Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,2-dibromoethane (ethylene dibromide)

SCOEL/SUM/166
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8-hour TWA:	not assigned (*see Recommendation*)
STEL (15 min):	not assigned
Notation:	"skin"
BLV:	not assigned
SCOEL carcinogen group:	A (*genotoxic carcinogen, no threshold*)
Additional guidance:	Any exposure to this compound should be avoided

Substance identification: 1,2-dibromoethane

Synonyms: ethylene dibromide

Structural formula: $Br-CH_2-CH_2-Br$

CAS no.:   106-93-4
Molecular formula: $C_2H_4Br_2$
Molecular weight: 187.86
Melting point: 9.9°
Boiling point: 131.6°
EU-Classification:

Carc. 1B	H350	May cause cancer
Acute tox 3	H331	Toxic if inhaled.
Acute tox 3	H311	Toxic in contact with skin.
Acute tox 3	H301	Toxic if swallowed.
Eye Irrit. 2	H319	Causes serious eye irritation.
STOT SE 3	H335	May cause respiratory irritation.
Skin Irrit. 2	H315	Causes skin irritation.
Aquatic Chronic 2	H411	Toxic to aquatic life with long lasting effects.

Conversion factor: 1 ppm = 7.69 mg/m³; 1 mg/m³ = 0.13 ppm

Criteria documents used: This summary rests mainly on the documentation of IARC (1999). This was further supplemented using data compiled by DFG (1976), WHO (1996), the U.S. NTP (2002), Guengerich et al. (2003), and a recent literature search conducted by SCOEL.

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1. Occurrence/use and occupational exposure

A primary use of 1,2-dibromoethane (ethylene dibromide) has been as a lead scavenger in antiknock mixtures added to gasolines. Lead scavenging agents transform the combustion products of lead alkyls to forms that are more easily vaporised from engine surfaces. This use has decreased with banning the use of lead-containing fuels in many countries.

Another major use in the past was as a pesticide and ingredient in soil and grain fumigant formulations. Currently, the compound is used as a chemical intermediate in synthesis and as a non-flammable solvent for resins, gums and waxes. The major chemical made from 1,2-dibromoethane is vinyl bromide. 1,2-Dibromoethane also has been used as an intermediate in the preparation of dyes and pharmaceuticals (NTP 2002).

2. Health significance

1,2-Dibromoethane is "reasonably anticipated to be a human carcinogen" based on sufficient evidence of carcinogenicity in experimental animals (IARC 1999).

2.1. Toxicokinetics

2.1.1. Human data (IARC 1999)

Human liver preparations metabolise 1,2-dibromoethane to water-soluble and to irreversibly protein- and DNA-bound metabolites by both cytochrome P450 and glutathione S-transferase (GST) enzymes (Wiersma et al., 1986). DNA adduct formation occurs also in isolated human hepatocytes (Cmarik et al., 1990).

There is convincing evidence that CYP2E1 is a major enzyme in the oxidative metabolism of 1,2-dibromoethane. Among heterologously expressed human cytochromes P450, only CYP2E1 (low K_m enzyme), CYP2B6 and CYP2A6 (high K_m enzymes) metabolized 1,2-dibromoethane to 2-bromoacetaldehyde (Wormhoudt et al., 1996), CYP2E1 having the highest intrinsic clearance. Interindividual variation in P450-catalysed microsomal metabolism, reflecting presumably variable amounts of CYP2E1 enzyme, was almost 50-fold.

Human fetal liver cytosol and several GST forms from human foetal liver also catalyse the conjugation of 1,2-dibromoethane (Kulkarni et al., 1992; Mitra et al., 1992). The alpha-class (Cmarik et al., 1990) and theta class (Thier et al., 1996) GST enzymes from human liver are especially active in the conjugation of 1,2-dibromoethane.

2.1.2. Animal data (IARC 1999, Guengerich 2003)

A scheme of the main metabolic pathways of 1,2-dibromoethane is shown in *Figure 1* (according to Hissink et al., 2000).

After intraperitoneal administration of radiolabelled 1,2-dibromoethane to Guinea pigs (30 mg/kg bw) or mice (40 mg/kg bw), the largest portion of the radioactivity was excreted in urine. The highest levels of radioactivity were found in kidney, liver and stomach. Enzymatic reaction with glutathione (GSH) in vitro and in vivo as well as excretion of glutathione-derived metabolites in urine of rats and mice have been demonstrated (IARC, 1977).

1,2-Dibromoethane was absorbed rapidly through the skin of guinea-pigs and reached maximal blood levels at 1 h (Jakobson et al., 1982). In rats, 24-h urinary excretion of radiolabelled 1,2-dibromoethane was > 70 %, and the highest amount at 24 h was found in the liver and kidneys (Plotnick et al., 1979).

