maximum percent carboxyhemoglobin saturation attained was about 9%. The maximum rate for metabolism of BCM to carbon monoxide was 54 umol metabolized/kg/hour. The glutathione-dependent cytosolic pathway producing CO2 and halide was low affinity but high capacity and a single first order process at all exposure concentrations.

Reliability : 1
04.28.06

In Vitro/in vivo : In vivo – distribution

Result : An inhalation study was conducted using various species (2 female dogs, 3 male rabbits, and 20 male rats). Animals were separately exposed for 7 hours per day, 5 days/week, for 14 weeks to 1000 ppm bromochloromethane. Both organic and inorganic bromide levels in brain and blood of treated animals were elevated at termination of a 7-hour exposure period compared to control. Total bromide levels in blood were 6.0 to 10.5 times higher than levels in brain. Levels of organic bromide in blood were 8.0 to 13.1 times the levels in the brain.

Reference Svirbely, J.L. et al., 1947 as cited in HA, 1989
Reliability 1
04.28.06

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : > 5000 mg/kg bw
Species : Rat
Sex : Male
Number of animals : 5 per group
Vehicle : Corn oil
Doses : 5000 or 7000 mg/kg
Method : other:
Year : 1960
GLP : No
Test substance : BCM, 99% as demonstrated by Infrared analysis

Remark : Aliquots of a 50% BCM in corn oil solution were gavaged to male rats. All rats gavaged with 7 g/kg died within 24 hours. All rats gavaged with 5 g/kg survived for the 14 day recovery period.

Reliability 1
Reference Dow Chemical Company, 1960 – published as Torkelson, T.R., 1960
04.28.06

Type : LD50
Value : 4,300 mg/kg bw
Species : Mice
Strain : Swiss
Number of animals : 10 per group
Vehicle : olive oil
Doses : 500 to 4400 mg/kg
Year : 1947
GLP : No

Test substance	:	Bromochloromethane, > 98% purity
Reliability		1
Remark	:	Doses ranged from 500 to 4400 mg/kg/day administered in corn oil to groups of 10 animals per dose. Surviving animals were observed for 6 days. CNS depression was noted in animals dosed higher than 500 mg/kg.
Reference		Literature: Svirbely, J.L. et al, 1947 as reported in Health Advisory, 1989.
04.28.06		

Type	:	Single gavage dose and 10 day repeated dose
Species	:	Mice
Strain	:	Swiss
Sex	:	Male/female
Vehicle	:	Corn oil in single dose; Olive oil in repeated dose
Doses	:	0, 500, 3,000 or 4,500 mg/kg single dose; 3,000 mg/kg/day for repeated dose
Year	:	1948
GLP	:	No
Test substance	:	Bromochloromethane, > 98% purity

Remark	:	Fatty degeneration of the liver and kidney, as well as focal necrosis and hydropic degeneration of the liver was observed in the 3,000 and 4,500 groups after single oral dose. Changes were most severe after 24 hours and were reversible in mice surviving 48 hours. No effects were noted at 500 mg/kg. Thirty two Swiss mice were gavaged with 3,000 mg/kg for 10 consecutive days. Control animals were gavaged with olive oil. Several mice were sacrificed after each of the doses. In mice that were sacrificed or died, fatty degeneration of the liver, kidney and sometimes the heart were observed. The effects were most severe 24-48 hours after the initial dose, and became slight after 80 hours. Opacity of the eyes was observed in 5/19 rats surviving 3 days.
Reliability		1
Reference		Literature: Highman, B., 1948 as reported in Health Advisory, 1989
04.28.06		

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Mortality from Single Exposures
Species	:	Rat
Sex	:	male/female
Number of animals	:	10 per sex most groups; one group had 11 per sex; one had 15 per sex
Vehicle	:	None
Doses	:	5,000, 10,000, 20,000, 40,000 or 80,000 ppm
Exposure time	:	0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 1.0, 1.5, 2.0, 4.0, 6.0 or 7.0 hour(s)
Method	:	Dow Laboratories method
Year	:	1960
GLP	:	No
Test substance	:	BCM, 99% as confirmed by infrared analysis

Remark	:	Exposures were made in 160-liter capacity glass walled chambers. Rats were introduced after vapor concentrations were established. Measured values were generally within 10% of calculated values. Maximum exposures causing no mortality were: 0.1 hr at 40,000 ppm; 0.4 hr at 20,000 ppm, 1.5 hr at 10,000 ppm and 7.0 hr at 5,000 ppm. Deaths that occurred were generally during the exposures and appeared to be totally related to anesthesia. Four hour exposure to 10,000 ppm killed 6 of 10 male rats, and 5/10 female rats. One hour exposure to the same concentration killed one female rat only; six hour exposure to 10,000 ppm killed all animals exposed.

Remark Female rats (4-5 treated, 10 control) from various single exposure scenarios (600, 800, 1500, 5,000, 10,000, or 40,000 ppm) for durations of 0.025 hours to 7 hours were examined to determine the most severe conditions that caused no significant organic damage. No gross pathological changes were seen at necropsy. Microscopic evidence of injury was detected only in the liver, although increases in organ weights were also seen in the kidneys. The liver injury was slight, being characterized as very small vacuoles in the parenchyma, but not typical of fatty degeneration.

Remark Significant liver weight increases accompanied the histopathological changes. The maximum exposures that caused no significant organic injury were 0.025 hours at 40,000 ppm; 0.1 hour at 10,000 ppm; 0.3 hour at 5,000 ppm; 3.0 hours at 1,500 ppm, and 7.0 hours at 600 ppm.

Reliability 1

Reference Dow Chemical Company, 1960 – published as Torkelson, TR, 1960
04.28.06

Type : Acute Inhalation Toxicity
Value : > 38.6 mg/l
Species : Rat
Strain : Sprague Dawley CD
Sex : male/female
Number of animals : 5 per sex in single group
Vehicle : None
Doses : 54.2 nominal, 38.6 mg/l achieved
Exposure time : 4 hour(s), nose only
Method : OECD 403 "Acute Inhalation Toxicity"
Year : 1998
GLP : Yes
Test substance : Bromochloromethane, > 98% purity

Remark : The mean achieved atmospheric concentration (as measured by a gas chromatographic method) was 38.6 mg/l bromochloromethane. Ten Sprague Dawley rats (5 male, 5 female) were exposed by nose only to this limit concentration for 4 hours. One male and one female rat died from this exposure. Common clinical signs observed were hunched posture, lethargy, piloerection, coma and hypothermia. Changes in respiratory rate, ataxia, ptosis, diuresis, loss of righting reflex, noisy respiration, and occasional incidents of wet fur, labored respiration, fasciculations and staining around the snout were noted. Surviving animals appeared normal within 2 to 4 days of exposure. One animal showed no bodyweight gain the the first week after exposure, and other survivors showed possible reduction in that time period. Normal body weight gains were seen in week 2. The animals that died during the study had lung abnormalities including hemorrhage, swelling, dark or pale patches and pale foci. At the end of the study, one male had hydroneprhosis, and one female had dark foci in the lungs and a dark liver. The other six animals had no abnormalities at necropsy. Acute inhalation median lethal concentration (LC50) in the Sprague Dawley rat under the conditions of the study was greater than 38.6 mg/l bromochloromethane.

Reference SafePharm Laboratories, Limited, 1998.
Reliability 1
04.28.06

Acute Inhalation Lethality Summary Table from HEED, 1990

Species	Strain/sex	Concentration mg/m^3	Concentration ppm	Exposure duration	Endpoint	Reference
Mouse	Swiss/NR	2,995	15,850	7 hours	8 hr LC50	Svirbely, 1947

Mouse	Swiss/NR	2,504	13,257	7 hours	24 hr LC50	Svirbely, 1947
Mouse	Swiss/NR	2,436	12,891	7 hours	48 hr LC50	Svirbely, 1947
Mouse	Swiss/NR	2,273	12,029	7 hours	72 hr LC50	Svirbely, 1947
Mouse	Swiss/NR	2,551	13,500	1 week	18/20 died	Svirbely, 1947
Mouse	Swiss/NR	2,268	12,2002	7 hours	72 hr LC50	Highman, 1948
Rat	NR/M	5,000	26,460	7 hours	0/11 died	Torkelson, 1960
Rat	NR/Fe	5,000	26,460	7 hours	0/11 died	Torkelson, 1960
Rat	NR/M	10,000	52,920	4 hours	6/10 died	Torkelson, 1960
Rat	NR/Fe	10,000	52,920	4 hours	6/10 died	Torkelson, 1960

Note: NR = not reported

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value : > 5000 mg/kg bw
Species : Rabbit
Number of animals : 5
Vehicle : None
Doses : 5 g/kg
Method : Modified Draize technique, 24 hour exposure
Year : 1960
GLP : No
Test substance : BCM, 99% as demonstrated by Infrared analysis

Remark : Belly hair was clipped from the rabbits, and a single application of BCM was applied using a modified Draize technique. One death occurred within 24 hours of exposure to 5 g/kg, and only a slight loss of body weight occurred in other animals over the observation period. Clinical observations included a burn and denaturation of the skin with occlusive application. When the material was allowed to evaporate freely, BCM only caused typical defatting effects to the skin.

Reliability 1
Reference Dow Chemical Company, 1960 – published as Torkelson, TR, 1960
04.28.06

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Remark : BCM was used as a vaporizable fire extinguishing agent. It was studied along with fluorinated halogen agents for effects on the heart. In a comparative study in anesthetized dogs, thirty eight variables reflecting cardiovascular dynamics and myocardial metabolism were monitored before, during and after exposure to 0.3 to 1.0% BCM in oxygen. Exposure to BCM was found to cause disturbances in myocardial energy metabolism that were connected to myocardial performance. Based on concentrations at which the effects occurred, BCM was more potent than the fluorinated halogens tested. (Van Stee, EW, 1975). Previous to this study, a moderate effect of exposure, defined as definite feeling of light headedness, moderate acceleration of heart rate, and occasional premature ventricular contraction was estimated to likely occur in humans with 20 minute of exposure to 0.33% BCM. (Van Stee, EW, 1974).

