SUMMARY OF DATA FOR CHEMICAL SELECTION

ETHYL BROMOACETATE

105-36-2

BASIS OF NOMINATION TO THE CSWG

The nomination of EBA is based on the potential for human exposure through its uses as a chemical intermediate and alkylating agent, a lack of adequate chronic toxicity data and a suspicion of carcinogenicity associated with halogenated aliphatic compounds.

EBA is used as a synthetic organic chemical intermediate as well as a pharmaceutical and agricultural intermediate. In addition, it has a history of prior use as a lacrimator and tear gas agent for chemical warfare, an odorant, and an illicit biocide in European food and beverage products. Potential low-level human exposures could occur in occupational or consumer settings by any of the three major routes—inhalation, ingestion or dermal.

Suspicion of carcinogenicity is based on EBA's bromo-substituted carboxylate structure. Because of the potential alkylating activity of EBA as an α-halo acetate. Because of a lack of supporting mutagenicity data, this chemical has been submitted to the National Cancer Institute's Division of Cancer Etiology (NCI/DCE) Short-Term Testing Program for Ames and mouse lymphoma assays. Nomination of EBA for testing would provide the opportunity for elucidating mechanisms of bromoacetate toxicity. It would also reinforce the nomination of the closely related compound monobromoacetic acid (MBAA), which was nominated to the National Toxicology Program (NTP) in 1991 as a water disinfection by-product and is currently under review for possible testing.

SELECTION STATUS

ACTION BY CSWG: 6/13/95

Studies Requested:

- Metabolism
- *In vitro* cytogenetics

Priority: Moderate

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Rationale/Remarks:

- Potential for human exposure
- Lack of chronic toxicity data
- Suspicion of carcinogenicity based on its potential alkylating ability
- Obtain more exposure information

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

The US Environmental Protection Agency (EPA) was contacted through Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC) for information on the annual production level of EBA and reported it to be within a range of 16 to 43 thousand pounds for 1989.

The NTP was contacted for information about the status of EBA's closely related parent acid, MBAA. According to a representative of the Central Data Management Section, MBAA was nominated to the NTP for carcinogenicity bioassay by the American Water Works Association in 1991 as one of a group of water disinfection by-products. MBAA is reported to be under review but not yet assigned for testing.

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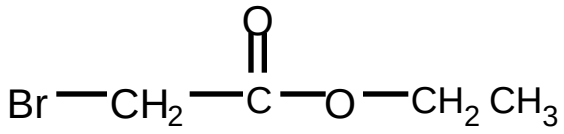
CHEMICAL IDENTIFICATION

CAS Registry No.: 105-36-2

Chemical Abstract Names: Acetic acid, bromo-, ethyl ester (8CI, 9CI)

Synonyms and Trade Names: Bromoacetic acid, ethyl ester; (ethoxycarbonyl)methyl bromide; ethyl α-bromoacetate; ethyl bromoethanoate; ethyl monobromoacetate; Antol; EBA

Structure, Molecular Formula and Molecular Weight:



$C_4H_7BrO_2$

Mol. wt.: 167.02

Chemical and Physical Properties:

Description: Clear, colorless to straw colored, flammable liquid with a fruity odor (Lewis, 1993a,b; Criswell *et al*., 1980)

Boiling Point: 162-163°C (Lide, 1993)

Melting Point: -13.8°C (Lide, 1993)

Flash Point: 47.8°C (Lewis, 1993b)

Density: 1.514 at 20°C/4°C (Lide, 1993)

Solubility: Soluble in water, benzene, chloroform, diethyl ether, and ethanol (Anon, 1991; Lewis, 1993a)

Volatility: Relative vapor density, 5.8 (Lewis, 1993a)

Reactivity: Flammable when exposed to heat, flame and oxidizers; will react with water or steam to produce toxic and corrosive fumes; when heated to decomposition or on contact with acid or acid fumes, emits highly toxic fumes of bromine (Lewis, 1993b)

Technical Products and Impurities: EBA is commercially available with purities ranging from 97 to 98% (Anon, 1991; Kuney, 1993; Dialog Information Services, 1995). In addition, several suppliers provide technical or practical grade products. It is available in research and bulk (drum) quantities. No information identifying any impurities was found in the available literature.