The metabolic pathways of 1,2-dibromoethane are known in detail. In rodents, the major routes are oxidation by CYP2E1 and conjugation by GST (Guengerich, 1994; Wormhoudt et al., 1996). The primary metabolite formed by CYP2E1 is 2-bromoacetaldehyde, which can be conjugated with glutathione and enter the mercapturic acid pathway (Guengerich, 1994). The excretion of thiodiacetic (thiodiglycolic) acid in urine has been suggested as a biomarker for P450-catalysed oxidation (Wormhoudt et al., 1997).

The CYP2E1-catalysed pathway appears responsible for a major part of protein binding and tissue toxicity, although glutathione conjugates also play a role (Khan et al., 1993; Wormhoudt et al., 1996). The ratio between the oxidation pathway and the GST pathway in rodents in vitro and in vivo is about 4. Debromination during oxidative metabolism may result in increased bromine concentrations (Guha et al., 1993).

The GSH conjugation pathway is responsible for the formation of DNA adducts and bacterial mutagenicity (Sipes et al., 1986). The major (> 95%) adduct is S-[2-(N7-guanyl)ethyl]glutathione (Cmarik et al., 1990). Three minor guanyl or adenyl adducts (1% or less) are also formed. Various forms of GST differ in their catalytic activities. The amount of the major adduct formed in vivo in liver and kidney DNA is directly proportional to the dose in rats (Kim & Guengerich, 1989). The amount of the adduct can be modulated by inducers of GST or inhibitors of CYP2E1 (Kim & Guengerich, 1990; Guengerich, 1994), with resultant consequences for hepatic carcinogenesis (Wong et al., 1982). More DNA adduct was formed in the livers of rats than in those of mice (Kim & Guengerich, 1990).

The glutathione S-transferase GSTT1 affects the mutagenicity of 1,2-dibromoethane. In Salmonella typhimurium TA1535 expressing the rat GSTT1 the number of revertants was increased compared to the control strain by 1,2-dibromoethane and related compounds (Thier et al. 1996).

In whole-body autoradiographic studies, covalently bound radioactivity from 1,2-dibromoethane was detected in the surface epithelia of the entire respiratory and the upper alimentary tracts of mice and rats (Brandt, 1986), in the epithelia of the oral cavity, oesophagus and forestomach of foetal mouse (Kowalski et al., 1986), and in vaginal epithelium of mice and rats (Brittebo et al., 1987). DNA damage was effected by 1,2-dibromoethane also in human and rat nasal mucosa cells in vitro (Holzer et al. 2008). According to toxicokinetic modelling data, the extrahepatic metabolism of 1,2-dibromoethane must not be neglected (Hissink et al., 2000).
Covalent binding of 1,2-dibromoethane to albumin has been demonstrated after in-vivo administration of 1,2-dibromoethane to rats and after in-vitro incubation of 1,2-dibromoethane with human albumin (Kaphalia & Ansari, 1992).
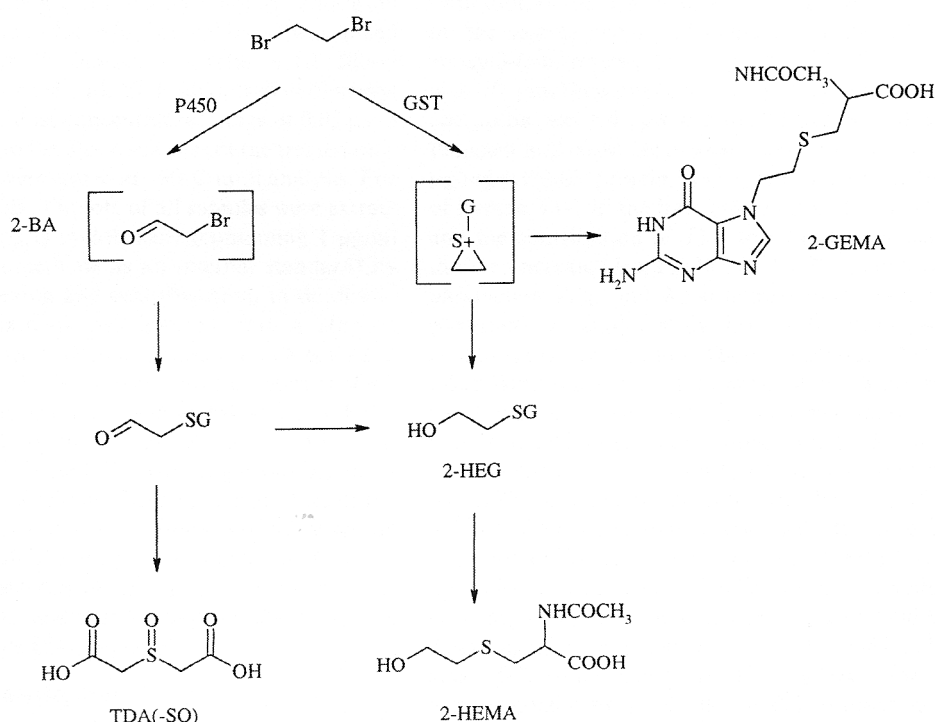
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Figure 1: Oxidative (Cytochrome P-450 dependent) and reductive (GSH dependent) pathways of 1,2-dibromoethane in experimental animals and in humans (2-BA: 2-bromoacetaldehyde; G: glutathione; 2-GEMA: 2-guanyl-ethylmercapturic acid; 2-HEG: 2-hydroxyethyl-glutathione; TDA: thiodiglycolic acid; SO: sulfoxide, 2-HEMA: 2-hydroxyethylmercapturic acid). The cyclic episulfonium (thiiranium) ion is regarded as the ultimately DNA-binding and genotoxic/carcinogenic metabolite (according to Hissink et al., 2000; modified)