08.02.2002

5.2.1 SKIN IRRITATION/ CORROSION

Species : rabbit
Exposure time : 4 hour(s)

Result	:	Non-corrosive
Method	:	21 CFR, Part 191, Paragraph 191.11 (revised 1970)
Year	:	1973
GLP	:	No
Test substance	:	Bromochloromethane, > 98% purity
Reference	:	Rampy, LW, 1973
Reliability		2
04.28.06		
Remark	:	In a dermal toxicity test, dermal application of 5000 mg/kg to clipped hair sites in 5 rabbits with occlusion resulted in burns and denaturation of the skin with 4/5 animals surviving after 24 hours. Application without occlusion only had a defatting effect
Reference		Torkelson, T.R., 1960 as reported in Health Advisory, 1989.
04.28.06		
Species	:	rabbit
Concentration	:	0.5 ml neat bromochloromethane
Exposure	:	Semi-occlusive
Exposure time	:	4 hour(s)
Number of animals	:	3 rabbits
Vehicle	:	None
Result	:	Corrosive
Method	:	OECD 404 "Acute Dermal Irritation/Corrosion“
Year	:	1998
GLP	:	Yes
Test substance	:	Bromochloromethane, > 98% purity
Reliability		1
Remark	:	The test was not extended to another group of 3 animals because of the severity of the effects seen in the first group.
Reference		Notox Laboratories, 1998

5.2.2 EYE IRRITATION

Species	:	Rabbit
Concentration	:	undiluted
Dose	:	0.1 ml
Number of animals	:	2
Vehicle	:	None
Method	:	Other:
Year	:	1960
GLP	:	No
Test substance	:	BCM, 99% as demonstrated by Infrared analysis
Remark	:	Moderate irritation was seen when BCM was instilled in the eyes of 2 rabbits. Considerable swelling of the conjunctiva and slight transitory irritation of the cornea occurred.
Reliability		1
Reference		Dow Chemical Company, 1960 – published as Torkelson, TR, 1960.
04.28.06		

5.3 SENSITIZATION

Type	:	Magnusson and Kligman Maximisation

Species	:	guinea pig
Number of animals	:	20 test and 10 control in main study
Vehicle	:	Arachis oil for id induction, and topical challenge
Result	:	20% sensitisation rate (4/20)
Classification	:	Mild sensitiser not meeting criteria for EU labelling
Method	:	OECD 406, “Skin Sensitisation“, 1992
Year	:	1997
GLP	:	Yes
Test substance	:	:Bromochloromethane
Reliability		1

Remark Based on preliminary tests, the following concentrations were chosen for the main study: 10% w/v in arachis oil for id induction, undiluted for topical induction, and 75% and 50% v/v in arachis oil for topical challenge. Sensitization reactions were seen in 4 of 20 animals, but the reactions did not meet the EU labelling requirements for sensitization.

Reference Allen, D.J., 1997.

3/12/2006

5.4 REPEATED DOSE TOXICITY

Type	:	Repeated dose, inhalation
Species	:	Rats
Sex	:	Male/female
Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week for 4 to 6 months
Doses	:	500 or 1000 ppm (5.3 mg/l) (m, f) 370 ppm (f)
Control group	:	Unexposed
Year	:	1960
GLP	:	No
Test substance	:	BCM, 99% as confirmed by infrared analysis

Remark : Repeated dose exposures to BCM were given to 20 (except 10 to 12 where indicated) rats per sex per group in 1700 liter capacity water sealed chambers. Male rats exposed to 1000 ppm (79-82 exposures in 114 days) had normal BUNs, appearance, activity and growth. Blood inorganic bromide levels at termination were 122 mg Br-/100 ml. Microscopic liver lesions were very slight proliferation of the bile duct epithelium with very slight portal fibrosis and inflammation. Cloudy swelling of parenchymal cells in midzonal areas spread to central areas of lobules. Numerous parenchymal cells had small vacuoles. Liver and kidney weight averages were increased. Female rats exposed to the same levels had fatty and enlarged livers grossly, with elevated liver and kidney weights. Similar microscopic changes were seen as in the males, and blood bromides were also elevated.

Remark Male rats exposed to 500 ppm (79-82 exposures in 114 days) were normal based on survival, growth, activity, growth, clinical signs, gross and microscopic pathology. Blood bromide levels were 58 mg Br-/100 ml compared to 8 mg Br-/100 ml. There was a slight difference in liver weights (increased with exposure) that was not accompanied by pathology. Female rats had elevated average liver weights, slight bile duct proliferation and very slight portal fibrosis, with occasional vacuolation of liver parenchymal cells.

Remark Female rats (10-12 per group) exposed to 370 ppm (135 exposures in 195 days) were normal except for a nonstatistically significant increase in liver weights, and blood bromide levels that were 73 mg/100 ml compared to controls of 0.9 to 5 mg/100 ml.

Reliability		1
Reference		Dow Chemical Company, 1960 – published as Torkelson, TR, 1960.

Type	:	Repeated dose, inhalation
Species	:	Guinea pigs
Sex	:	Male/female
Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week for 4 to 6 months
Doses	:	500 or 1000 ppm (5.3 mg/l) (m, f)
Control group	:	Unexposed for each species
Year	:	1960
GLP	:	No
Test substance	:	BCM, 99% as confirmed by infrared analysis

Remark	:	Repeated dose exposures to BCM were given to 10 guinea pigs per sex per group in 1700 liter capacity water sealed chambers. Male guinea pigs exposed to 1000 ppm (79-82 exposures in 114 days) had normal appearance,and growth. Average body weights were below control. Liver and kidney weights were elevated. Blood inorganic bromide levels at termination were 33-38 mg Br-/100 ml compared to 5.2 mg Br-/100 ml for control. Microscopically, decreased spermatogenesis was seen in testicular tublules with fibrosis in numerous tubules, and only germinal epithelium remaining in others. Female guinea pigs exposed to the same levels had slightly lower body weights but within normal limits. No pathology or organ weight effects were seen, and blood bromides were also elevated compared to controls.
Remark		Male and female guinea pigs exposed to 500 ppm (79-82 exposures in 114 days) were normal based on survival, growth, activity, growth, clinical signs, gross and microscopic pathology. Blood bromide levels were elevated compared to control.
Reliability		1
Reference		Dow Chemical Company, 1960 – published as Torkelson, TR, 1960.

Type	:	Repeated dose, inhalation
Species	:	Mice
Sex	:	Female
Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week for 4 to 6 months
Doses	:	500 or 1000 ppm (f)
Control group	:	Unexposed
Year	:	1960
GLP	:	No
Test substance	:	BCM, 99% as confirmed by infrared analysis

Remark	:	Repeated dose exposures to BCM were given to 10 female mice per group in 1700 liter capacity water sealed chambers. Female mice exposed to 1000 ppm (79-82 exposures in 114 days) were normal in all aspects, except for slight increases in liver and kidney weights.
Remark		Female mice exposed to 500 ppm (79-82 exposures in 114 days) were normal based on survival, growth, activity, clinical signs, gross and microscopic pathology. Body weights were slightly lower.
Reliability		1
Reference		Dow Chemical Company, 1960 – published as Torkelson, TR, 1960.

Type	:	Repeated dose, inhalation
Species	:	Rabbits
Sex	:	Male/female

Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week for 4 to 6 months
Doses	:	500 or 1000 ppm (5.3 mg/l) (m, f)
Control group	:	Unexposed for each species
Year	:	1960
GLP	:	No
Test substance	:	BCM, 99% as confirmed by infrared analysis

Remark : Repeated dose exposures to BCM were given to 2 rabbits per sex per group in 1700 liter capacity water sealed chambers. Male rabbits exposed to 1000 ppm (79-82 exposures in 114 days) had normal BUNs, appearance, activity and growth. Blood inorganic bromide levels at termination were 67 mg Br-/100 ml compared to 5 mg/100 ml for control rabbits. Microscopic examination revealed testicular changes characterized by decreased spermatogenesis with replacement fibrosis occurring in the tubules of one rabbit. The other male rabbit was normal. Female rabbits exposed to the same level were normal except for apparent increased liver weight and elevated blood bromides.

Remark Male and female rabbits exposed to 500 ppm (79-82 exposures in 114 days) were normal based on survival, growth, activity, growth, clinical signs, gross and microscopic pathology. Blood bromide levels were 50 to 60 mg Br-/100 ml in treated animals compared to 5 mg Br-/100 ml in controls.

Reliability 1

Reference Dow Chemical Company, 1960 – published as Torkelson, T.R., 1960

Type	:	Repeated dose, inhalation
Species	:	Dogs
Sex	:	Male/female
Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week for 4 to 6 months
Doses	:	370 ppm (m,f)
Control group	:	Unexposed for each species
Year	:	1960
GLP	:	No
Test substance	:	BCM, 99% as confirmed by infrared analysis

Remark : Repeated dose exposures to BCM were given to 1 dog per sex per group in 1700 liter capacity water sealed chambers. Male and female dogs exposed to 370 ppm (79-82 exposures in 114 days) were normal in all aspects. Blood inorganic bromide levels at various intervals in male dogs were 22-41 compared to 0.9 to 3.9mg Br-/100 ml in control males and 25-60 compared to 0.7 to 2.7 mg/100 ml for female control dogs.

Reliability 1

Reference Dow Chemical Company, 1960 – published as Torkelson, T.R., 1960.

Type	:	Repeated dose, inhalation
Species	:	Rats (Wistar)
Sex	:	Male
Route of admin.	:	Inhalation
Exposure period	:	6 hours per day, 5 days per week
Frequency of treatm.	:	124 exposures in 6 months
Doses	:	500 (515 ppm measured) or 1000 (1010 ppm measured)
Control group	:	Unexposed
Year	:	1966
GLP	:	No
Test substance	:	BCM, 98.8%

Remark	Groups of 50 male and 50 female rats were exposed to nominal concentrations of 0, 500 or 1000 ppm BCM for 6 hours per day, 5 days per week for 6 months for a total of 124 exposures. Body weights, serum bromide levels and survival were evaluated throughout the experiment. After 2 and 4 months of exposure, groups of 10 rats in treated groups, and 5 rats from the control group were subjected to white blood cell counts, and clinical chemistry determinations, and sacrificed for organ weight and histopathologic exam. Clinical chemistry tests included SGOT, SGPT, total protein, albumin and albumin/globulin ratio. Tissues weighed and examined included liver, kidney and spleen. The only treatment related effect was a significantly decreased body weight gain in male rats at and greater than 149.51 mg/kg/day (estimated dose from air concentration of 515 ppm). Blood bromide levels were increased in both treatment groups throughout the treatment period.
Reliability	1
Reference	MacEwen, J.D., 1966

Type	:	Repeated dose, inhalation
Species	:	Dogs (Beagle)
Sex	:	Male and female
Route of admin.	:	Inhalation
Exposure period	:	6 hours per day, 5 days per week
Frequency of treatm.	:	124 exposures in 6 months
Doses	:	500 (515 ppm measured) or 1000 (1010 ppm measured)
Control group	:	Unexposed
Year	:	1966
GLP	:	No
Test substance	:	BCM, 98.8%