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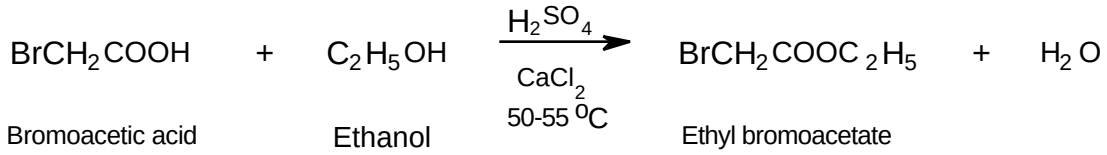
EXPOSURE INFORMATION

Production and Producers: EBA is commonly synthesized by sulfuric acid catalyzed esterification of monobromoacetic acid (MBAA). After reaction completion, excess acid is washed out and the product purified via distillation under reduced pressure if necessary (Stenger, 1978; Korhonen, 1984). The following general scheme described this synthesis.



EBA is listed on the US EPA's TSCA Inventory (STN International, 1995a). The annual US production of EBA was reported to be in the range of 16,376 to 42,937 pounds based on nonconfidential data received by the EPA for 1898. No other annual US production data for EBA were found in the available literature, including recent issues of *Synthetic Organic Chemicals, Production and Sales*, for 1988-1992 (US International Trade Commission, 1989-1994).

EBA is current available from the following suppliers in the United States (Kuney, 1993; Van, 1994).

Aldrich Chemical Co.
Alfa Products
American Tokyo Kasei, Inc.
Fairfield Chemical Co.
J.T. Baker, Inc.
Chem Service, Inc.
Crescent Chemical Co., Inc. (Riedel-de Haen)
Eastman Chemical Co.
Fluka Chemical Corp.
Janssen Chimica
Lancaster Synthesis Ltd.
Morre-Tec Industries, Inc.
MTM Research Chemicals, Inc
Pfaltz & Bauer, Inc.
Rhone-Poulenc, Inc.
R.S.A. Corp.
SAF Bulk Chemicals
Spectrum Chemical Mfg. Corp.
Wall Chemical Corp.
White Chemical Co.

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Several major US pharmaceutical manufacturers have recently been assigned patents in which EBA is reportedly used in the synthesis of a variety of pharmaceutical products including drugs and therapeutic aids, such as diagnostic imaging agents. Some companies whose patents are cited in the open literature include: Bristol-Myers Squibb; Ciba-Geigy Corp.; Eastman Kodak Co.; ICI Americas, Inc.; Merck and Co., Inc.; Merrill Dow Pharmaceuticals, Inc.; Rorer, Inc.; Sterling Winthrop, Inc.; and the Upjohn Co. (STN, 1995b).

Imports: Major producers of EBA for the world market have been reported to include two companies in France, one in Great Britain, one in Germany, one in Japan and two in Israel (Chemical Information Services, Inc., 1994). According to the Journal of Commerce Piers Imports database, Ameribrom, Inc., reported imports of 1,300 lbs of EBA in 1994 and approximately 1,000 lbs of EBA in 1993 from a manufacturer in Israel (Dialog Information Services, 1995b). No other information on specific import volumes was found in the available literature.

Use Pattern: EBA, a lacrimator, has been used as a chemical warfare agent, tear gas agent, and warning agent for poisonous, odorless gases (NLM, 1995). It was reportedly first used as a tear gas by the French in 1914 (Holmberg, 1975). Arena (1979) listed EBA as one of several extensively used tear gases. EBA is also widely used as an alkylating agent and as a versatile intermediate in organic, pharmaceutical and agrochemical syntheses (O-, N- and S-alkylations).

As a synthetic organic reagent and chemical intermediate, EBA and similar α-halo esters are commonly used as alkylating agents in the Reformatsky reaction for the alkylation of aldehydes and ketones, using zinc as catalyst. The aldehyde or ketone can be aliphatic, aromatic, heterocyclic or contain various functional groups (March, 1992). According to Van Ness (1981) α-bromo esters generally give the best results in the Reformatsky reaction, which is analogous to the Grignard reaction; α-chloro esters react slowly or not at all, and the α-iodo esters are generally not available. For example, Williams (1978) described the Reformatsky reaction of benzaldehyde with EBA, a condensation reaction yielding cinnamic acid. Variations on the Reformatsky reaction include the reaction of nitriles with EBA (called the Blaise reaction) and substitution reactions of EBA with other carboxylic esters (March, 1992). Criswell and coworkers (1980) reported EBA to be widely used for

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modification of enzymes and other proteins based on its much higher reactivity with sulfhydryl groups than with amino groups.