A comparative quantitation of the DNA adducts of 1,2-dibromoethane and related compounds was performed by Watanabe et al. (2007). Rats and mice were treated i.p. with ^{14}C-labeled dichloromethane, dibromomethane, 1,2-dichloroethane, or 1,2-dibromoethane [5 mg per kg body weight], and livers and kidneys were collected to isolate DNA. The level of liver or kidney S-[2-(N(7)-guanyl)ethyl]GSH in rats treated with 1,2-dibromoethane was approximately 1 adduct/10^5 DNA bases; in male or female mice, the level was approximately one-half of this. The levels of adducts after administration of 1,2-dichloroethane were 10-50-fold lower.

Toxicokinetic models to quantitatively describe the metabolism of 1,2-dibromoethane and of the chemically related 1,2-dichloroethane in experimental animals have been refined (Ploemen et al. 1997; Hissink et al. 2000, Sweeney et al. 2008). Assuming that the GSH-dependent pathway is relevant for the biological activation of 1,2-dibromoethane, it has been concluded that humans will be less sensitive to the chemical than rodents (Hissink et al., 2000).

2.1.3. Biological monitoring

Following animal experiments in rats after dosing 1,2-dibromoethane, the excretion of urinary thiodiglycolic acid (thiodiacetic acid) has been recommended as a selective biomarker of exposure (Wormhoudt et al. 1997). The same urinary metabolite is also formed after exposure to vinyl chloride (see SCOEL recommendation on vinyl chloride). Human field studies involving biomonitoring of 1,2-dibromoethane, however, are lacking.

2.2. Acute toxicity

2.2.1. Human data

Cases of fatality following acute exposure of humans to 1,2-dibromoethane have been reported (Humphreys et al. 1999). Two workers died following inhalation exposure while cleaning a tank used to temporarily store fertilizer mixtures. Neither worker had respiratory or skin protection. The air inside the tank was sampled approximately 20 h after the accident, and 1,2-dibromoethane concentrations ranged from 15 to 41 ppm with an average of 28 ppm. The first worker was exposed for approximately 5 min and the second for approximately 20-30 min. The first worker died approximately 12 h after exposure, and the second died 64 h after having entered the tank (Letz et al., 1984).

Another fatal poisoning occurred in a woman who intentionally ingested a capsule containing 6.5 g 1,2-dibromoethane. On admission to hospital, the patient was drowsy, disoriented and jaundiced with mild hepatomegaly. She died eight days later and a post-mortem liver biopsy revealed congestion and focal liver cell necrosis (Singh et al., 1993).

Recently, Singh et al. (2007) reviewed the data of sixty-four patients with 1,2-dibromoethane poisoning. All the patients were from Gwalior/India and neighbouring districts. Out of sixty-four cases 26 patients survived and 38 patients died. Nausea, vomiting and pain in the abdomen were most common symptoms at presentation. Diarrhoea, drowsiness, palpitations and oliguria were other features. Half of an ampoule (1.5 ml) of 1,2-dibromoethane was sufficient to be fatal. Death occurred anywhere between twelve hours and five days. Gastrointestinal toxicity was predominant at presentation. Nausea, vomiting and abdominal pain was present in all the patients. Nephrotoxicity, hepatotoxicity, cardiotoxicity, central nervous system toxicity and hypoglycemia were also observed.

2.2.2. Animal data

The experimental data on acute toxicity of 1,2-dibromoethane have been compiled by DFG (1976). In rats, the LC-50 (5 h inhalation) was about 400 ppm. Short-term exposures of a few minutes to concentrations of 5000 ppm and higher were lethal for all animals.
Oral LD-50 values reported were 0.146 g/kg for male rats, 0.117 g/kg for female rats, 0.420 g/kg for male mice, 0.055 g/kg for female rabbits. In rats, a dermal application of 0.25 ml of neat 1,2-dibromoethane was lethal (DFG 1976).

2.3. Irritation and corrosivity

2.3.1. Human data

After application of 0.5 ml neat 1,2-dibromoethane to human skin painful erythema and oedema occurred after 10 min. After 15-20 min blisters were formed (DFG 1976).

2.3.2. Animal data

Dermal applications of 10% 1,2-dibromoethane to rabbits produced erythema and oedema. Similarly, application of 10% 1,2-dibromoethane in 1,2-propanediol to rabbit eyes causes severe conjunctival irritation (DFG 1976).

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2.4. Sensitisation

No data were reported (DFG 1976).

2.5. Repeated dose toxicity

2.5.1. Human data

No human data were reported following repeated dosing. All available clinical data are related to acute accidental poisonings (see 2.2.1).