Remark	Groups of 4 male and 4 female dogs were exposed to nominal concentrations of 0, 500 or 1000 ppm BCM for 6 hours per day, 5 days per week for 6 months for a total of 124 exposures. Body weights, serum bromide levels and survival were evaluated throughout the experiment. After 2 and 4 months of exposure, 2 dogs in treated groups, and 1 rats from the control group were subjected to white blood cell counts, and clinical chemistry determinations. Clinical chemistry tests included SGOT, SGPT, total protein, albumin and albumin/globulin ratio. The only treatment related effects were increased blood bromide levels in both treatment groups throughout the treatment period.
Reliability	1
Reference	MacEwen, J.D., 1966

Type	:	Repeated dose, inhalation
Species	:	Dogs
Sex	:	Female
Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week for 14 weeks
Doses	:	500 (515 ppm measured) or 1000 (1010 ppm measured)
Control group	:	Unexposed
Year	:	1966
GLP	:	No
Test substance	:	BCM, > 98% purity

Remark	Groups of 4 male and 4 female dogs were exposed to nominal concentrations of 0, 500 or 1000 ppm BCM for 6 hours per day, 5 days per week for 6 months for a total of 124 exposures. Body weights, serum bromide levels and survival were evaluated throughout the experiment. After 2 and 4 months of exposure, 2 dogs in treated groups, and 1 rats from the control group were subjected to white blood cell counts, and clinical chemistry determinations. Clinical chemistry tests included SGOT, SGPT, total protein, albumin and albumin/globulin ratio, bromsulfalein excretion, and urinalysis. At termination there was a slight increase in hemosiderin in the spleen and kidneys, and an increase in fat in the kidneys. Inorganic bromide levels increased in the blood of the dogs throughout treatment with terminal concentrations being from 300 to 360 mg/dl.
Reliability	1
Reference	Svirbely, J.L. et al, 1947

Type	:	Repeated dose, inhalation
Species	:	Rats
Sex	:	Male
Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week for 14 weeks
Doses	:	1000 (893 ppm approximately)
Control group	:	Unexposed
Year	:	1966
GLP	:	No
Test substance	:	BCM, > 98% purity

Remark	Groups of 20 male rats were exposed to nominal concentrations of 0 or 1000 ppm BCM for 7 hours per day, 5 days per week for 14 weeks. Body weights and survival were evaluated throughout the experiment. After 67 exposures, 19 rats were terminated and evaluated histologically. Bromide levels in the blood and brain were evaluated immediately after the last exposure. At termination there was a slight increase in hemosiderin in the spleen. Inorganic bromide levels were increased in the blood and brains of treated rats .
Reliability	1
Reference	Svirbely, J.L. et al, 1947

Type	:	Repeated dose, inhalation
Species	:	Mice (Strain A and C3H)
Route of admin.	:	Inhalation
Exposure period	:	7 hours per day
Frequency of treatm.	:	5 days per week with interruptions over 4 to 5 months
Doses	:	1000 ppm (893 ppm approximately)
Control group	:	Unexposed
Year	:	1966
GLP	:	No
Test substance	:	BCM, > 98% purity

Remark	Groups of 100 Strain A mice (2 months of age at initiation) and 45 C3H mice (3 to 7 months at initiation) were exposed to nominal concentration of 1000 ppm BCM for 3-7 hours per day, 5 days per week with interruptions due to mortality or adverse effects observed. Strain A mice received a total of 64 exposures of 3-7 hours in a period of about 5 months. Surviving C3H mice received a total of 49 exposures of 3-7 hours in a period of 4 months. Most mice died at various intervals during treatment, and others were sacrificed or died at various intervals after treatment. A total of 21 mice (1 Strain A, remainder C3H) survived until terminal sacrifice at 13 to 16 months of age. Histological examination of mice that died during exposure generally showed fatty changes in the liver or kidneys. Extensive tubular necrosis in the inner zone of the renal cortex was observed in two strain A mice during the 4th daily exposure. Several other mice that died during exposure were reported to have coagulation or karyorrhetic necrosis of a few isolated liver cells. At terminal sacrifice, no treatment related effects were observed.
Reliability	2
Reference	Svirbely, J.L. et al, 1947

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Bacterial reverse mutation and mitotic recombination in Saccharomyces
System of testing	:	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100 and Saccharomyces cerevisiae D3
Test concentration	:	+/- S9: 10, 20 or 50 ul in dessicators for Salmonella
Metabolic activation	:	with and without S-9
Result	:	Positive response in TA 100 Negative in Saccharomyces
Method	:	other: Based on Ames et. al. (1975)
Year	:	1976
GLP	:	No data
Test substance	:	Bromochloromethane, > 98% purity
Reliability		1
Remark	:	TA 100 consistently showed positive responses without activation in reverse mutation assays. The ability of BCM to induce mitotic recombination was evaluated in Saccharomyces cerevisiae D3 at levels of 0, 0.10, 0.20, and 0.3% concentrations in presence or absence of S-9. BCM did not cause a significant increase in mitotic recombinations, with or without S-9 activation.
Reference	:	Simmon et al, 1976, 1977, 1978

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Type	:	Bacterial reverse mutation: plate incorporation
System of testing	:	Salmonella typhimurium TA97 TA98, TA100, TA 104
Test concentration	:	10 to 1000 ug/plate
Metabolic activation	:	with and without S-9
Result	:	Positive in all strains, S9 enhanced response in TA98 and TA100
Method	:	other: Based on Ames et. al. (1975)
Year	:	1987
GLP	:	No data
Test substance	:	Bromochloromethane, > 98% purity
Remark	:	BCM showed positive responses in test strains TA97, TA98, TA 100, and TA 104 with and without S9 activation. Responses in TA 98 and TA 100 were enhanced with metabolic activation.
Reliability		1
Reference		Strobel, K, and T. Grummt, 1987.

Type	:	Bacterial reverse mutation and lamda prophage induction in E.Coli
System of testing	:	Spot test for TA 1535 and 100, and E. Coli Preincubation for TA 100
Test concentration	:	Spot test: 10 ul/disk 20 to 60 mM in preincubation
Metabolic activation	:	with and without S-9
Result	:	Positive in all strains
Method	:	other: based on Ames et. al. (1975)
Year	:	1983
GLP	:	No data
Test substance	:	Bromochloromethane, > 98% purity
Remark	:	BCM was reported to give a positive dose related response for reverse mutation with liquid incubation at dose concentrations of 0, 20, 40, 60 mM without activation in Salmonella typhimurium TA 100 and TA 1535. The response was greater in TA 1535. BCM gave a positive dose related response for reverse mutation in vapor phase at a dose concentration of 10 ml/plate without metabolic activation in Escherichia coli Wu361089 and Escherichia coli-SD-4.. A positive response for forward mutation (prophage induction) in vapor phase at a dose concentration of 10 ul/plate without metabolic activation in Escherichia coli K394.
Reference		Osterman-Golkar, S., et al., 1983.

Type	:	In vitro: mammalian cells
System of testing	:	Chinese hamster FAF cells
Test concentration	:	1×10^{-6} to 5×10^{-5} M
Cycotoxic concentr.	:	Highest concentration tested
Metabolic activation	:	No
Result	:	Positive response, SCE and chromosomal aberrations
Year	:	1987
GLP	:	No data
Test substance	:	Bromochloromethane
Remark	:	BCM induced dose related sister chromatid exchanges and chromosome aberrations in Chinese hamster cells in vitro.
Reliability		1
Reference		Strobel, K. and T. Grummt, 1987

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

I U C L I D

Data Set

Memo	:	DBM HPV dossier
CAS No.	:	74-95-3
Common name	:	Dibromomethane
Molecular Formula	:	C H2 Br2
Number of pages	:	37

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

Smiles Code	**:**	BrCBr
Molecular formula	**:**	C H2 Br2
Molecular weight	**:**	173.86 (Lide, DR, ed, 1998-1999)

15.02.2002

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	**:**	Typical for marketed substance
Substance type	**:**	Organic
Physical status	**:**	Liquid
Purity	**:**	= > 98% w/w
Colour	**:**	Colorless to light yellow
Odour	**:**	Sweet

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1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Substance	Methylene Bromide
Substance	Methylene Dibromide
Substance	Dibromomethane
Trade Name	DBM

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling	:	provisionally by manufacturer/importer
Specific limits	:	No
Symbols	:	Xn
Nota	:	
R-Phrases	:	(20) Harmful by inhalation
S-Phrases	:	(23) Do not breathe fumes/vapour

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1.6.2 CLASSIFICATION

Classified	:	provisionally by manufacturer/importer
Class of danger	:	Harmful
R-Phrases	:	(20) Harmful by inhalation

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1.6.3 PACKAGING

1.7 USE PATTERN

Remark : DBM has limited usage in synthesis, as a solvent and in gage fluids. (Stenger, VA, 1978). It has potential use as a dense, volatile media for mineral and salts gravity separations.

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1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Remark : Methylene bromide (dibromomethane) is prepared by reacting methylene chloride with anhydrous aluminum bromide (treatment with bromine and aluminum) or by reaction with hydrogen bromide in the presence of an aluminum halide catalyst, followed by water washing and distillation (Stenger, V.A., 1978).

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1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : No recommended exposure limit values
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1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT/FREEZING POINT

Value	:	< 253 +/- 0.5 K (< -20.0 +/- 0.5 ° C)
Method	:	BS4633: Method for the Determination of Crystallizing Poing, Method 102 of OECD Guidelines for Testing of Chemicals, 27, July, 1995
Year	:	2007
GLP	:	Yes
Test substance	:	Dibromomethane, 99.4% purity
Reliability	:	1
Remark	:	An aliquot of test article was placed in a test tube containing a thermometer and a wire loop with which to agitate the sample. The test tube was surrounded by a glass jacket and then placed in a beaker containing a mixture of dry ice and acetone. Temperature and observations of the test article were made approximately every 30 seconds. The test would continue until the temperature of the test material reached approximately -20° C or until the test material solidified. The test was conducted in duplicate. In both tests, the test material remained a clear, colorless liquid upon cooling. Conclusion was that the freezing point was less that 253 K.
Reference		O'Connor, B.G., 2007

05/15/07

2.2 BOILING POINT

Value	:	367 +/- 1 K (94 +/- 1 degree C) at 100.00 to 100.62 kPa
Method	:	Siwoloboff method, according to ISO 918, Method 103 OECD Guidelines for Testing of Chemicals, 27 July, 1995
Year	:	2007
GLP	:	Yes
Test substance	:	Dibromomethane, 99.4% purity
Reliability	:	1
Remark	:	An aliquot of test material was placed in a test tube, which was then fastened to a thermometer, and the apparatus placed in a silicone oil bath. A capillary tube, fused 1 cm from one end, was immersed in the test materail such that the fused section was below the surface of the test material. The oil bath was then heated steadily with a heating mantle and the temperature raised to the point where the fused capillary tube emitted a steady stream of bubbles. At that point, the heat source was removed and the bath allowed to cool. The temperature at which the fused capillary tube ceased to emit bubbles and the test material rose rapidly up the inside of the capillary tube was recorded as the boiling point. The atmospheric pressure was measured with a Fortin's barometer. The test was conducted in duplicate. The temperature at which the heat source was removed in both tests was 373 K. The boiling point in each case was 367 K. Atmospheric pressure was 100.00 kPa in the first test, and 100.62 in the second.
Reference		O'Connor, B.J., 2007