EBA is used as a starting material or chemical intermediate in the preparation of a wide variety of drugs and cosmetics (*e.g.*, UV protectants, perfumes). For example, Bock and coworkers (1989) of the Merck Sharp & Dohme Research Laboratories in West Point, PA, in a report on their drug development work with benzodiazepines, described the use of EBA as an alkylating agent for the preparation of aminobenzodiazepine derivatives. A research group at Alcon Laboratories, Inc., in Fort Worth, TX, reported using EBA as an alkylating reagent in the synthesis of a group of aldose reductase inhibitors for the treatment of diabetes (DuPriest *et al*., 1991). EBA has also been patented for use in the synthesis of complexing agents as contrast media for diagnostic/therapeutic imaging by several pharmaceutical manufacturers, including Bristol-Myers Squibb and Schering (Desreux *et al*., 1994; Gries *et al*, 1987).

American Cyanamid Co. has patented the use of EBA in the manufacture of agricultural chemicals. This company was assigned a patent for the synthesis of bioregulators in which EBA is used as a chemical intermediate in the preparation of benzopyran and tetrahydronaphthalene derivatives as herbicide safeners. These safeners are applied to barley seeds to act as carbamate pesticide antidotes (Cary & Quinn, 1994). A safener is a chemical used in conjunction with the application of a pesticide to protect against damage from a pesticidal ingredient (Plimmer, 1980).

A Japanese manufacturer and processor of plastics has described (in a patent) the use of EBA as a component of a hydrochlorofluorocarbon (HCFC) decomposition inhibitor and stabilizing agent for polyurethane foam (Ide *et al*., 1993). Furthermore, EBA has reportedly been used as a tear gas in joke-type toys, (a use now prohibited), and illicitly as a preservative in alcoholic beverages in Europe (Christoph *et al*., 1985; Hild, 1990). According to Christoph and coworkers, EBA has been in use in Europe for the last 50 years, frequently under the trade names of STERIL or STABILO. EBA has been considered to be a highly efficient biocide which could be used safely at low concentrations. It has been used in small quantities in beverages, including wine, beer and champagne, and is also in some food products to prevent molding or fermentation.

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Human Exposure: There is potential for occupational exposure to EBA in commercial, industrial and research laboratory settings mainly by the inhalation or dermal route. In addition, exposures to the general public could occur through the reported use of EBA as a lacrimator or tear gas agent in chemical warfare or odorant/warning agent in odorless toxic gases. Consumer exposure to EBA could possibly have resulted from its now banned use in joke-type toys as well as by ingestion of low levels through the illicit use of EBA as a preservative in alcoholic beverages (Christoph, 1985; Hild, 1990).

The National Occupational Exposure Survey (NOES) which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1989, estimated that 851 workers, including 187 female employees, were potentially exposed to EBA in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

Environmental Occurrence: EBA is not known to occur naturally. EBA may be present in air as a result of its tear gas and chemical warfare agent uses as well as its other odorant and reagent/chemical intermediate uses. A method for analysis has been described which is based on derivatization and evaluation by gas chromatography coupled with atomic emission and mass spectral analysis (Schoene *et al*., 1993).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace maximum allowable levels of EBA. The American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) for this compound.

The US Department of Transportation (DOT) regulates EBA as a flammable liquid and poison and has issued standards for the labeling, packaging and transportation of EBA in FR 55(246), 52 402-729, 21 Dec. 1990. EBA has been given a hazardous materials rating by the National Fire Protection Association (Business & Legal Reports, Inc., 1990). In Germany, the use of EBA as a tear gas agent in toys and joke items has been prohibited as a health hazard (Hild, 1990).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to EBA and cancer risk in humans were identified in the published literature. EBA is toxic by ingestion, inhalation and skin absorption and is a strong irritant and a lacrimator (Anon., 1991; Lewis, 1993a, 1993b). According to Grant (1974) EBA vapors are especially irritating to the eyes. Exposure to a concentration of 8 ppm in air for more than a minute is reported to be unbearable. Ocular exposures to high concentrations of EBA vapor from tear gas shells can cause temporary lesions, while eye contact with liquid EBA has been known to cause permanent damage.