2.5.2. Animal data (IARC 1999)

Male and female Fischer 344 rats were exposed by inhalation to 0, 3, 10 or 40 ppm 1,2-dibromoethane for 6 h per day on five days per week for 13 weeks for a total of 67-68 exposures in 95-96 days. Animals were killed after one, six or 13 weeks of exposure and after a recovery period of 88-89 days. At 10 ppm, 1,2-dibromoethane caused slight epithelial hyperplasia of the nasal turbinates in animals killed after one, six or 13 weeks of exposure. However, 88 days after the last exposure, nasal turbinate changes were not observed. Rats exposed to 40 ppm 1,2-dibromoethane had increased liver and kidney weights, hyperplasia and non-keratinising squamous metaplasia of the respiratory epithelium of the nasal turbinates. After the recovery period of 88 days, the turbinates had reverted to normal histology. The most sensitive response associated with repeated subchronic exposure of rats to 10 or 40 ppm 1,2-dibromoethane involved pathological changes in the respiratory epithelium of the nasal turbinates (Nitschke et al., 1981). In these studies, 3 ppm was defined as the NOEL.

Male and female Fischer 344 rats and B6C3F$_1$ mice were exposed to 3, 15 or 75 ppm 1,2-dibromoethane for 6 h per day on five days per week for 13 weeks. Rats and mice examined after 13 weeks of exposure showed severe necrosis and atrophy of the olfactory epithelium in the nasal cavity after inhalation of 75 ppm 1,2-dibromoethane. Lower concentrations induced squamous-cell metaplasia, hyperplasia and cytomegaly of the epithelium of the respiratory nasal turbinates. Metaplasia, hyperplasia and epithelial cytomegaly were also seen in other respiratory tissues (larynx, trachea, bronchi, bronchioles) at this dose (Reznik et al., 1980).
The characteristics of the nasal lesions in mice following chronic inhalation of 1,2-dibromoethane were investigated. Male and female B6C3F$_1$ mice were exposed to 10 or 40 ppm 1,2-dibromoethane for 6 h per day an five days per week for 103 (10 ppm) or 90 (40 ppm) weeks. The incidence of hyperplastic lesions was related to the dose of 1,2-dibromoethane and was equivalent in males and females. Lesions consisted of focal areas of cuboidal to columnar cells arranged in a glandular pattern with foci of hyperplastic squamous epithelium also seen occasionally. Lesions were usually located in the anterior (respiratory turbinates) of the nasal cavities. A broad spectrum of proliferative lesions was observed (Stinson et al., 1981).

Female B6C3F$_1$ mice were administered 100, 125, 160 or 200 mg/kg bw 1,2-dibromoethane in corn oil by gavage daily for 14 days. Host resistance was not altered after challenge with a variety of agents. Decreases were seen in relative thymus and spleen weights, red blood cells, haemoglobin, haematocrit and responses of immunological cells in culture. Increases in relative weights of liver and kidney were seen. The authors concluded that even in animals exhibiting clinical signs of toxicity, short-term exposure to 1,2-dibromoethane did not alter the immune integrity of mice as measured by host resistance assays in vivo (Ratajczak et al., 1994).

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2.6. Genotoxicity

The genotoxicity of 1,2-dibromoethane has been extensively reviewed by IARC (1999). The following gives a summary of the most relevant data, as highlighted by IARC.

2.6.1. In vitro (IARC, 1999)

1,2-Dibromoethane was mutagenic in bacteria, Streptomyces coelicolor, Aspergillus nidulans. Salmonella typhimurium TA1535 expressing human GST1-1 showed greatly enhanced mutagenicity when treated with 1,2-dibromoethane. 1,2-Dibromoethane was highly mutagenic in Salmonella typhimurium NM5004, which has high levels of GST (Oda et al., 1996).

1,2-Dibromoethane induced delayed sex-linked recessive lethal mutations in spermatozoa and spermatids of adult Drosophila males. Mutations were detected in F_3 generations as well as in the conventional F_2 generations.

1,2-Dibromoethane was mutagenic to Drosophila melanogaster and studies in repair-proficient and deficient strains suggested that the compound is mutagenic through modification of ring nitrogens of purines (N7 of guanine and N1 of adenine).

1,2-Dibromoethane induced gene mutations, sister chromatid exchanges, chromosomal aberrations and cell transformation in animal cells. It induced mutations in two human lymphoblastoid cell lines, AHH-1 and TK6, in the absence of exogenous metabolic activation. Administration of radiolabelled 1,2-dibromoethane to Wistar rats and BALB/c mice resulted in binding to DNA, RNA and proteins (IARC, 1999).

2.6.2. In vivo - human data

There have been two studies of 1,2-dibromoethane workers for cytogenetic effects upon peripheral lymphocytes. In one of these (Steenland et al.,1985), full working shift breathing zone samples of 14 sprayers of felled pine trees in Colorado, United States, indicated an average eight-hour time weighted average concentration of 1,2-dibromoethane of 60 ppb, with a range of 5 to 281 ppb; short-term samples taken over 4 to 15 min in the breathing zone during times of peak exposures averaged 463 ppb, with a range of 8 to 2165 ppb. Exposure was for a few months and blood samples were taken before and after exposure. Six non-exposed controls were available who provided blood samples at the same time.