05.02.07

2.3 DENSITY

Type : Density
Value : = 2.49 at 25 ° / 2.497 g/cu cm at 20 °C
Test substance : Dibromomethane, Purity > 98%

Remark : Albemarle Corporation MSDS / Literature (Stenger, V.A.,1978)
04.28.06

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Type : Vapor Pressure
Value : = 4.7 x 10^3 Pa (35.3 mm Hg) at 25 °C
Method : Method 104 of the OECD Guidelines, 27 July 1995, isoteniscope
Year : 2007
GLP : Yes
Test substance : Dibromomethane, 99.4% purity,
Reliability : 1

Remark : Vapour pressure was determined using an isoteniscope system with measurements being made at several temperatures and linear regression analysis used to calculate the vapour pressure at 25 °C. The isoteniscope system used mercury in a glass manometer to measure the pressure, and the sample temperature was regulated with a silicone oil bath. Three runs were made. The first sample was degassed for 12 minutes and temperature and pressure readings were taken between 78 and 55 °C. The same sample was degassed for a further 20 minutes and run 2 was made with temperatures ranging from 85 to 63 °C. A fresh sample degassed for 10 minutes was used for the third run, with a temperature range of 87 to 60 °C. A plot of Log10 Vp (Pa) versus reciprocal temperature (1/T(K) was graphed, and statistical analysis using an unweighted least squares treatment was conducted. The resulting equations indicated the vapor pressure relationships. The vapor pressure of the sample was measured over a range of temperature in order to extrapolate to 298.15 K.

Run	Log 10 [Vp (25° C)]
1	3.650
2	3.683
3	3.681
Mean	3.671
Vapor Pressure	4.69 x 10^3 Pa

.

Reference Tremain, S.P., 2007.

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Type : Vapor Pressure
Value : = 31 mmHg at 25 °C
Method : other: estimate from PBT Profiler
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Type : Vapor Pressure

Value : = 44.2 to 44.4 mmHg at 25 °C

Reference : Literature (Kudchadker, A.P., 1979)
04.28.06

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 1.68 at 22.5 +/- 0.5°C
pH value : 6.2
Method : Shake Flask method, Method 107 of the OECD Guidelines for Testing of Chemicals, 27 July 1995
Year : 2007
GLP : Yes
Reliability : 1
Remark For the definitive test, a stock solution was prepared by diluting test material (0.8096 g) to 500 ml with water-saturated n-octanol. Six partitions were performed, with two duplicates each at three different octanol/water volume ratios. Shaking was performed by inversion of the flasks over a 5 minute period. After separation, aliquots of both phases were taken for analysis by gas chromatography. The analyzed concentration for aqueous phase 6 was confirmed to be a statistically significant outlier using Grubb's test, P = 0.05, and therefore has been excluded from further calculatoins. Mean Pow was determined to be 47.5 corresponding to a Log_{10} P_{ow} of 1.68. Standard deviation of the Pow was 5.20.

Remark :

Sample	Octanol/water Volume Ratio	P_{ow}	Log_{10} P_{ow}	Mean P_{ow}
1	1:2	46.7	1.67	44.8
2		42.8	1.63	
3	1:1	60.0	1.75	49.9
4		43.9	1.64	
5	2:1	48.0	1.68	35.2
6		22.4	1.35	

Reference : O'Connor, B.J, 2007.

05.02.07

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 9.00 g/l (worst case)
= 8.60 g/l (mean value)
pH value : = 6.0 to 6.4
concentration : at 20.0 +/- 0.5 °C

Method : Flask Method, Method 105 of the OECD Guidelines for Testing of Chemicals, 27 July, 1995.
Year : 2007
GLP : Yes
Test substance : Dibromomethane, 99.4% purity

Remark : In a preliminary test, 6.2302 grams of test material was diluted to 100 ml with glass double-distilled water. After shaking at 30°C for 17 1/2 hours and

standing at 20°C for 4 hours, the solution was centrifuged at 13500 rpm for 10 minutes and analyzed. Preliminary estimate of water solubility was 7.59 g/l.

Based on the preliminary test, three separate flasks were prepared. Mass of test material was 5.5001 to 5.5005 g/100 ml glass double-distilled water. After the water was added, flasks were shaken at about 30°C, and after standing at 20 °C for not less than 24 hours, the contents of the flasks were centrifuged at 13500 rpm for 10 minutes and sampled, excluding excess undissolved test material. The concentration of the test material in the sample solutions was determined by gas chromatography.

Sample	Time shaken	Time standing	Concentration	pH
1	24 hours	24 hours	9.00 g/l	6.4
2	48 hours	24 hours	8.60 g/l	6.2
3	72 hours	24 hours	8.20 g/l	6.0

No additional short term water solubility testing was considered necessary because of the limited extent of hydrolysis observed, and the absence of significant degradation product peaks in the GC chromatograms on analysis and the approximately neutral sample pH values indicating no significant accumulation of HBr. The value of 9.00 g/l was selected as the worst case scenario for environmental assessment.

Reliability 1
Reference O'Connor, B.J., 2007

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Solubility in : Water
Value : 11.5 g/l at 25 °C / 1.9 g/l at 30 °C / 11.7 g/1000 g water at 15 °C

Remark : Literature values: Hine and Mookerjee, 1975 / Gross and Saylor, 1931 / The Merck Index, 1996, p. 1035

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2.6.2 SURFACE TENSION

Remark : 33.32 dynes/cm @ 20 °C
Literature value: Dean, JA, 1987

2.7 FLASH POINT

Test substance : Dibromomethane

Remark : No flash point or fire points could be demonstrated by standard tests in air.
Literature: Clayton, GD, 1994

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2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Type : Viscosity
Value : = 1.32 mPa @ 0 °C

Remark : Literature: Lide, DR, 1998-1999, p 6-170
04.28.06

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	Photodegradation
Remark	:	DBM does not absorb UV light at >290 nm (US EPA, 1987). Therefore, photolysis is probably not a major factor in degradation
Type	:	Estimation of overall hydroxyl rate constant
Remark	:	Calculation of the rate constant for the atmospheric reaction between photochemically produced hydroxyl radicals and the test substance in the vapor phase gives an overall rate constant value of $0.07324e^{-12}$ cm^3/molecule-sec. This rate constant calculates to an estimated half-life of 146.069 days. (12 hr day, $1.5e^6$ OH/cm3, AOP Program v. 1.92 from EPISUITE v. 4.0)

3.1.2 STABILITY IN WATER

Type	:	Abiotic
t1/2 pH3	:	122 day(s) at 25 °C
t1/2 pH7	:	143 day(s) at 25 °C
t1/2 pH11	:	50.2 day(s) at 25 °C
Deg. product	:	
Method	:	TSCA Test Standard 796.3500 as described in the US Federal Register, Vol. 50, No. 188, Sept 27, 1985, and amended to conform to Federal Register, Vol. 53 No. 115, June 15, 1988.
Year	:	1989
GLP	:	Yes
Test substance	:	Dibromomethane, 99.95% purity
Reliability	:	1
Remark	:	Three 250 mL stock solutions were prepared in sterilized pH buffers. Approximately 1.1 mg samples of dibromomethane were placed in 250 mL of three buffer solutions (pH 3, 7 and 11) in 250 ml volumetric flasks stoppered with glass stoppers and covered with aluminum foil. Solutions were analyzed at various time intervals to determine rate of hydrolysis and half-life of the material at 25 °C. Temperature was maintained by placing the flasks in a shaking waterbath. Initial concentrations of the test solutions were confirmed by gas chromomatography. At every sampling interval, each of the three pH values was sampled. In triplicate, exactly 1.00 ml samples were taken and analyzed by GC. The method validation yielded a mean (n = 9) percent recovery of 94.0% with a standard deviation of 7.3%. Mean recovery of quality assurance samples taken during the testing was 96.3% with a standard deviation of 4.1% (n = 36). The pH of each flask was monitored weekly over the 28 day study, and never deviated more than 0.05 pH units Hydrolysis rate constants (k) and correlation coefficient were calculated using linear regression least squares fitting techniques. The simplified formula was: $C = C_o e^{(-kt)}$ Where k = rate constant (day^{-1}) C = mean dibromomethane concentration (mg/L) t = time (days) C_o = mean initial dibromomethane concentratin (mg/L) e = 2.718 The half-life was calculated as: $t_{½}$ = (ln 2)/k

There was no evidence for the formation of degradation products appearing in the chromatograms obtained by GC analysis. Any degradation products formed were either not detectable using the electron capture detector or had sufficiently different retention properties on the column such that it did not elute within the utilized run time.

The following table shows the rate constants (first order) and half-lives for the three pH values. The second order rate constants were also calculated and shown as k_A, k_B, and k_N.

pH	Rate Constant ($days^{-1}$)	Coefficient of Determination (R^2)	Half-life (days)
3.0	0.00569	NA	122
7.0	0.00484	NA	143
11.0	0.0138	0.7977	50.2

: NA = not applicable; at this pH and temperature, only 2 measurements were used in the calculation. The rate constants were as follows: k_A = 0.851, k_B= 8.96, k_N = 0.00484

Reliability: 1
Remark **:** Fackler, P.H., 1989.

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3.1.3 STABILITY IN SOIL

Remark **:** A Koc of 24 can be estimated. The Koc estimates suggest that DBM is not tightly bound to soil through adsorption. It is also unlikely that DBM adsorbs to sediment, thus not interfering with volatilization or biodegradation in disappearance from aquatic environment.

Remark **:** Literature reference (Hazardous Substance Data Base citing Syracuse Research Corporation)
Reliability 1

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Remark **:** Calculation of Koc using KOCWIN v. 2.00 (EPISUITE v. 4.0) estimates a Koc value of 21.73 based on molecular connectivity index and 29.86 based on an experimental log Kow of 1.7.

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type **:** other: adsorption/desorption
Media **:** water - soil
Value Log Koc = 24 (estimated)
Method **:** other: estimation using PCKOC (v 1.66)

Remark **:** Cited in Hazardous Substance Data Base from Syracuse Research Corporation

15.02.2002

3.3.2 DISTRIBUTION

Remark : Distribution as per PBT Profiler for DBM
Water 36%
Soil 29%
Sediment 0%
Air 34%

:

Remark Literature reference: estimated by Syracuse Research Corporation as cited in Hazardous Substances Database and estimation using PBT Profiler

Remark : Level III Fugacity-Based Environmental Partitioning Modelling
The following table represents the fugacity modelling calculated using the parameters: Molecular weight 173.84, Henry's Law Constant 0.000822 atm-m^3/mole (Henry database), Vapor pressure 48.8 mm Hg (MPBWIN program), Log Kow 1.7 (KOWWIN program) and Soil Koc 21.7 (KOCWIN MCI method).