Animal Data: Van Duuren and coworkers (1974) studied EBA for carcinogenic effects in female ICR/Ha Swiss mice by various routes of administrating. Following skin applications of 0.5 mg/0.1 ml acetone 3 times per week for 580 days to a group of 50 mice (animal median survival time, 526 days) no papillomas or carcinomas were observed. In a mouse skin initiation-promotion study in which a single dose of 0.5 mg EBA as initiator in 0.1 ml acetone was applied dermally to a group of 30 mice followed 2 weeks later by application of 2.5 μg of phorbol myristate acetate (PMA) in 0.1 ml acetone 3 times per week for 385 days, the incidence of papillomas and carcinomas in EBA-treated animals was found to be non-significant ($P > 0.05$) when compared with animals receiving only PMA. Another group of 30 mice received ip injections of 0.1 mg EBA in 0.05 ml of Nujol once a week for 450 days. No local sarcomas were observed in the test animals; furthermore, there was no increased incidence of papillary tumors of the lungs when compared with control animals. Finally, when EBA was administered in doses of 0.1 mg in 0.05 ml Nujol by sc injection to a group of 50 mice once a week for the 580 day duration of the experiment (animal median survival time, 441 days), there was a significant increased incidence ($P < 0.01$) of malignant sarcomas at the injection sites.

Theiss and coworkers (1979) tested EBA as one of 28 organohalides for induction of lung tumors in Strain A mice in a 24 week study. EBA did not produce an elevated pulmonary adenoma response under the conditions of the study. EBA was administered to groups of 20 mice (10 males and 10 females) by ip injections in doses of 0.01, 0.02 and 0.03 mM/kg of EBA in tricaprylin 3 times per week for a total of 24, 24 and 9 injections, respectively, and a total dose of 0.2, 0.4 and 0.3 mM/kg, respectively. No statistically significant elevation ($P >$

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0.05) in lung tumor incidence was observed. The authors suggested that the greater toxicity or organobromides, such as EBA, relative to similar organochlorides, may have masked potential tumorigenic activity since these compounds could not be administered in sufficient quantities to elicit a tumorigenic response.

Short-Term Test: No *in vitro* or *in vivo* studies evaluating EBA for mutagenic effects were found in the published literature. EBA was submitted to the DCB Short-Term Test Program for mutagenicity testing and the following results have been reported. EBA was negative in an Ames *Salmonella* assay with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 both with and without S9 activation. When tested in a mouse lymphoma assay using an L5178Y $TK^{+/-}$ cell line, EBA gave a weakly positive results without S9 activation and a positive result with S9 activation.

Metabolism: No studies on the metabolism of EBA were found in the available literature.

Other Biological Effects: An academic research group in Texas has studied EBA as one of a small group of "chemically active odorants" for inhibitory effects on the frog olfactory mucosa. EBA was chosen for study as a fast-acting tear gas with a high vapor pressure and an identifiable fruity odor. It was reported to block all olfactory responses of the frog nose, except responses to certain aliphatic amines. This specific pattern of inhibition was thought to be effected through its alkylating ability and reactivity with protein sulfhydryl or amino groups in the olfactory mucosa. Isoamyl acetate and several closely-related ester odorants were found to act as protectants against the inhibitory action of EBA (Criswell *et al*., 1980; Schafer *et al*., 1984a,b).

Structure/Activity Relationships: EBA is an ester of an α-halo aliphatic carboxylic acid. A group of 15 related bromo- or chloro-substituted carboxylates as well as the corresponding acid, MBAA, were screened for relevant information associating these structurally similar compounds with a mutagenic or carcinogenic effect. The limited amount of short-term test data available indicate mixed genetic toxicity results for this group of compounds. A summary of the carcinogenicity and mutagenicity information identified for EBA and several of the structurally related compounds is presented in Table 1. No information from genetic toxicity or carcinogenicity studies of the following structurally related compounds was found

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in the available literature: ethyl 2-bromobutyrate [533-68-6]; ethyl 2-chloropropionate [535-13-7]; ethyl 2-bromoisobutyrate [600-00-0]; ethyl 3-chloropropionate [623-71-2]; butyl 2-bromoacetate [18991-98-5]; propyl 2-bromoacetate [35223-80-4].

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Table 1. Summary of Toxicological Evidence on EBA and Structurally Related Compounds

Chemical name [CAS RN]	Carcinogenicity data	Mutagenicity data	Other related data
Ethyl Bromoacetate [105-36-2] $BrCH_2COOC_2H_5$	injection site tumors in mice (Van Duuren *et al.*, 1974)	NDF	Alkylating agent/sulfhydryl reagent
Monobromoacetic Acid [79-08-3] $BrCH_2COOH$	nominated to NTP; not yet on test (NTP, 1995a,b)	negative in *E. coli* paper disk screening assay (Szybalski, 1958)	DNA strand breakage, possible antitumorigenesis (Stratton *et al.* 1981)
Ethyl 2-Bromopropionate [535-11-5] $CH_3CH(Br)COOC_2H_5$	NDF	negative in *S. typhimurium* TA 100 without S9 (Dolzani *et al.*, 1992)	NDF
Ethyl Chloroacetate [105-39-5] $ClCH_2COOC_2H_5$	non-tumorigenic after sc injection in mice (Van Duuren *et al.*, 1974); equivocal for induction of lung adenomas in Strain A mice (Theiss *et al.*, 1979)	negative in *S. typhimurium* TA 1535 without S9; negative in *S. cerevisiae* with and without S9 (Kringstad *et al.*, 1981; Nestmann & Lee, 1985)	NDF
n-Butyl Bromide [109-65-9] $BrCH_2CH_2CH_2CH_3$	NDF	positive in *S. typhimurium* TA 100 & TA 1535; positive in *E. coli* WP2; negative in *E. coli* $PolA^+$ & $Pol A^-$ (Simmon & Poirier, 1976; Fluck *et al.*, 1976)	NDF
Methyl 2-Bromoacetate [96-32-2] $BrCH_2COOCH_3$	negative for induction of lung adenomas in Strain A mice (Theiss *et al.*, 1979)	NDF	NDF
Methyl 2-Chloroacetate [96-34-4] $ClCH_2COOCH_3$	negative for induction of lung adenomas in Strain A mice (Theiss *et al.*, 1979)	NDF	NDF

NDF: no data found.

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Carcinogenic Effects

Monobromoacetic acid. According to Linder and coworkers (1994) halogenated acetic acids, including EBA precursor and parent acid, MBAA, have been identified as a major class of water disinfection by-products. MBAA is one of a group of water disinfection by-products nominated to the NTP for carcinogenicity bioassay in March, 1991, by the American Water Works Association. According to a spokesperson for NTP's chemical data management, this chemical is not on test, and at this time is under review and no testing is planned (NTP, 1995a,b). In an early study for the identification of agents which might inhibit tumor growth, MBAA was classified as a radiation protector, modifying lethal effects caused by ionization radiation in mice and an *E. coli* bacterial system (Price *et al.*, 1965). Stratton and coworkers (1981) tested a solution of MBAA in two murine tumor cell cultures, C-1300 neuroblastoma (NB) cells and mouse leukemia L-1210 cells and suggested that the cytotoxic effects may be due to the alkylation of bromoacetate (BrAc), followed by DNA strand breakage. BrAc was reported to inhibit NB cell growth *in vitro* with dependence on both concentration and exposure duration. In addition, they demonstrated cytotoxicity in L-1210 cells *in vitro* and attributed it to DNA strand breakage based on an alkaline elution assay following treatment of the cells with 100μM BrAc. Survival as determined by colony formation of L-1210 cells was inhibited by treatment with BrAc for 1 hour. A log linear dose-response effect was observed up to a dose of approximately 250μM, and there was a plateau effect reflecting no further effect on cell survival at concentrations greater than 500μM. The absence of a shoulder effect in the survival curve was interpreted as an indication that the treated cells had little ability to accumulate or repair sublethal damage.

Ethyl 2-chloroacetate. Van Duuren and coworkers (1974) administered ethyl chloroacetate (ECA) sc at a dose of 1.0 mg/0.05 ml of tricaprylin to ICR/Ha Swiss mice. They reported that 1/50 mice developed a local sarcoma and considered ECA non-tumorigenic in this assay whereas the subject chemical, EBA, as reported above, was considered to have shown notable tumorigenicity at the site of injection. Theiss and coworkers (1979) studied 28 organohalides for induction of pulmonary adenomas in Strain A mice. ECA was administered by ip injections 3 times weekly for a total of no more than 24 injections to groups of 20 mice (10 males and 10 females) at the maximum tolerated dose, one-half the maximum tolerated dose, and one-fourth or one-fifth the maximum tolerated dose. The authors reported that the results of the ECA study were inconclusive because the pulmonary tumor response was

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significant by only one of two statistical tests. EBA, as reported above, was non-tumorigenic in this study.

Methyl 2-bromoacetate; methyl 2-chloroacetate. Theiss and coworkers (1979) also tested methyl 2-bromoacetate and methyl 2-chloroacetate for induction of pulmonary adenomas in Strain A mice in a 24 week study in which the compounds were administered by ip injections in tricaprylin. They reported that both of these compounds were negative, i.e. did not produce a pulmonary tumor response in this assay.

Mutagenic Effects

Monobromoacetic acid. Szybalski (1958) reported screening a number of compounds, including MBAA, in a search for prospective antineoplastic agents. MBAA was classified as a non-mutagen based on a paper-disk assay method in which an increase in the frequency of reversion from streptomycin dependence to independence in strain Sd-4-73 of *E. coli* was utilized as a measure of mutagenicity.

Ethyl 2-bromopropionate. Ethyl 2-bromopropionate, a closely related compound, was tested for mutagenic activity in an Ames/*Salmonella* assay. Dolzani and coworkers (1992) reported that this chemical, when tested over a dose range of 100-4,000 µg/plate, caused a non-significant increase in the number of his^- revertants in *S. typhimurium* strain TA100 without metabolic activation of up to 343±110 per mg per plate at a dose of 1,000µg. This chemical was reported inactive, with a peak response of just under 2× spontaneous revertants which averaged 131±5 per plate, followed by a toxic effect possibly masking a potential dose-response effect.

Ethyl 2-chloroacetate. Kringstad and coworkers (1981) reported that ethyl 2-chloroacetate (ECA) tested negative for mutagenicity in an Ames/*Salmonella* assay in strain TA1535 without metabolic activation. Nestmann and Lee (1985) tested ECA for genetic activity in a yeast assay using *Saccharomyces cerevisiae* strains D7 and XV185-14C with and without S9. They reported a negative result in both strains.

Rosenkranz *et al*. (1990) examined a database of NTP-tested chemicals to develop a predictive SAR methodology based on structural characteristics associated with induction of

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sister chromatid exchanges (SCEs) and chromosomal aberrations (CAs) in Chinese hamster ovary (CHO) cells, using the CASE (Computer Automated Structure Evaluation) system. They reported that the structural determinant, Br-CH_2-, was an active biophore in each of 4 occurrences with a probability (P value) of 0.063 reported only for SCEs, not for CAs. The same biophore was reported associated with mutagenicity in *Salmonella* with a probability of 0.125.

Related Biological Effects

Monobromoacetic acid. Jones and Wells (1981) studied the metabolism of the parent acid, MBAA, and related compounds, 2-bromoethanol and bromoacetaldehyde, in rats. They reported that after administration of MBAA the unchanged compound together with a metabolite, N-acetyl-S-(carboxymethyl)cysteine, appeared in the urine within the first 24 hours. They identified the same minor metabolite after administration of 2-bromoethanol and proposed an oxidative metabolic pathway in which this compound is partially metabolized via bromoacetaldehyde and MBAA to the cysteine-conjugated metabolite.
MBAA has also been described as a metabolic inhibitor with efficacy as a protective agent in plants. Castro and Loureiro-Dias (1994) reported that MBAA competitively inhibited the transport of lactic acid in the yeast, *Fusarium oxysporium* var. *lini*.

Linder and coworkers (1994) investigated MBAA for short-term spermatotoxicity, specifically for changes that may impact spermatogenesis, sperm transit or sperm and semen quality. They reported observing no effects on these endpoints 2 or 14 days after rats were given a single [oral] dose of 100 mg MBAA/kg or after 14 daily doses of 25 mg MBAA/kg/day. They concluded that MBAA was non-spermatotoxic in this short duration test but did not rule out the possibility that cumulative effects could occur with exposures of longer duration

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