In the other study (Steenland et al., 1986), full working shift breathing zone samples of 60 papaya-packing workers at six different plants in Hawaii, United States, indicated geometric mean exposures to 1,2-dibromoethane ranging from 16 to 175 ppb. Controls consisted of 42 sugar workers from a plant in the same area. In this study, there was control for sex, age, smoking, alcohol use, prescription and nonprescription drug use and recent illness. There were no increases in levels of either sister chromatid exchanges or total chromosomal aberrations as a result of exposure in either study.

2.6.3. In vivo – animal data (IARC, 1999)

1,2-Dibromoethane gave rise to micronuclei in binucleated peripheral human lymphocytes after a 4-h exposure, whereas a comparable effect in mononucleated cells was observed only after continued exposure.

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1,2-Dibromoethane caused a dose-dependent increase in liver DNA alkaline-labile sites and single-strand breaks (as determined by alkaline elution assay) in female Sprague-Dawley rats. It was positive in an unscheduled DNA synthesis assay in rat spermatocytes in vitro but was negative in the spermatocytes of rats dosed in vivo. 1,2-Dibromoethane gave positive results in an amphibian (Pleurodeles waltl) micronucleus test but gave negative results in dominant lethal tests.
The binding of 1,2-dibromoethane to DNA of human and rat hepatocytes is mediated by GST-catalysed conjugation to glutathione.

Administration of a single intraperitoneal dose of 1,2-dibromoethane gave rise to S-[2-(N7-guanyl)ethyl]glutathione DNA adducts in livers of several strains of rats (Fischer 344, Sprague-Dawley and Osborne-Mendel) and mice ($B6C3F_1$, ICR and A/J), with levels in rats being four to five times higher than those in mice.

2.7. Carcinogenicity

2.7.1. Human data (IARC 1999)

In one study, die mortality of 161 men exposed to 1,2-dibromoethane in two factories since the mid-1920s and 1942, respectively, was investigated. By January 1976, 36 workers had diel, seven of them from cancer (5.8 expected) (Ott et al., 1980). In another study, the mortality of 2510 male workers employed at a chemical plant was investigated. 1,2-Dibromoethane was one of the several chemicals used and was apparently a minor component of the mixed exposure. No significant excess of cancer at any site was found (Sweeney et al., 1986).

In the United States, 1,2-dibromoethane has been used as a fumigant in the grain industry since the 1940s. Alavanja et al. (1990) analysed mortality during 1955-85 in 22 938 white men who were enrolled in the life insurance programme of the American Federation of Grain Millers. Among a subset of 9660 who worked in flour mills (where pesticides were used more frequently), 1914 deaths were recorded, giving a standardized mortality ratio (SMR) of 0.9 based an national rates ($p < 0.05$). These included 25 deaths from leukaemia (SMR, 1.4, not significant) and 21 from non-Hodgkin's lymphoma (SMR, 1.5, not significant). In a nested case-control study, having ever been employed in a flour mill was significantly associated with mortality from non-Hodgkin's lymphoma (21 cases; odds ratio, 4.2; 95% confidence interval (CI), 1.2-14.2) and pancreatic cancer (33 cases; odds ratio, 2.2; 95% CI, 1.1-4.3) but not leukaemia (25 cases; odds ratio, 1.8; 95% CI, 0.8-3.9). [IARC noted in its evaluation that the interpretation was difficult in the absence of information about individual exposures to specific fumigants.]

2.7.2. Animal data (according to IARC, 1999)

Oral administration
Groups of 50 male and 50 female $B6C3F_1$ mice, five weeks of age, were administered daily time-weighted average doses of 62 and 107 mg/kg bw technical-grade 1,2-dibromoethane (purity 99.1%) in corn oil by gavage an five days per week for 53 weeks, followed by observation for 24-37 weeks. A group of 20 males and 20 females received corn oil alone and served as vehicle controls, and a further group of 20 males and 20 females served as untreated controls. Squamous-cell carcinomas of the forestomach were observed in both sexes (males: vehicle control, 0/20; low dose, 45/50; high dose, 29/49; females, 0/20, 46/49, 28/50). The incidence of alveolar/bronchiolar adenomas was significantly higher in treated mice of each sex than in vehicle controls (males, 0/20, 4/45, 10/47 ($p = 0.02$); females, 0/20, 11/43 ($p = 0.009$), 6/46) (United States National Cancer Institute, 1978).

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Groups of 30 male and 30 female B6C3F$_1$ mice were administered 4 mmol/l 1,2-dibromoethane (purity > 99%), a dose equivalent to 116 mg/kg bw for males and 103 mg/kg bw for females) in distilled drinking-water for 450 days. A control group of 60 males and 60 females was given distilled drinking-water. 1,2-Dibromoethane induced squamous-cell carcinomas of the forestomach in 26/28 males and 27/29 females and squamous-cell papilloma of the oesophagus in 3/30 females compared with none in 45 male and 50 female controls (Van Duuren et al., 1985).