Persistence Time: 207 hours
Reaction Time: 922 hours Percent reacted: 22.4%
Advection time: 267 hours Percent advected: 77.6%

Reference : Modelling using EPISUiTE v. 4.0

Environmental Compartment	Mass Amount (percent)	Half-life (hours)	Emissions (kg/hr)	Fugacity (ATM)	Reaction (kg/hr) (percent)	Advection (kg/hr) (percent)
Air	33.9	2,272	1000	$2.96e^{-010}$	64.2 2.14	$2.1e^{+003}$ 70.1
Water	35.9	360	1000	$5.26e^{-009}$	429 14.3	223 7.42
Soil	30.1	720	1000	$5.93e^{-008}$	180 6	0 0
Sediment	0.0983	3,240	0	$4.74e^{-009}$	0.131 0.00435	0.0122 0.00407

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : ca. 4.06
Method : Estimated by Syracuse Research Corporation as cited in Hazardous Substances Database and estimation using PBT Profiler
Remark : An estimated BCF of 4.06 would suggest that the potential for bioaccumulation in aquatic organisms is low.

Remark		Estimation of BCF using BCFBAF v. 3.00 (EPISUITE 4.0) gives a value of 6.147 L/kg wet weight.

BCF	**:**	ca. 2.791
Method	**:**	Cited in US EPA, 1987
Remark	**:**	An estimated BCF of 2.791 would suggest that the potential for bioaccumulation in aquatic organisms is low.

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	Semistatic
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= 32 mg/l
LC50	:	= 45 mg/l
Limit test	:	No
Analytical monitoring	:	Yes
Method	:	"Fish Acute Toxicity Test“ Method 203 of OECD Guidelines forTesting of Chemicals, 1992; US CFR 40 Part 797 section 1400, and ASTM Standard E 729-96
Year	:	2007
GLP	:	Yes
Test substance	:	Dibromomethane, 99.4% purity
Reliability	:	1

Remark : Stock solutions were made by dissolving test article in dechlorinated tap water with ultrasonication for one hour. Aliquots of the stock solution were added to final volumes of 25 liters of dechlorinated tap water and stirred for one minute to give the final concentrations. Each test concentration was prepared in duplicate to give replicates R1 and R2. Test chambers were 25 liter glass exposure vessels. Temperatures were maintained at 13.2 to 14.9°C and the photoperiod of the room was 16 hours light and 8 hours darkness with dawn and dusk transitions of 20 minutes. The test vessels received no auxiliary aeration, and test preparations were renewed daily to ensure concentrations remained near nominal and there was no buildup of nitrogenous waste. Feeding of fish was discontinued 48 hours prior to the start of the definitive test. There was zero mortality in the 7 days prior to the test, and the fish had a mean standard length of 4.9 cm at the start of the definitive test, and a mean weight of 1.66 grams at the end of the test giving a loading weight of 0.67 gm body weight/liter.

Following a range-finding test, fish (10 per group) were exposed to aqueous solutions of test material over the concentrations of 10, 18, 32, 56, and 100 mg/l for a period of 96 hours at a temperature of 13.2°C to 14.9°C. Test vessels were sealed with minimal headspace under semi-static test conditions. Number of mortalities and observations were determined at 3 and 6 hours after start of exposure, then daily through 96 hours.

No mortalities were noted in the definitive test at concentrations of 32 mg/l and below. At 100 mg/l, all fish in both replicates were dead by 3 hours of exposure. At 56 mg/l, a total of 3 fish in both replicates were dead, and by 96 hours, 9 fish in each replicate were dead (90% mortality). Observations of fish swimming near the top of the vessel were noted in the 56 mg/l group.

The LC50 values and associated confidence limits at 3, 6, 24, 48, 72, and 96 hours were calculated by the trimmed Spearman-Karber method using the ToxCalc computer software package. The 96 hour LC50 based on nominal test concentrations was 45 mg/l (95% confidence limits 42-48 mg/l). The NOEC was 32 mg/l.

Reference : Goodband, T.J., 2007.

05.03.2007

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	66 mg/l (based on nominal concentrations)
NOEC		32 mg/l (nominal)
Method	:	US CFR 40 Part 797 Section 1300 and ASTM 729-96
Year	:	2007
GLP	:	Yes
Test substance	:	Dibromomethane, 99.4% purity
Reliability	:	1

Remark : Stock solutions were prepared by adding test material (500 mg) to dechlorinated tap water with the aid of ultrasonication for 30 seconds, and volumes adjusted to 5 liters. Aliquots were then further diluted to give the appropriate nominal concentration. Test vessels were 300 ml stoppered conical flasks filled completely to minimize volatile loss. The test was conducted in a temperature controlled room with photoperiod of 16 hours light and 8 hours dark with 20 minute transitions. Daphnids were not fed during the test, and test solutions were not renewed.

In the definitive test, twenty daphnids (2 replicates of 10 animals) were exposed to aqueous solutions of test material at concentrations of 10, 18, 32, 56, and 100 mg/l in sealed vessels for 48 hours at a temperature of approximately 20°C under static test conditions. The number of immobilized Daphnia were recorded after 24 and 48 hours. Analysis of the test preparations at 0 and 48 hours showed measured test concentrations to range from 83% to 115% of nominal value, so calculations were based on nominal concentrations.

EC50 values and the associated confidence limits and the slope of the dose response curve and its standard error were calculated by the maximum-likelihood probit method using the ToxCalc computer software package. The 48 hour EC50 for the test material based on nonimal test concentrations was 66 mg/l with 95% confidence limits of 58-76 mg/l. The No Observed Effect Concentration was 32 mg/l.

Reference : Goodband, T.J., 2007.

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4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Pseudokirchneriella subcapitata (Algae)
Endpoint	:	Growth rate, yield, biomass integral
Exposure period	:	72 and 96 hour(s)
Unit	:	mg/l
EC50	:	ErC_{50}: 190 (72 hr) and 210 (96 hr) – growth $EyC_{50:}$ 100 (72 hr) and 130 (96 hr) – yield $EbC_{50:}$ 96 (72 hr) and 110 (96 hr) – biomass integral
Method	:	"Alga, Growth Inhibition Test" Method 201 of OECD Guidelines for the Testing of Chemicals, 1984
Year	:	2007
GLP	:	Yes

Test substance : Dibromomethane, 99.4% purity

Remark : Stock solutions of the test material were dissolved in culture medium with the aid of ultrasonication for about 20 minutes. Pseudokirchneriella subcapitata strain CCAP 278/4 were exposed to aqueous solutions of test material at concentrations of 10, 32, 100, 320, and 1000 mg/l (three replicates per concentration) for 96 hours under constant illumination (7000 lux) and shaking (150 rpm) at a temperature of 24 +/- 1°C. Test chambers were 250 ml glass conical flasks, each completely filled with test or control solution. Initial cell density of 10^4 cells per ml were used. Samples of algal populations were removed daily (0, 24, 48, 72 and 96 hours) and cell concentrations determined for each control and treatment group, using a Coulter Multisizer Particle Counter. pH of each control and test flask were determined at initiation and 96 hours. Temperature measurements were made hourly. Analytical determinations were made on control and pooled test group replicates at 0 and 96 hours. Duplicate samples were taken on each occasion and stored at -20°C for further analysis if necessary. A fourth replicate was prepared at each test concentration and incubated alongside the test remaining unopened until the end of the test. Chemical analysis of these additional relplicates was made at 96 hours. The cell concentrations of control cultures increased by a factor of 110 at 72 hours and 205 at 96 hours, and coefficient of variation for average specific growth rate of control cultures over the test period was 4%, demonstrating validity of the test. A positive control chemical (zinc chloride) gave acceptable EC_{50} values using the same system. Test concentrations were near nominal at initiation, with the exception of 32 mg/l being 79% of nominal. Analysis at 96 hours showed slight decline in concentrations to 64% to 101% of nominal. Analysis of the unopened replicate flasks at 96 hours showed measured concentrations of 81% ot 106% of nominal. Since a decline in measured concentrations was seen, EC_{50} values were also calculated from geometric mean measured concentrations.

EC_{50}	Based on nominal	Based on Geometric means
Growth, 72 hr	190 mg/l	140 mg/l
Growth, 96 hr	210 mg/l	150 mg/l
Growth NOEC	32 mg/l	23 mg/l
Yield, 72 hr	100 mg/l	76 mg/l
Yield, 96 hr	130 mg/l	95 mg/l
Yield, NOEC	32 mg/l	23 mg/l
Biomass, 72 hr	96 mg/l	72 mg/l
Biomass, 96 hr	110 mg/l	87 mg/l
Biomass, NOEC	32 mg/l	23 mg/l

A regrowth experiment showed that the test material was algistatic in effect.

Reliability : 1

Reference : Vryenhoef, H., 2007

05.03.07

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	> 1000 mg/kg
Species	:	Rats, rabbits
Year	:	1957 and later
GLP	:	No
Test substance	:	Dibromomethane, > 98% purity
Reliability	:	1

Remark : Torkelson, T.R., "Results of Range-finding Toxicological Tests on Methylene Bromide," 1957, unpublished Dow studies cited in Keyes, et al, 1982.

Remark : Various studies were conducted at the Toxicological Research Laboratory, Dow Chemical, USA, to determine acute toxicity of dibromomethane. These studies were also cited by Torkelson, 1981, and in the US EPA Health and Environmental Effects Profile for Methylene Bromide, 1987.

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5.1.2 ACUTE INHALATION TOXICITY

Remark : An acute rat inhalation LC50 is cited as 40 g/cu meter for a 2 hour exposure.

Reference Literature: Izmerov, N.F., et al. "Toxicometric Parameters of Industrial Toxic Chemicals Under Single Exposure, Moscow, Center of International Projects, GKNT 1982, pg. 83, 1982.

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5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 4000 mg/kg
Species	:	Rabbit
Reliability	:	1

Remark : Torkelson, T.R., "Results of Range-finding Toxicological Tests on Methylene Bromide," 1957, unpublished Dow studies cited in Keyes, et al, 1982.
Various studies were conducted at the Toxicological Research Laboratory, Dow Chemical, USA, to determine acute toxicity of dibromomethane. These studies were also cited by Torkelson, 1981, and in the US EPA Health and Environmental Effects Profile for Methylene Bromide, 1987

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5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION/ CORROSION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	14 Day Oral Repeated Dose
	:	Rats
Species	:	Sprague Dawley Crl:CD(SD)IGS BR strain
Strain	:	Male and female
Sex	:	24 (3 males, 3 females per group)
Number of animals	:	Polyethylene glycol 400
Vehicle	:	0, 75, 150, 500 or 1000 mg/kg/day
Doses	:	Oral gavage
Method	:	2007
Year	:	Yes
GLP	:	Dibromomethane, 99.4% purity
Test substance		
Remark	:	This test was a preliminary 14 day range-finder for the oral reproduction/developmental screen test. Fresh formulations using propylene glycol 400 were made daily and the animals were dosed within 3 hours of preparation. Control animals were dosed with the same volume (4 ml/kg) of vehicle only. Control animals and animals receiving 75, 150, or 500 mg/kg/day were dosed on 14 consecutive days. Animals receiving 1000 mg/kg/day were dosed for 3 consecutive days. Male animals weighed 339 to 412 grams, and female rats weighted 198 to 267 grams at the start of the study. Animals were housed 3 per cage with environmental enrichment, and water access throughout the study. Room temperature was 21 +/- 2 degrees C, and relative humidity was 55 +/- 15%. All animals in the 75, 150 and 500 mg/kg groups survived to scheduled termination and at necropsy were not observed to have treatment related effects. Animals dosed at 1000 mg/kg showed adverse effects on body weight and clinical condition (particularly males) and were sacrificed after three days of exposure. Top dose chosen for the reproduction screening test was 500 mg/kg/day.
Reference		Dhinsa, N.K., 2007.

Reliability : **1**

Type	:	Repeated dose, inhalation
Species	:	Rats
Sex	:	Male and female
Strain	:	Sprague Dawley
Route of admin.	:	Inhalation
Exposure period	:	6 hours per day,
Frequency of treatm.	:	5 days per week for 62 (male) or 63 (female) exposures in 90 days
Post exposure period	:	Recovery male rat group held for 2 years
Doses	:	0, 25, 75, and 150 ppm
Control group	:	Exposed to room air in holding area
NOAEL		25 ppm based on carboxyhemoglobin
LOAEL		75 ppm based (> carboxyhemoglobin, > liver weight, < body weight) (US EPA, 1987)
Year	:	1982
GLP	:	Prior to FDA GLP requirements, but Quality Assurance audited
Test substance	:	Dibromomethane, > 98% purity

Remark :

Inhalation exposures were conducted under dynamic airflow conditions in 4.1 cubic meter stainless steel chambers. Air temperature and humidity were controlled to 22 degrees C and 50% humidity in the exposure chambers and holding rooms. Desired concentrations of methylene bromide in each chamber was generated by metering the liquid at a calculated rate into a warmed (about 210 degrees C) glass vaporization flask. The resultant vapor was then swept into the chamber via the main airflow at a rate of about 825 liters per minute. Nominal concentration of test article was calculated daily as the ratio of the rate at which the liquid compound was dispensed into the vaporization flask to the rate of total chamber airflow. The analytical concentration of methylene bromide was determined by infrared spectrophotometry using 2 Miran I spectrophotometers in series. The first IR monitored concentrations of 25 to 75 ppm, and the second 150 ppm methylene bromide. Chamber concentrations were determined at least twice during each exposure day.

Four groups of animals consisting of 115 male (15 for 90 day portion and 100 for 2 year recovery portion) and 15 female Sprague Dawley albino rats were exposed to air containing either 0, 25, 75, or 150 ppm methylene chloride for 6 hours per day, 5 days per week for a total of 62 (males) or 63 (females) exposures over a three month period. Control animals were housed in the holding room during the exposure periods. Animals were acclimated for at least one week prior to exposures. Test animals were maintained on a 12 hour light/dark cycle at temperatures of about 75 degrees F and 50% humidity. Rats were housed in groups of 4 per cage. Animals were not fed during exposure periods. Animals were observed for clinical signs during each exposure day. Rats in the recovery group were examined monthly for tumors. Rats were weighed twice weekly during the first two months of the test, weekly in the second 2 weeks. For the duration of the test, all were weighed twice monthly. During the two year recovery, male rats were weighed twice during the first month of recovery, and monthly thereafter. Hematological parameters (RBCs, hemoglobin concentration, packed cell volume, differential and total white blood cell counts) were evaluated on 7 rats per exposure level both before initiation of exposures, and at study termination. Blood samples were taken from the tail vein. Urinalysis were also performed on each animal (pH, glucose, protein, ketones, bilirubin, urobilinogen, and occult blood, as well as

specific gravity and urine sediment exam). Clinical chemistry determinations were made on blood of 10 rats per exposure level at termination. Clinical chemistry determinations included blood urea nitrogen, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, and alkaline phosphatase. Clinical chemistries were also conducted on 10 male rats/exposure level at the time of the 1 year interim sacrifice. Specific ion electrode analysis of bromide levels (inorganic bromide) in plasma of 3 rats/sex/level prior to exposure and at 41 days of exposure. Total bromine levels in plasma were determined by neutron activation analysis prior to initiation and at days 30, 51, and 61 days of exposure (samples taken at 1, 2, 6, and 18 hours following termination of exposure). Carboxyhemoglobin levels were made on tail vein samples of 3 rats/sex/exposure on test after 90 experimental days.

After 58 (males) or 59 (females) exposure days, 5 rats per sex per group were killed, and their bone marrow cells were collected for cytogenetic evaluation. Four hours prior to sacrifice, each rat was given 0.4 mg/kg colchicine via i.p. injection. The rats were killed by decapitation, the head of the femur removed, adn the bone marrow aspirated into Hank's balanced salt solution for preparation of slides for chromosomal cytogenetic examination. However, the slides were improperly prepared and were not evaluated.

All rats which died spontaneously during the study were subjected to full gross pathological examination. After 61 (males) or 62 (females) exposures, complete gross necropsies were performed on 10 rats per sex per exposure level. Complete gross necropsy was also conducted on 10 male rats per level at the 1 year interim sacrifice, and on all surviving male rats at the 2 year sacrifice. The rats were killed by decapitation following clamping of the trachea under methoxyflurane anesthesia. The eyes of all rats were examined in situ immediately after decapitation by the glass slide technique and fluorescent light illumination. Each rat was examined externally and internally for gross pathological lesions. At necropsy, weights of brain, heart, liver, kidneys, and testes were recorded. Representative portions of the following organs and tissues were collected from each animal and preserved in formalin.

Liver	Aorta
Kidney	Urinary bladder
Pancreas	Peripheral nerve (sciatic)
Spleen	Pituitary gland
Heart	Mesenteric adipose tissue
Lungs/bronchus	Parathyroid glands
Esophagus	Skin
Trachea	Testes and epididymides
Mesenteric lymph node	Prostate
Brain	Uterus, ovary, oviduct, mammary gland
Salivary Gland	Nasal turbinates
Spinal Cord	Sternum
Vertebra	All gross lesions
Coagulating gland	Thyroid gland
Large and small intestine	Stomach
Skeletal muscle	Thymus (if present)
Thoracic lymph node	Eyes (preserved in Zenkers)

In general, H&E stained paraffin sections were prepared from the tissues listed previously from 5 male and 5 female rats in the control and 150 ppm groups killed after the 90 day sacrifice. Similarly, sections were prepared from the list of tissues for 5 male rats per exposure level in the 0 and 150 ppm group at the 1 year interim sacrifice. Sections were also

prepared of all grossly observed tumors in the remaining control and treated rats of the 1 year sacrifice. No histopathology was conducted in the tissues of rats dying spontaneously, killed moribund, or sacrificed at 2 years. Assessment of tumorigenic potential was based upon evaluation of gross pathology data.

Statistical evaluation of body weights, organ weights, organ to body ratios, and clinical laboratory data was conducted by analysis of variance and Dunnett's test with a probability of $p < 0.05$. For the 2 year portion of the test, mortality, palpable mass, gross pathology, histopathology and tumor incidence were analyzed with Fisher's Exact Probability Test, $p < 0.05$. Statistical evaluation of the cumulative results compared the data of each of the treatment groups against the data of the control group.

Exposure related adverse effects were not observed at any exposure level during the study.

In the 90 day study, body weights on male rats were generally comparable to those of controls during the study except for the 5th day of exposure when the mean body weights of the 75 and 150 ppm groups were lower than control. There was also a significantly decreased mean body weight in male rats of the 75 ppm group on the 47th experiment day. This was not considered exposure related. Body weights of female rats were comparable to those of control rats for the entire exposure period except for an isolated decrease in mean body weight in the female 150 ppm group. In the 2 year recovery portion, male rats in the 150 ppm exposure group showed decreased mean body weight during days 121 to 607 of the study. In these intervals, there were 9 occasions on which the body weights were statistically decreased from control values. Rats of the 75 ppm group showed trend to decreased mean body weights from days 121 to 361 of the study, but there were no statistically significant differences from control weights. Rats in the 25 ppm exposure group had 2 instances of statistically significant differences from control values (decrease at 47 days, and increase at 75 days of the study). There was no pattern or trend to these differences.

At necropsy, there was a significant decreased mean relative liver weight in male rats of the 25 ppm male rats compared to control rats. This may have been due to the greater body weight of these animals compared to controls. This was not observed among male rats exposed to 75 or 150 ppm methylene bromide. Organ weight data for all other groups were comparable to controls. In female rats at necropsy, there was a trend towards increased mean absolute and relative liver weights in the 150 ppm group. The mean liver weight of female rats exposed to 75 ppm also showed a trend toward an increased absolute weight and also a statistically significant increase in relative liver weight. This trend toward slightly increased liver weight in female rats exposed to 75 or 150 ppm was considered related to exposure. At the 1 year interim sacrifice, fasted body weights of the male rats of the 75 and 150 ppm groups were slightly decreased. However, there were no significant differences in the weights of the brain, heart, liver, kidneys or testes. At 2 year termination, there was a trend toward an increase in relative and absolute weight of both liver and kidneys in the 150 ppm group. However, the differences were not significant and probably not a result of exposure.

Hematological values at the 90 day termination in treated male rats were comparable to those of controls. The total WBC counts for control and exposure animals were greater at the preexposure bleeding than at the

preterminal bleeding. This was not thought to be a result of exposure. The same effect was seen in female rats. There were no significant differences in values of treated animals at the 1 year interim sacrifice compared to control. Urinalysis values for male and female rats showed no exposure related alterations in the 90 day study and at the 1 year interim sacrifice in male rats. Clinical chemistry values for exposed rats were comparable to control values upon determination prior to 90 day termination or at the 1 year interim sacrifice.