Groups of 50 male and 50 female Osborne-Mendel rats, five weeks of age, were administered daily time-weighted average doses of 38 or 41 (males) and 37 or 39 (females) mg/kg bw technical-grade 1,2-dibromoethane (purity, 99.1%) in corn oil by gavage an five days per week for 36-57 weeks followed by observation for 2-13 weeks. A group of 20 males and 20 females received corn oil alone and served as vehicle controls. Squamous-cell carcinomas of the forestomach were observed in 45/50 low-dose males, 33/50 high-dose males, 40/50 low-dose females and 29/50 high-dose females, while none was observed in controls. The lesions, seen as early as week 12, were locally invasive and eventually metastasised. A significantly higher incidence of haemangiosarcomas of the spleen was observed in low-dose males (0/20 controls, 10/50 low-dose and 3/49 high-dose) (United States National Cancer Institute, 1978).

Inhalation exposure
Groups of 50 male and 50 female B6C3F$_1$ mice, five weeks of age, were exposed by whole-body inhalation to air containing 0 (control), 10 or 40 ppm 1,2-dibromoethane (purity, 99.3-99.4%) for 78-106 weeks. The incidence of alveolar/ bronchiolar carcinomas and alveolar/bronchiolar adenomas was significantly higher in exposed male and female mice than in controls. The incidence of haemangiosarcomas of the circulatory system, fibrosarcomas in subcutaneous tissue, carcinomas of the nasal cavity and adenocarcinomas of the mammary gland was significantly increased in females (see Appendix) (United States National Toxicology Program, 1982).

Groups of 50 male and 50 female Fischer 344 rats, five weeks of age, were exposed by whole-body inhalation to air containing 0 (control), 10 or 40 ppm 1,2-dibromoethane (purity, 99.3-99.4%) for 88-106 weeks. The incidence of carcinomas, adenocarcinomas and adenomas of the nasal cavity and haemangiosarcomas of the circulatory system was significantly increased in exposed male and female rats. The incidence of mesotheliomas of the tunica vaginalis and adenomatous polyps of the nasal cavity in males and of fibroadenomas of the mammary gland and alveolar/bronchiolar adenomas and carcinomas (combined) in females was also significantly increased (see Appendix) (United States National Toxicology Program, 1982).

Groups of 48 male and 48 female Sprague-Dawley weanling rats were exposed by whole-body inhalation to 0 or 20 ppm 1,2-dibromoethane (purity 99%) for 7 h per day an five days per week for 18 months. Rats inhaling 20 ppm 1,2-dibromoethane vapour had significantly higher mortality than the controls. Among treated rats, 10/48 males and 6/48 females developed haemangiosarcomas of the spieen compared with 0/48 male and 0/48 female controls. Mammary tumours (benign and malignant combined) occurred in 25/48 treated females compared with 2/48 controls. Subcutaneous mesenchymal tumours were found in 11/48 males compared with 3/48 controls (Wong et al., 1982).

Skin application
Mouse: Groups of 30 female Ha:ICR Swiss mice, six to eight weeks of age, received thrice-weekly skin applications of 25 or 50 mg per animal 1,2-dibromoethane (purity, > 99%) in 0.2 mL acetone an the shaved dorsal skin, or applications of acetone alone or served as untreated controls. The times to the first appearance of skin tumour (papilloma) were 434

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days for the 25-mg group and 395 days for the 50-mg group. In comparison with controls, both groups showed a significantly increased incidence of lung papillary adenomas (24/30 low-dose, 26/30 high-dose) and, in the 50-mg group, a significant increase in the incidence of skin papillomas (8/30) (Van Duuren et al., 1979).

2.8. Reproductive toxicity

2.8.1. Human data (IARC, 1999)

A retrospective assessment of the potential antifertility influence of 1,2-dibromoethane was conducted by studying the reproductive performance of men exposed to 1,2-dibromoethane in the workplace. Data were obtained from four chemical plants manufacturing 1,2-dibromoethane located in the Southern part of the United States (Arkansas and Texas). Exposures in the plants ranged from less than 0.5 ppm to 5 ppm. Evaluations were made exclusively an the basis of the men's reproductive histories of live births to their wives, subsequent to their occupational exposure. The number of live births was compared with the expected number derived from national fertility tables. One of the four plants studied showed a significant decrease in fertility; however, when data from the four plants were combined, there was no significant effect of 1,2-dibromoethane exposure an reproductive performance (Wong et al., 1979).

The effect of long-term exposure to 1,2-dibromoethane on semen quality was studied among 46 men employed in the Papaya fumigation industry in Hawaii, United States, with an average duration of exposure of five years and an average exposure to 1,2-dibromoethane of 8 ppb as an 8-h time-weighted average, with peak exposures up to 262 ppb. The comparison group was 43 unexposed men from a sugar refinery. Significant decreases in sperm count, viable and motile sperm and increases in sperm with morphological abnormalities were observed among exposed men. The authors suggested that exposure to 1,2-dibromoethane may increase the risk of reproductive impairment in workers at exposure levels near the recommended limit at that time of 45 ppb (Ratcliffe et al., 1987).