There was some discrepancy in values for bromide ion (by ion "specific" electrode) and for total bromide (by neutron activation analysis. In the preexposure values and 41 day exposure values, it is evident that serum free bromide ion values increased in a dose dependent manner. At 41 days of exposure, the bromide ion levels of all exposed rats were significantly increased over control values. In the neutron activation analyses of total bromine levels in rat serum, the values were increased in all exposed rats over control levels by 30 exposure. A further increase was seen at 51 days of exposure, but no further increase by 61 days of exposure. From the determinations after 61 exposures, apparent excretion of bromine occurred as indicated by the decrease in serum bromine concentrations from 1 to 18 hours after exposure. In rats, the maximum bromine concentrations were 1135 +/- 50 ppm and 1101 +/- 27 ppm as determined by neutron activation analysis (1097 +/- 51 ppm and 1292 +/- 61 ppm by ion specific electrode analysis).

Methylene bromide consistently increased blood % carboxyhemoglobin saturations in rats exposed to 75 or 150 ppm. There was a single statistically increased value in female rats exposued to 25 ppm after 61 exposures.

Gross pathologic examinations at the end of the 90 day study on all 10 rats per sex in the control and treated groups showed no lesions that could be attributed to exposure. There were no histopathologic observations that could be attributed to exposure. At the 1 year interim sacrifice, no gross lesions could be attributed to exposure, and there were no histopathologic lesions attributable to exposure either. At the 2 year termination, there were certain statistically significant differences in nontumorous observations. The liver observations included an increase in livers with atrophy, accompanied by decreases in incidence of small red and dark red foci. These liver observations were thought to be the result of various spontaneous age-related processes such as chronic renal disease or malocclusion which can cause secondary liver atrophy. All other nontumorous gross pathological lesions were similar to concurrent or historical control rates and were considered spontaneuous in nature. There were also certain statistically significant tumorous gross pathologic observations differing in incidence in treated and concurrent control groups. These observations included increases in numbers of rats in the 75 ppm exposure group with (1) enlargement of the mesenteric lymph nodes, (2) enlargement of the pituitary glands, or (3) nodules in the region of the pancreas. These observations were not considered to be related to exposure because of similar incidence rates in historical control groups, and lack of a dose response relationship. Thus, gross pathological examination of male rats exposed to 25, 75, or 150 ppm showed no indications of any increased incidence of nontumorous or tumorous-like lesions at any of the 3 exposure levels.

Reliability 1

Reference Keyes, D.G, 1982

Type	:	Repeated dose, inhalation
Species	:	Dogs
Sex	:	Male
Strain	:	Beagle
Route of admin.	:	Inhalation
Exposure period	:	6 hours per day,
Frequency of treatm.	:	5 days per week for 70 exposures in 90 days
Doses	:	0, 25, 75, and 150 ppm
Control group	:	Exposed to room air in holding area
NOAEL	:	75 ppm (US EPA, 1987)
LOAEL		150 ppm (US EPA, 1987)
Year	:	1982
GLP	:	Prior to FDA GLP requirements, but Quality Assurance audited
Test substance	:	Dibromomethane

Reliability 1

Remark : Inhalation exposures were conducted under dynamic airflow conditions in 4.1 cubic meter stainless steel chambers. Air temperature and humidity were controlled to 22 degrees C and 50% humidity in the exposure chambers and holding rooms. Desired concentrations of methylene bromide in each chamber were generated by metering the liquid at a calculated rate into a warmed (about 210 degrees C) glass vaporization flask. The resultant vapor was then swept into the chamber via the main airflow at a rate of about 825 liters per minute. Nominal concentration of test article was calculated daily as the ratio of the rate at which the liquid compound was dispensed into the vaporization flask to the rate of total chamber airflow. The analytical concentration of methylene bromide was determined by infrared spectrophotometry using 2 Miran I spectrophotometers in series. The first IR monitored concentrations of 25 to 75 ppm, and the second 150 ppm methylene bromide. Chamber concentrations were determined at least twice during each exposure day.

Four groups of animals consisting of 3 male beagle dogs were exposed to either 0, 25, 75, or 150 ppm methylene chloride for 6 hours per day, 5 days per week for a total of 70 exposures over a three month period. Control animals were housed in the holding room during the exposure periods. Animals were acclimated for at least one week prior to exposures. Test animals were maintained on a 12 hour light/dark cycle at temperatures of about 75 degrees F and 50% humidity. Dogs were housed in groups of 3 during nonexposure periods, and individually during exposures. Animals were not fed during exposure periods. All dogs on test were given eye exams prior to initiation of exposures and at termination. Animals were observed for clinical signs during each exposure day. Dogs were weighed weekly during the test. Hematological parameters (RBCs, hemoglobin concentration, packed cell volume, differential and total white blood cell counts) were evaluated on all dogs both before initiation of exposures, at 1 ½ months into the study and at study termination. Blood samples were taken from the jugular vein. Urinalysis were also performed on each animal (pH, glucose, protein, ketones, bilirubin, urobilinogen, and occult blood, as well as specific gravity and urine sediment exam). Clinical chemistry determinations were made on blood of dogs twice before study initiation and at termination. Clinical chemistry determinations included blood urea nitrogen, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, and alkaline phosphatase. Specific ion electrode analysis of bromide levels (inorganic bromide) in plasma of all dogs were made twice prior to exposure, at 31 and 50 exposures. Total bromine levels in plasma were determined by neutron activation analysis prior to initiation and at days 31, 40, 50, and 60

days of exposure (samples taken at 1, 2, 6, and 17.5 hours following termination of exposure). Carboxyhemoglobin levels were made on jugular vein samples of all dogs on test after 90 experimental days. In order to determine a pharmacokinetic profile, blood was taken after 90 experiment days and determinations of methylene bromide were made at 50, 100, 300, and 350 minutes after termination of exposure.

At necropsy, weights of brain, heart, liver, kidneys, and testes were recorded. Representative portions of the following organs and tissues were collected from each animal and preserved in formalin.

Liver	Aorta
Kidney	Urinary bladder
Pancreas	Peripheral nerve (sciatic)
Spleen	Pituitary gland
Heart	Epiglottis
Lungs/bronchus	Parathyroid glands
Esophagus	Skin
Trachea	Testes and epididymides
Mesenteric lymph node	Prostate
Brain	Gall bladder
Salivary Gland	Nasal turbinates
Spinal Cord	Tongue
Vertebra	All gross lesions
Cervical lymph nodes	Thyroid gland
Large and small intestine	Stomach
Skeletal muscle	Thymus (if present)
Thoracic lymph node	Eyes (preserved in Zenkers)

Statistical evaluation of body weights, organ weights, organ to body ratios, and clinical laboratory data was conducted by analysis of variance and Dunnett's test with a probability of $p < 0.05$.

Exposure related adverse effects were not observed at any exposure level during the study. Body weights on all dogs were comparable to those of controls during the study. At necropsy, terminal body weights, organ weights, and organ to body weight ratios were comparable to controls. Hematological values in treated dogs were comparable to those of controls. Clinical chemistry values for exposed dogs were comparable to control dogs upon determination prior to termination. There was some discrepancy in values for bromide ion (by ion "specific" electrode) and for total bromide (by neutron activation analysis). For example, in control dogs, prexposure no. 1, the mean bromide ion was 38 ppm, but bromine was only 9 ppm by neutron activation analysis. The difference was much less at the higher levels: for example, in dogs exposed 50 times to 150 ppm, plasma bromide ion was 793 ppm, and total bromine was 625 ppm. Serum total bromine was observed to increase in dogs after 32 exposures when compared to control. Bromine levels continued to increase with time at 42 and 52 days of exposure, but were not increased over the 52 day values at 62 days of exposure. The maximum dog plasma Br concentrations by neutron activation analysis were 625 +/- 58 ppm; by ion specific analysis the values were 793 +/- 145 ppm. Dogs exposed to 150 ppm methylene bromide showed small increases relative to control animals (6% increase at the one sampling time where the difference from control mean was statistically significant).

All gross and histopathologic observations on control and treated dogs were considered spontaneous in nature, and not a result of treatment. Among the spontaneous lesions was a frequent occurrence of chronic inflammatory lestions of the lungs, that varied in severity. In some animals, the lesions were clearly related to aspiration of food material, and in others typical of a parasitic infestation common in dogs.

Reference : Keyes, D.G., 1982

5.5 GENETIC TOXICITY 'IN VITRO'

Type : In vitro bacterial mutagenicity
System of testing : Salmonella typhimurium TA100
Test concentration : 0 – 10 ul/desiccator
Metabolic activation : No
Result : Positive
Method : Plate incorporation, desiccator method
Year : 1977
GLP : No
Test substance : Dibromomethane

Remark : Salmonella typhimuriam strains at this laboratory were obtained from Dr. Bruce Ames. Indicator strains are stored at –80 degrees C. At the time of the experiment, an inocculum from frozen stock was grown overnight at 37 degrees C in a nutrient broth. After stationary overnight growth, cultures were shaken for 3 or 4 hours. Each culture was checked for sensitivity to crystal violet. Desiccator tests at this laboratory involved salmonella agar plates with lids removed placed in a desiccator. A known volume of the test chemical or positive control was then added to a glass petri plate in the desiccator. The desicattor was then sealed and placed in an incubator at 37 degrees C. A magnetic stirrer with vanes was placed in the base of each desicator to ensure dispersion of volatiles. All test chemicals were evaporated in the first hour. After incubation for 8 hours, the plates were removed from the desiccator, lids were replaced and the plates incubated for another 40 hours at 37 degrees C.
Reliability 1
Reference : Simmon, V.F et al., 1977.

04.28.06

Type : Chromosomal Aberration, in vitro
System of testing : Human lymphocytes
Test concentration : +/- S-9: 27.19, 54.38, 108.75, 217.5, 435, 870 ug/ml

Cycotoxic concentr. : 870 ug/ml pulse exposure; 1740 ug/ml 24 hr continuous exposure
Metabolic activation : with and without S-9 from liver homogenate from rats induced with phenobarbitone and B-naphthoflavone
Result : Clastogenic
Method : "Genetic Toxicology: Chromosome Aberration Test", Guideline 473 of OECD Guidelines for Testing of Chemicals (1997).
Year : 2007
GLP : Yes
Test substance : Dibromomethane, 99.4% purity

Remark : Human lymphocytes from a volunteer donor were used for this test. Cell cycle time for the lymphocytes (as determined using bromodeoxyuridine incorporation to assess the number of first, second and third division metaphase cells) was used by the laboratory to calculate Average Generation Time. Average AGTs for donors for this lab was 17 hours. Cells are grown in Eagles's minimal essential medium with HEPES buffer, supplemented in house with L-glutamine, penicillin/streptomycin,

amphotericin B and 15% foetal calf serum, at 37°C with 5% CO2 in air. The lymphocytes of fresh heparinized whole blood were stimulated to divide by addition of phytohaemagglutinin at 90 ug/ml final concentration. The test material was dissolved in dimethyl sulphoxide and dilutions prepared. Positive control materials were Mitomycin C at 0.4 ug/ml in the absence of S-9, and dissolved in the media. In the presence of S-9, cyclophosphamide at 5 ug/ml was used. S-9 microsomal enzyme fraction was prepared from livers of male Sprague-Dawley rats that had received three daily oral doses of a mixture of phenobarbitone (80 mg/kg) and B-naphthoflavone (100 mg/kg).