A longitudinal study was conducted in 10 forestry employees and six unexposed men in Colorado, United States, with an exposure time of approximately six weeks. Sperm velocity decreased in all 10 exposed men and in only two unexposed men. Semen volume was also decreased. The time-weighted average exposure of these men was 60 ppb with peak exposures in the order of 2165 ppb. The authors suggested that the exposure may have effected the accessory sex glands and that 1,2-dibromoethane may have multiple sites of action (Schrader et al., 1988).

2.8.2. Animal data (IARC, 1999)

The effect of 1,2-dibromoethane on reproduction was studied in male and female CD rats exposed to 0, 19, 39 or 89 ppm 1,2-dibromoethane for 7 h per day on five days per week for 10 weeks. Morbidity and mortality were observed at the highest concentration. Males in this group had reduced testicular weight, reduced serum testosterone concentration and failed to impregnate any females during a twoweek mating period. Atrophy of the testes, epididymis, prostate and seminal vesicles was also observed. Reproductive performance of males exposed to the lower doses (19 or 39 ppm) was not impaired. Females in the highest-dose group did not cycle normally until several days after termination of exposure. However, the reproductive performance of females in the lower-dose groups was normal (Short et al., 1979).

Male New Zealand white rabbits were given subcutaneous injections of 15, 30 or 45 mg/kg bw 1,2-dibromoethane per day for five days. Semen samples were taken before exposure, during treatment and during 12 weeks after exposure and analysed for serum concentration, number, morphology, viability and motion parameters. Fertility was assessed by artificial insemination. Mortality, hepatotoxicity and alterations in measured semen parameters were observed in the highest-dose group. Fertility and fetal structural development were unaffected. The authors noted that semen parameters (velocity, percentage motility, amplitude of lateral head displacement) were affected only at doses close to the LD_{50} (55 mg/kg) (Williams et al., 1991).

The effect of exposure to 1,2-dibromoethane on oestrus cycling was investigated in female $B6C3F_1$ mice given by gavage 31.25, 62.5 or 125 mg/kg bw on five days per week for 12 weeks. Vaginal smears showed that the oestrous cycle was significantly longer at die highest dose (Ratajczak et al., 1995). The effect of inhaled 1,2-dibromoethane during die gestation period in rats and mice was investigated by exposing pregnant CD rats and CD-1 mice to 20, 38 and 80 ppm 1,2-dibromoethane for 23 h per day over 10 days, beginning an day 6 of gestation. Rats and mice were killed an gestational days 20 and 18, respectively. 1,2-Dibromoethane was more toxic to pregnant mice than pregnant rats. All of the mice exposed to 80 ppm died during the study. A significant increase in adult mortality occurred in rats exposed to 80 ppm and in mice exposed to 38 ppm or 80 ppm 1,2-dibromoethane. 1,2-Dibromoethane produced adverse effects on maternal welfare as measured by weight change, feed consumption and survival in both species at all doses tested. Fetal mortality was increased in rats exposed to 80 ppm and in mice exposed to 38 ppm. Reduced body weights were observed in fetuses from rats exposed to 38 ppm and in mice exposed to 20 or 38 ppm 1,2-dibromoethane. Signs of fetal toxicity occurred at 1,2-dibromoethane concentrations that adversely affected the dam (Short et al., 1978).

The effects of 1,2-dibromoethane exposure in male rats were studied through behavioural assessments of their F_1 progeny. Fischer 344 male rats were treated by subacute intraperitoneal injection of a daily dose of 1.25, 2.5, 5 or 10 mg/kg bw 1,2-dibromoethane on five successive days. Four weeks or nine weeks after the last injection, males were crossed with virgin females. Behavioural assessment of motor reflexes and motor coordination were examined in the offspring up to 21 days of age. Significant differences in the development of motor coordination and motor activity were observed in the F_1 progeny (Fanini et al., 1984). In a review of experimental male-mediated behavioural and neurochemical disorders, Nelson et al. (1996) noted that, although the above study is suggestive of effects in offspring following paternal exposures, only one laboratory has studied these effects.

Rat embryo cultures were used by Brown-Woodman et al. (1998) to assess effects of halogenated hydrocarbons on embryonic development. A no-effect-level for 1,2-dibromoethane was found below 0.18 micromol/ml medium.

Recommendation

1,2-Dibromoethane is clearly carcinogenic based on amimal experiments (IARC 1999). When adiministered by gavage in oil, technical-grade 1,2-dibromoethane induced squameous cell carcinomas in the forestomach of rats of both sexes, hepatocellular carcinomas in females, and haemangiosarcomas in males. By the same route of administration it induced squameous cell carcinomas of the forestomach and alveolar-bronchiolar adenomas in mice of both sexes (U.S. NCI 1978, U.S. NTP 2002). When administered by inhalation, 1,2-dibromoethane induced increased incidences of carcinomas, adenocarcinomas and adenomas of the nasal cavity and haemangiosarcomas of the circulatory system in male and female rats; mesotheliomas of the tunica vaginalis and adenomatous polyps of the nasal cavity in males; and fibroadenomas of the mammary gland and alveolar-bronchiolar adenomas and

carcinomas in females. 1,2-Dibromoethane administered by inhalation induced alveolar-bronchiolar carcinomas and adenomas in mice of both sexes, and haemangiosarcomas, subcutaneous fibrosarcomas, carcinomas of the nasal cavity, and adenocarcinomas of the mammary gland in females (U.S. NTP 1982). The carcinogenic effect in rodents was already very clear at inhalation exposures to 10 ppm 1,2-dibromoethane. Topical application induced tumours of the skin, lung and forestomach in mice (IARC 1999). No adequate epidemiological data are available to evaluate the potential carcinogenicity of the compound in humans. The epidemiological studies that examined occupational exposure to 1,2-dibromoethane were considered inconclusive, due to exposures to mixtures of chemicals and the low statistical power of the studies (IARC 1999).

Thus, 1,2-dibromoethane presents itself as a both a local and systemic experimental carcinogen. Its mode of action is clearly genotoxic. The biological activation pathway is mediated by glutathione-S-transferases, leading to formation of a very reactive episulfonium (thiiranium) ion. As these enzymes is also active in humans, a carcinogenic effect in humans, qualitatively similar to that in rodents, appears likely. Quantitatively, toxicokinetic modellings suggest that humans ought to be less sensitive than rodents, so that conventional risk analyses could overestimate the human cancer risk at occupationally relevant exposure concentrations (Hissink et al., 2000). However, the glutathione-dependent activation pathway remains active even at low concentrations of 1,2-dibromoethane (Ploemen et al., 1997), without indication of a deviation from linearity.

1,2-Dibromoethane is much more active (10-50 times, based on DNA adduct formation; Watanabe et al., 2007) than its chlorinated analogue, 1,2-dichloroethane, although the activation pathway is similar in both cases.

Hence, 1,2-dibromoethane is categorised into the SCOEL carcinogen group A (Bolt and Huici-Montagud, 2008), as a genotoxic carcinogen without a threshold.

The quantitative data on carcinogenicity and the present state of toxicokinetic inter-species modelling do not permit a reasonable and reliable quantitative cancer risk assessment for humans at the present time. It is therefore recommended that occupational contact with 1,2-dibromoethane should be avoided. In this context, it must be noted that experimentally the carcinogenicity is already clear-cut at airborne concentrations of 10 ppm, and that lower concentrations have not been tested (see Appendix).

1,2-Dibromoethane as also a reproductive toxicant, both experimentally (see 4.9.2) and in humans (see 4.9.1). The data of Ratcliffe et al. (1987), which are basically supported by those of Schrader et al. (1988), point to an increase in reproductive impairment in workers already at airborne concentrations around 45 ppb (0.045 ppm).

Based on the available experimental toxicity data (see 2.2.2) a "skin" notation appears justified.

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Appendix

Inhalation carcinogenicity data, as compiled by IARC (1999)

Appendix 1. Incidence of tumours in mice exposed to ethylene dibromide by inhalation exposure

(compilation by IARC, 1999)

Tumour type	Males			Females		
		10	40 ppm	0	10 ppm	40 ppm
Lung, alveolar/bronchiolar Adenoma	0/41	0/48	11/46**	3/49	7/49	13/50*
Carcinoma	0/41	3/48	19/46**	1/49	5/49	37/50**
Circulatory System Haemangiosarcoma				0/50	11/50**	23/50**
Subcutaneous tissue Fibrosarcoma				0/50	5/50*	11/50**
Nasal cavity Carcinoma				0/50	0/50	6/50*
Mammary gland Adenocarcinoma				2/50	14/50**	8/50*

From: United States National Toxicology Program (1982) *p<0.05
**p<0.001

Appendix 2. Incidence of tumours in rats exposed to ethylene dibromide by inhalation exposure (compilation by IARC, 1999)

Tumour type	Mal			Females		
	0	10 ppm	40 ppm	0	10 **ppm**	40 ppm
Nasal cavity Adenoma	0/50	11/50**	0/50	0/50	11/50**	3/50
Carcinoma	0/50	0/50	21/50**	0/50	0/50	25/50**
Adenocarcinoma	0/50	20/50**	28/50**	0/50	20/50**	29/50**
Circulatory System Haemangiosarcoma	0/50	1/50	15/50**	0/50	0/50	5/50*
Tunica vaginalis Mesothelioma	0/50	7/50**	25/50**			
Mammary gland Fibroadenoma				4/50	29/50**	24/50**
Lung alveolar/bronchiolar Adenoma and carcinoma				0/50	0/48	5/47*

From; United States National Toxicology Program (1982) * p < 0.05
**p<0.001

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