Duplicate culture of human lymphocytes, treated with test material, were evaluated for chromosomal aberrations at up to three dose levels, together with vehicle and positive controls. Sterile plastic flasks were used for the cultures. Two treatment conditions were used: 1) 4 hour exposure in the presence of an induced rat liver homogenate metabolizing system at a 2% final concentration with cell harvest after a 20 hour expression period and 2) a 4 hour exposure in the absence of metabolic activation with a 20 hour expression period. Dose levels ranged from 27.19 to 870 ug/ml for the 4 hour exposures (20 hr expressions) with and without S-9.

To prepare the metaphase spreads, lymphocytes were resuspended in several milliliters of fresh fixative before centrifugation and resuspension in a small amount of fixative. Several drops of suspension were then dropped onto clean, wet microscope slides and allowed to dry. Dry slides were stained with 5% Gurrs Giemsa for 5 minutes before rinsing, drying and coverslipping. Slides were checked microscopically to determine quality of the metaphase and also toxicity and presence of precipitation. These observations were used to select dose levels for mitotic index evaluation. A total of 2000 lymphocyte cell nuclei were counted and the number of cells in metaphase recorded and expressed as the mitotic index and as a precentage of the vehicle control value. When possible, the first 100 consecutive well-spread metaphases from each culture were counted, except where there were approximately 50% cells with aberrations – then counting terminated with 50 cells. If a cell had 44-48 chromosomes, any gaps, breaks, or rearrangements were noted according to the simplified system of Savage (1976). The frequency of cells with aberrations excluding gaps and the frequency of polyploid cells were compared, where necessary with the concurrent vehicle control value using Fisher's Exact Test.

Vehicle controls gave frequencies of cells with aberrations in the range expected for normal cells. Positive control materials induced statistically signficant increases in the frequencies of cells with aberrations indicating satisfactory performance of the test and of the activity of the metabolizing system.

The test material induced a statistically significant increase in the frequency of cells with aberrations, in both exposure groups, using a dose range that included a level that induced greater than 50% mitotic inhibition. The test material did not induce a statistically significant increase in the numbers of polyploid cells at any dose level in either of the exposure groups.

The test material was considered to be clastogenic to human lymphocytes in vitro because of a statistically significant dose-related increase in the frequency of cells with chromosome aberrations both in the presence and absence of a liver enzyme metabolizing system.

Reliability : 1

Reference : Wright, N.P., 2007.

05.02.07

Type In vitro yeast mitotic recombination assa
System of testing : S. cerevisiae D3 on Tryptone-yeast agar plates
Test concentration : +/- S9: 0.2, 0.3, 0.4%
Cycotoxic concentr. : 0.2 % and higher
Metabolic activation : with and without S-9 f
Result : Equivocal
Year : 1976
GLP : No
Test substance : Dibromomethane, > 98% purity

Remark : The Saccharomyces test strain was removed from storage in liquid nitrogen and grown overnight at 30 degrees C with aeration in 1.0% tryptone and 0.5% yeast extract. The cells were washed twice in 0.067M PO_4 buffer (pH 7.4) and resuspended in the same buffer at a concentration of 10^8 cells/ml. The in vitro yeast mitotic recombination assay in suspension consists of 5 x 10^7 washed, stationary-phase yeast cells in 1 ml of 0.067M PO_4 buffer (pH 7.4) and 50 mg/ml of the test chemical (or a fraction of the concentration required to give 50% killing). The suspension was incubated for 4 hours at 30 degrees C. After incubation, the sample was diluted serially in sterile saline and plated on tryptone-yeast agar plates. Plates of a 10^{-3} dilution were incubated for 2 days at 30 degrees C, followed by 2 days at 4 degrees C to enhance the development of the red pigment indicative of adenine-negative homozygosity. To detect red colonies or red sectors, plates are scanned under a dissecting microscope. Plates of a 10^{-5} dilution were incubated for 2 days at 30 degrees C for determination of the total number of colony forming units. The assay with metabolic activation was conducted as above with the addition of liver S9 from Arochlor 1254 induced adult male mice.

Remark Although the number of mitotic recombinants per milliliter was not increased by increasing the concentration of test article, the higher concentrations tested were toxic. Therefore, the number of mitotic recombinants per 10^5 survivors increases. Criteria for a positive test with this assay were to be an increase in number of mitotic recombinants per milliliter as well as an increase in number of recombinants per 10^5 survivors as demonstrated by the positive control. The study authors could make no conclusion about the mutagenicity of dibromomethane under the conditions of the test.

Reliability : 1
Reference : Simmons, V.F., and D.C. Poole, 1976

Compound	Metabolic activation	Concentration (w/v or v/v)	Surviving cells per ml (x 10^{-7})	% of survivors	Recombinants/ ml (x 10^{-3})	Recombinants per ml of survivors
Control, neg	-		6.1	100	5	8.2
	+		5.6	100	5	8.9
Control, pos	-	0.04	6.0	98	845	1408
	+	0.04	6.6	118	745	1129
Dibromomethane	-	0.2	4.5	74	2	4.4
	-	0.3	1.5	25	5	33.3
	-	0.4	0.8	13	6	75.0

Dibromomethane	+	0.2	4.3	77	7	16.3
	+	0.3	3.3	59	3	9.1
	+	0.4	0.9	16	10	111.1

Type : In vitro bacterial mutagenicity
System of testing : Salmonella typhimurium TA 98, 100, 104, 97,
Test concentration : 10 to 1000 ug/plate
Metabolic activation : With and without
Result : Positive
Method : Standard plate method
Year : 1987
GLP : No
Test substance : Dibromomethane, > 98% purity
Remark : Test material solvent was DMSO. S-9 was derived from livers of Aroclor 1254 induced rats.
Reliability : 1
Reference : Strobel, K. and T. Grummt, 1987.

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : Reproduction/Developmental Screening Study
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : oral gavage
Exposure period : 40 days (14 days premating, throughout mating, gestation, parturition and early lactation)
Frequency of treatm. : Daily
Premating exposure
Male : 14 days
Female : 14 days
No. of generation studies : 1
Doses : 50, 150, 500 mg/kg
Control group : Polyethylene glycol 400
NOEL parental : = 150 mg/kg
NOEL offspring : = 150 mg/kg

Result : Treatment at 500 mg/kg/day was associated with a clear effect on mating performance and a reduction in litter size at birth, most probably from increased in utero mortality. The NOAEL for reproduction in this study was 150 mg/kg/day.

Method : "Reproduction/Developmental Toxicity Screening Test," Guideline 421 of OECD Guidelines for Testing of Chemicals, 1996
Year : 2007

GLP : Yes
Test substance : Dibromomethane, 99.4% purity
Remark : The test material was gavaged to three groups of Sprague-Dawley Crl:CD (SD) IGS BR strain rats (10m, 10f per group) for approximately forty days (to include a two week maturation phase, pairing maximum of 14 days, gestation, and early lactation). A control group was similarly dosed with vehicle only (Polyethylene glycol 400). Clinical signs, bodyweight development, food and water consumption were monitored during study. Animals were paired one male:one female on Day 15 of the study, with females being allowed to litter and raise offspring to Day 5 of lactation. During lactation, clinical observations of all surviving offspring were made daily, along with notation of litter size, offspring weight and assessment of righting reflex. Survivimg parental males were terminated on Day 43 of the study, with parental females and offspring terminated on Day 5 postpartum. All animals were subjected to gross necropsy, and histopathological examination of reproductive tissues were performed.

One high dose male was terminated on Day 2 of the study, and one control female was found dead on Day 41 of the study. These deaths were not the consequence of treatment. There were no significant treatment related clinical signs of toxicity in any dose group. Body weight gain during gestation was lower for 500 mg/kg/day females, but this was considered related to smaller litter size in that group. No differences were seen between control animals and those at 50 or 150 mg/kg/day. Similarly, lower food conversion efficiency was apparent in the high dose females.

No effects on mating performance, fertility or gestation length were seen in low and middose animals. Clear increase in pre-coital interval, compared with control, was seen in the high dose females, with only 4 females mating during the first four days of pairing. Fertility was not affected with eight females achieving pregnancy. Gestation length of these females was longer, possibly due to smaller litter size.

No effect on litter size was seen in the 50 or 150 mg/kg/day groups. The high dose litter size was lower than control on day one due to increased post-implantation loss. One high dose female lost her entire litter in utero. Offspring bodyweights on Day 1 and subsequent survival, growth, and development to day 4 were unaffected by maternal treatment. Necropsy findings among adult animals and their offspring did not indicate any effect of maternal treatment at dosages of 50, 100, or 500 mg/kg/day.

Histopathology of adult reproductive tissue did not reveal any treatment related effects at dosages of 50, 150, or 500 mg/kg/day. High dose males had lower absolute and relative epididymal and testes weights compared to controls. At 150 mg/kd/day, males also had lower absolute and relative testes weights.

Dose level (mg/kg/ day)	Mating index (%)	Pregnancy index (%)	Days to mating 4 or less	Days to mating 5 to 14	Gestation length 22-221/2 days	Gestation length 23-231/2 days	Parturition index (%)
0	100	100	100%	0%	70%	30%	90
50	100	100	90%	10%	70%	30%	100
150	100	100	100%	0%	50%	50%	100
500	90	89	45%	55%	0%	100%	88

Dose level (mg/kg/day)	Number of litters	# Corpora lutea	# implant sites	Total offspring born (mean)	Pre-implant loss (%)	Post implant loss (%)	Live birth Index
0	8	17.8	15.1	14.5	14.1	4.0	99.3
50	10	17.4	15.3	13.6	11.0	11.7	92.6
150	10	16.8	14.0	13.0	17.0	6.3	98.6
500	6	15.7	14.2	6.8	9.7	52.2	100.0

Dose level (mg/kg/day)	Number of litters	Viability Index	% Males at birth	Live offspring Day 4	% Males day 4
0	8	100.0	54.0	14.4	53.6
50	10	99.2	49.4	12.8	50.2
150	10	99.3	45.7	12.7	45.0
500	6	100.0	50.5	6.8	50.5

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Reliability 1

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT