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1,2-Dibromoethane in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

Acknowledgements

1,2-Dibromoethane in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document published in the Addendum to the second edition of the Guidelines.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
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The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
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Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
LD_{50}	median lethal dose
LOEC	lowest-observed-effect concentration
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	106-93-4
Molecular formula:	$C_2H_4Br_2$

1,2-Dibromoethane is also known as ethylene dibromide and 1,2-ethylene dibromide.

1.2 Physicochemical properties (IPCS, 1996)[1]

Property	*Value*
Physical state	Colourless liquid
Melting point	9.9 °C
Boiling point	131.4 °C
Vapour pressure	1.47 kPa at 25 °C
Water solubility	4.3 g/litre at 30 °C

1.3 Organoleptic properties

1,2-Dibromoethane has a chloroform-like odour. No data on taste or odour thresholds have been identified.

1.4 Major uses

1,2-Dibromoethane is used as a lead scavenger in tetra-alkyl lead petrol and antiknock preparations and as a fumigant for soils, grains and fruits. However, with the phase-out of leaded petrol and the cancellation of the use of 1,2-dibromoethane in agricultural applications in many countries, use of this substance for these purposes has declined significantly. In addition to its continued use as a petrol additive in some countries, 1,2-dibromoethane is currently used principally as a solvent and as an intermediate in the chemical industry.

1.5 Environmental fate

Because of its volatility, 1,2-dibromoethane's principal environmental sink is the atmosphere. The half-life for volatilization from surface waters is about 1–5 days under typical conditions (Mackay et al., 1982). 1,2-Dibromoethane is moderately mobile in soil, with the rate of penetration being greatest in sandy soils with low organic content (Townshend et al., 1980), although a small fraction may persist in the top layers for several years. For example, application of 1,2-dibromoethane into fine sandy loam at a "standard" rate of 70 kg/ha resulted in a concentration nearly 1 year later of 130 µg/kg; in another case, levels of up to 200 µg/kg were measured in soil 19 years after the last known application (rate unknown) (Steinberg et al., 1987). Diffusion of residues from soil to water is slow, with a diffusion coefficient of 10^{-16} cm^2/s (Pignatello et al., 1987). 1,2-Dibromoethane is biodegraded within days in

[1] Conversion factor in air: 1 mg/m^3 = 0.13 ppm.

surface soils, whereas it may persist for months in aquifer materials (Pignatello & Cohen, 1990). It is not expected to bioconcentrate or biomagnify in terrestrial or aquatic food-chains (ATSDR, 1992).

2. ANALYTICAL METHODS

1,2-Dibromoethane is usually recovered from water samples by purge-and-trap methods, direct absorption and thermal desorption, solvent extraction or headspace collection, followed by analysis by gas chromatography (often in combination with mass spectrometry) with electron capture detection or flame or chemical ionization detection. Reported levels of detection for 1,2-dibromoethane in water range from 0.001 to 300 µg/litre (Keough et al., 1984; Koida et al., 1986; Stottmeister et al., 1986; Woodrow et al., 1986).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Mean levels of 1,2-dibromoethane in ambient air in 12 cities across Canada surveyed between 1989 and 1992 ranged from non-detectable (i.e., <0.1 µg/m^3) to 0.13 µg/m^3; 1,2-dibromoethane was detected in 144 of 4298 samples analysed (Environment Canada, 1994). Concentrations ranging from 0.008 to 0.515 µg/m^3 were measured in 71 samples from five urban and five mountainous locations in Japan in 1983 (Environment Agency Japan, 1985). In seven sites in the USA, average levels ranged from 0.122 to 0.450 µg/m^3 (Singh et al., 1982). Mean ambient concentrations in and around London, England, in 1982 and 1983 ranged from 0.15 to 1.2 µg/m^3 (Clark et al., 1984a,b). In the vicinity of waste and landfill sites in the USA, mean concentrations of 1,2-dibromoethane ranged from <0.038 to 5.4 µg/m^3 (Harkov et al., 1983, 1984).

3.2 Water

Few data on levels of 1,2-dibromoethane in drinking-water supplies have been identified. Based on a review of available surveys, Pignatello & Cohen (1990) reported that "typical" concentrations of 1,2-dibromoethane in samples from the wells in which it was detected (detected in 1959 of 15 450 wells surveyed) ranged from 0.01 to 15 µg/litre in the USA, from 1 to 2 µg/litre in Israel and from 0.03 to 0.2 µg/litre in Australia. A maximum concentration of 94 µg/litre was measured in 15 samples from three irrigation wells surveyed between 1981 and 1983 in an area of Georgia, USA, in which 1,2-dibromoethane had been used extensively as a fumigant (Martl et al., 1984). 1,2-Dibromoethane was detected (detection limit not specified) in 34 of 421 samples of groundwater and in 11 of 175 samples of surface water from New Jersey, USA, during 1977–1979; the highest concentrations were 48.8 and 0.2 µg/litre in groundwater and surface water, respectively (Page, 1981). Concentrations of 0.06–0.55 µg/litre were detected between 1983 and 1984 in samples of groundwater from nine sites in an area of Japan where 1,2-dibromoethane had been applied to the soil (Terao et al., 1985). 1,2-Dibromoethane was not detected (detection

limit 0.3–2 µg/litre) in 27 samples of surface water collected in Japan in 1982 (Environment Agency Japan, 1985).

3.3 Food

Few recent data on levels of 1,2-dibromoethane in foodstuffs have been identified. Daft (1989) detected (detection limit 1 ng/g) 1,2-dibromoethane in 2 of 549 samples of 234 foodstuffs collected in market basket surveys in the USA in the mid-1980s; 1,2-dibromoethane was detected in 1 sample each of whiskey and peanut butter at concentrations of 2 and 11 ng/g, respectively. Suzuki et al. (1989) measured concentrations of <0.02–0.51, 16.6–61.6 and 22.6–179 µg/kg in respective samples of mango (n = 9), papaya (n = 10) and grapefruit pulp (n = 30) imported into Japan in 1989. 1,2-Dibromoethane has been detected at levels of 0.33–0.47 mg/kg in bread made from wheat or flour that had been fumigated with the substance (FAO/WHO, 1972). Although 1,2-dibromoethane was detected at concentrations up to 0.4 mg/kg in flour, bran and middlings of wheat that had been fumigated with a formulation containing the substance in Canada, no residues were detected (detection limit not specified) in 24 loaves of bread made from the exposed wheat (Berck, 1974).

3.4 Estimated total exposure and relative contribution of drinking-water

Based on a daily inhalation volume for adults of 20 m^3, a mean body weight of 60 kg, the assumption that concentrations of 1,2-dibromoethane are similar indoors and outdoors (as no data were identified on levels in indoor air) and the range of mean concentrations in ambient air determined in Canada (the most recent survey available is considered most appropriate, as use of this substance has declined significantly) of <0.1–0.13 µg/m^3, the mean intake of 1,2-dibromoethane from air is estimated to range from <0.03 to 0.04 µg/kg of body weight per day. Although monitoring data are limited, intake of 1,2-dibromoethane in drinking-water is estimated to range from <0.0003 to 0.5 µg/kg of body weight per day, based on the daily consumption of 2 litres of drinking-water, a mean body weight of 60 kg and the range of "typical" concentrations reported in drinking-water supplies in the USA, Israel, Australia and Japan of <0.01–15 µg/litre. It should be noted, however, that these estimates for drinking-water are largely based on data collected before the use of 1,2-dibromoethane in agricultural practices was discontinued in many countries. Although 1,2-dibromoethane was not detected in >99% of samples of prepared foodstuffs in the USA in the mid-1980s, which would suggest that intake in food is negligible, food may be a significant source of exposure in areas where the substance is still being used as a grain fumigant; however, the lack of adequate monitoring data for such areas precludes quantitative estimation.

Available data are inadequate to allow a quantitative estimation of the relative contribution of various environmental media to total exposure to 1,2-dibromoethane; however, air likely represents a principal source for the general population, with drinking-water being a major source in areas with significant groundwater contamination and food being a major source where the substance is still used as a grain fumigant.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The concentration of 1,2-dibromoethane in the blood of guinea-pigs dermally exposed to the undiluted substance for 6 h increased rapidly within the first hour and then slowly declined (Jakobson et al., 1982). Ingested 1,2-dibromoethane is rapidly and completely absorbed by the gastrointestinal tract, based on the recovery within 24 h of radioactivity in the excreta and tissues of rats administered 15 mg of the ^{14}C-labelled compound per kg of body weight. The majority (72%) of the radioactivity was recovered in the urine, whereas, of the tissues examined, the liver contained the greatest amount of the label (1.8%) (Plotnick et al., 1979).

1,2-Dibromoethane can be metabolized by an oxidative pathway (cytochrome P-450 system) and a conjugation pathway (glutathione *S*-transferase system) (ATSDR, 1992). In the first pathway, 1,2-dibromoethane is oxidized via mixed-function oxidases to 2-bromoacetaldehyde, which may subsequently be converted directly by aldehyde dehydrogenase to 2-bromoethanol or 2-bromoacetic acid. In addition, 2-bromoacetaldehyde may be conjugated with glutathione, ultimately resulting in the formation of thioglycolic acid and mercapturic acids (the primary urinary metabolites). In the second pathway, 1,2-dibromoethane may be conjugated with glutathione via glutathione *S*-transferase to form *S*-(2-bromoethyl)glutathione. This highly reactive intermediate may be detoxified by further conjugation to form ethylene, which is exhaled, and glutathione disulfide, which is eliminated in the faeces, or it may bind to DNA through direct nucleophilic substitution or through the ethylene-*S*-glutathionyl-episulfonium ion.

The reactive metabolite bromoacetaldehyde, formed via the oxidation pathway, is believed to be responsible for non-genotoxic tissue damage (via covalent binding to proteins) (van Duuren et al., 1985), whereas *S*-(2-bromoethyl)glutathione, formed via the conjugation pathway, has been associated with genotoxicity and perhaps carcinogenicity (via interaction with DNA) in experimental systems (van Bladeren, 1983). Simula et al. (1993) demonstrated that human glutathione was capable of converting 1,2-dibromoethane to reactive metabolites, based on an increased mutagenicity in *Salmonella typhimurium* expressing human glutathione A1-1. Ploemen et al. (1995) reported genetic polymorphism in the ability of human erythrocytes to conjugate 1,2-dibromoethane via the class theta glutathione-*S*-transferases.

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Ingested 1,2-dibromoethane is moderately acutely toxic in experimental animals. Reported oral LD_{50}s for rats, mice, guinea-pigs, rabbits and chickens range from 55 to 420 mg/kg of body weight; rabbits appear to be the most sensitive species, whereas mice are the least sensitive (Rowe et al., 1952; McCollister et al., 1956). The dermal LD_{50} in rabbits is 450 mg/kg of body weight; dermal and eye contact with 1% 1,2-dibromoethane in solution also causes irritation in animals (Rowe et al., 1952).

5.2 Short-term exposure

Information on the short-term toxicity of ingested 1,2-dibromoethane is limited. In short-term studies preliminary to longer-term carcinogenicity bioassays, groups of five male or female Osborne-Mendel rats or $B6C3F_1$ mice were administered 1,2-dibromoethane in corn oil by gavage at doses of 0, 40, 63, 100, 163 or 251 mg/kg of body weight per day, 5 days per week, for 6 weeks, followed by a 2-week observation period (NCI, 1978). In rats, there were mortalities at 100 mg/kg of body weight per day, and decreased body weight gain was observed at 100 mg/kg of body weight per day and above; in mice, deaths were observed at 100 and 251 mg/kg of body weight per day, and body weight gain was depressed at the highest dose. No other end-points appear to have been examined.

5.3 Long-term exposure and carcinogenicity

In a long-term bioassay (NCI, 1978), groups of 50 male or female Osborne-Mendel rats (n = 20 in controls) were administered technical-grade 1,2-dibromoethane in corn oil by gavage at time-weighted average doses of 0, 38 or 41 mg/kg of body weight per day (males) or 0, 37 or 39 mg/kg of body weight per day (females), 5 days per week.[2] Surviving male and female rats were sacrificed after 49 and 61 weeks, respectively. Body weight depression was apparent in the exposed rats after the first 10 weeks. Hyperkeratosis and acanthosis of the forestomach were observed in 12/50 males and 18/50 females administered the high dose, in 4/50 females at the low dose and in 1/20 female controls. Other non-neoplastic lesions observed to occur with increased frequency in exposed rats included degenerative changes in the liver in males and in the adrenal gland in both sexes. Testicular atrophy was noted in 14/49 and 18/50 rats administered the low and high doses, respectively, but not in controls. Although early mortality was high in exposed rats, there were significant increases in the incidence of squamous cell carcinomas of the forestomach in both sexes; these were observed as early as week 12 of exposure and were locally invasive and eventually metastasized. The incidence of hepatocellular carcinomas or neoplastic nodules was significantly increased in females at the higher dose compared with controls. There were also

[2] Rats in the high-dose groups were initially administered 80 mg/kg of body weight per day; however, owing to high mortality after 16 weeks (18 males and 20 females), exposure was suspended for 13 weeks and commenced again at 40 mg/kg of body weight per day.

increases in the incidence of haemangiosarcomas; the increase was significant at the lower dose in males. When early mortality was considered, the incidence of adenomas or carcinomas of the adrenal cortex was significantly elevated in females administered the high dose.

The NCI (1978) also conducted a similar study in which groups of 50 $B6C3F_1$ mice of either sex (n = 20 in controls) were administered time-weighted average 1,2-dibromoethane doses of 62 or 107 mg/kg of body weight per day in corn oil by gavage, 5 days per week, for 53 weeks.[3] Surviving animals were sacrificed after 78 weeks, except for females in the lower dose group, which were killed after 90 weeks. In both sexes, there were significant dose-related decreases in body weight gain and survival in exposed mice and significant increases in the incidence of acanthosis and hyperkeratosis of the forestomach at the higher dose. Testicular atrophy was noted in 10/47 males administered 107 mg/kg of body weight per day, compared with none in controls or the low-dose group. The incidence of squamous cell carcinomas of the forestomach was significantly increased in exposed mice of both sexes; as in rats, metastasis to distant sites was reported. Squamous cell papillomas were also observed in 2/49 males in the high-dose group and in 1/49 females in the low-dose group. There was also a significant increase in the incidence of alveolar/bronchiolar adenomas in both sexes; an alveolar/bronchiolar carcinoma was observed in one female mouse administered 62 mg/kg of body weight per day.

Based on the results of these studies, the NCI (1978) concluded that 1,2-dibromoethane administered by gavage was carcinogenic to male and female Osborne-Mendel rats and $B6C3F_1$ mice.

Van Duuren et al. (1985) exposed groups of 30 male or female $B6C3F_1$ mice (n = 45 [males] or 50 [females] in controls) to 1,2-dibromoethane at a concentration of 4 mmol/litre in drinking-water (equivalent to a dose of 116 mg/kg of body weight per day for males and 103 mg/kg of body weight per day for females) for up to 456 (males) and 512 (females) days. Tissues from the lung, liver, kidneys, forestomach, and glandular stomach and any tissues appearing abnormal were examined histopathologically. Body weight was 10–20% depressed in exposed animals compared with controls (no other non-neoplastic effects were described). There were exposure-related increases in the incidences of squamous cell carcinomas or papillomas of the forestomach. Papillomas of the oesophagus were observed in 3/29 female mice, whereas none was observed in controls or exposed males. Groups of mice were also exposed to the metabolites bromoethanol or bromoacetaldehyde at a concentration of 4 mmol/litre (equivalent to doses of 76 [males] or 71 [females] mg/kg of body weight per day and 62 [males] and 85 [females] mg/kg of body weight per day, respectively). Exposure to bromoethanol induced a significant increase in the incidence of papillomas of the forestomach, whereas consumption of bromoacetaldehyde was not associated with a significant increase in tumour incidence at any site.

[3] The actual doses administered ranged from 60 to 100 mg/kg of body weight per day and from 60 to 200 mg/kg of body weight per day for the low- and high-dose groups, respectively.

In an additional study in $B6C3F_1$ mice in which 1,2-dibromoethane was administered in drinking-water at a concentration of 2 mmol/litre (equivalent to a dose of 50 mg/kg of body weight per day) as a positive control for 18 months, there were significant increases in the incidences of squamous carcinomas of the forestomach in females and males, papillomas of the forestomach in females, papillomas of the oesophagus in males and squamous carcinomas of the oesophagus in males (van Duuren et al., 1986).

Repeated dermal exposure of male and female Ha:ICR Swiss mice to 25 or 50 mg of 1,2-dibromoethane in acetone for up to 594 days induced a significant increase in the incidence of skin and pulmonary tumours (van Duuren et al., 1979).

Exposure to 1,2-dibromoethane via inhalation has also been carcinogenic in experimental animals. $B6C3F_1$ mice exposed to concentrations of 77 mg/m^3 and above for up to 2 years had increased incidences of several tumour types, including alveolar/bronchiolar carcinomas and adenomas, haemangiosarcomas, fibrosarcomas of the subcutaneous tissue, carcinomas of the nasal cavity and adenocarcinomas of the mammary gland (NTP, 1982). Similarly, exposure to 1,2-dibromoethane at 77 mg/m^3 and above for up to 2 years induced carcinomas, adenocarcinomas, adenomas and adenomatous polyps of the nasal cavity, haemangiosarcomas, mesotheliomas of the tunica vaginalis, fibroadenomas of the mammary gland and alveolar/bronchiolar adenomas and carcinomas (combined) in groups of F-344 rats (NTP, 1982). Adkins et al. (1986) also reported an increase in pulmonary adenomas in female A/J mice exposed to 1,2-dibromoethane at 154 or 384 mg/m^3 for 6 months. 1,2-Dibromoethane did not demonstrate an ability to initiate tumour promotion in a dermal initiation/promotion assay in mice (van Duuren et al., 1979), although positive results were reported for initiation of liver foci in rats (Moslen, 1984).

5.4 Reproductive and developmental toxicity

Testicular atrophy was observed in Osborne-Mendel rats administered time-weighted average doses of 38 mg/kg of body weight per day or more for up to 48 weeks and in $B6C3F_1$ mice administered a time-weighted average dose of 107 mg/kg of body weight per day for up to 78 weeks in the long-term bioassays conducted by the NCI (1978) (discussed above in section 5.3). Effects on sperm density and motility and abnormal spermatozoa were observed in bulls orally administered 1,2-dibromoethane doses of 2 or 4 mg/kg of body weight per day for 12 months or 2 weeks, respectively (Amir & Volcani, 1965). In addition, Short et al. (1979) reported reduced testicular weights, reduced serum testosterone concentrations, inability to impregnate females and atrophy of the testes, epididymis, prostate and seminal vesicles in groups of 9 or 10 male Sprague-Dawley CD rats exposed to 1,2-dibromoethane at 684 mg/m^3 for 10 weeks, although increased mortality and decreased body weight gain were also noted; no effects were reported at 146 or 300 mg/m^3. However, there were no effects on reproductive parameters in groups of 10 male albino rats administered 1,2-dibromoethane at concentrations of 100 or 500 mg/kg of diet (equivalent to 10 and 50 mg/kg of body weight per day) for 90 days and mated with unexposed females.

Histological examination of the testes revealed no exposure-related changes, and the mean number of litters per group, mean pup weight at birth and sex ratio of pups were similar to controls (Shivanandappa et al., 1987).

Short et al. (1979) also reported reversible abnormalities in the estrous cycle in groups of 20 female rats exposed to 614 mg/m^3 but not 154 or 300 mg/m^3; decreased body weight gain and increased mortality were also observed at 614 mg/m^3. No differences in the numbers of total implants, viable implants or resorptions per dam were observed at any concentration. Morphological changes and abnormalities, including haematomas, exencephaly and skeletal variations, were observed in fetuses of female Sprague-Dawley rats and CD-1 mice exposed to 1,2-dibromoethane via inhalation at concentrations that were also toxic to the dams (LOECs of 292 and 154 mg/m^3, respectively) (Short et al., 1978).

5.5 Mutagenicity and related end-points

The genotoxicity of 1,2-dibromoethane has been extensively investigated in both *in vitro* and *in vivo* assays. In *in vitro* tests in prokaryotic organisms, 1,2-dibromoethane was generally genotoxic, both with and without exogenous metabolic activation (e.g., Principe et al., 1981; Zoetemelk et al., 1987), although negative results were obtained in some assays (e.g., Buselmaier et al., 1972; Shiau et al., 1980). In cultured mammalian cells, 1,2-dibromoethane caused forward mutations (e.g., Clive et al., 1979; Brimer et al., 1982), sister chromatid exchanges (Tezuka et al., 1980; Tucker et al., 1984), unscheduled DNA synthesis (Tennant et al., 1986; Working et al., 1986) and cell transformation (Perocco et al., 1991; Colacci et al., 1995). In *in vivo* assays, 1,2-dibromoethane induced recessive lethal mutations (e.g., Vogel & Chandler, 1974; Kale & Kale, 1995), gene mutations (Graf et al., 1984) and mitotic recombination (Graf et al., 1984) in *Drosophila melanogaster*. DNA damage was observed in the liver of mice and rats exposed orally or by intraperitoneal injection (e.g., Nachtomi & Sarma, 1977; Storer & Conolly, 1983). However, the substance did not induce dominant lethal mutations (e.g., Short et al., 1979; Barnett et al., 1992) or specific locus mutations (Russell, 1986; Barnett et al., 1992) in the germ cells of rodents. Similarly, negative results were obtained for sister chromatid exchange (Krishna et al., 1985), chromosomal aberrations (Krishna et al., 1985), unscheduled DNA synthesis (Bentley & Working, 1988) and micronucleus induction (Krishna et al., 1985; Asita et al., 1992) in mice or rats.

Although the oxidative pathway of metabolism of 1,2-dibromoethane can generate metabolites capable of damaging DNA (i.e., bromoacetaldehyde and 2-bromoethanol), glutathione conjugation likely also contributes to the genotoxicity of this substance. DNA adduct formation has also been observed following administration of 1,2-dibromoethane, mostly (>95%) due to the glutathione conjugate (Sundheimer et al., 1982; Ozawa & Guengerich, 1983; Inskeep & Guengerich, 1984). Depletion of cellular glutathione inhibited unscheduled DNA synthesis in rat hepatocytes exposed to 1,2-dibromoethane, whereas inhibition of cytochrome P-450 mediated oxidation had no effect (Working et al., 1986).

5.6 Immunotoxicity

Administration of oral doses of up to 200 mg/kg of body weight per day for 14 days to groups of 8–20 female $B6C3F_1$ mice resulted in a number of changes in immune parameters, including numerical alterations and effects on *in vitro* function of various cell types, at doses that also induced changes in organ weights. However, no effects were observed in *in vivo* host resistance to infectious agents (Ratajczak et al., 1994).

6. EFFECTS ON HUMANS

Little information on the toxicity of ingested 1,2-dibromoethane in humans was identified. It was estimated that 200 mg/kg of body weight is lethal to humans, based on the death of a 60-kg woman who had ingested 12 g (Alexeeff et al., 1990).

There were no significant increases in mortality due to neoplastic or non-neoplastic causes in two studies of populations exposed to 1,2-dibromoethane in the workplace (Turner & Barry, 1979; Ott et al., 1980), although these studies were limited by the small size of the study populations, lack of accounting for possible confounding factors (such as smoking or exposure to other substances) and inadequate data on exposure.

No differences in the frequency of sister chromatid exchanges or chromosomal aberrations were observed in 60 workers at six papaya packing plants exposed to a mean 1,2-dibromoethane concentration of 0.68 mg/m^3 (with peak levels of up to 2.0 mg/m^3) for an average of 5 years compared with a group of 40 controls, even when only workers with long-term exposure (>5 years) or those with the highest peak exposure were considered (Steenland et al., 1986).

Adverse effects on reproductive ability, including reduced sperm counts, viability and motility and an increase in sperm abnormalities, were also observed in a cross-sectional study of 46 papaya fumigators exposed to a time-weighted average 1,2-dibromoethane concentration of 0.68 mg/m^3 for an average of 5 years, compared with a control group of 43 unexposed men, taking into account smoking and both caffeine and alcohol consumption (Ratcliffe et al., 1987; Schrader et al., 1987). Similar effects, along with reduced fertility, were also observed in other limited investigations of occupationally exposed men (Ter Haar, 1980; Takahashi et al., 1981; Wong et al., 1985; Schrader et al., 1988). However, limitations of these studies, including lack of appropriate controls, small group sizes and lack of controlling for potentially confounding factors, preclude determination of an effect level.

7. PROVISIONAL GUIDELINE VALUE

1,2-Dibromoethane has induced an increased incidence of tumours at several sites in all carcinogenicity bioassays identified in which rats or mice were exposed to the compound by gavage (NCI, 1978), ingestion in drinking-water (van Duuren et al., 1985, 1986), dermal application (van Duuren et al., 1979) and inhalation (NTP, 1982; Adkins et al., 1986), although many of these studies were limited by high early

mortality, limited histopathological examination, small group sizes or use of only one exposure level. The substance acted as an initiator of liver foci in an initiation/promotion assay (Moslen, 1984) but did not initiate skin tumour development (van Duuren et al., 1979). 1,2-Dibromoethane was consistently genotoxic in *in vitro* assays, although results in *in vivo* assays were mixed. Biotransformation to active metabolites, which have been demonstrated to bind to DNA, is likely involved in the induction of tumours. Available data do not support the existence of a non-genotoxic mechanism of tumour induction. Therefore, based on the available data, it is concluded that there is sufficient evidence that 1,2-dibromoethane is a genotoxic carcinogen in rodents. As data on the potential carcinogenicity in humans are inadequate, and as it is likely that 1,2-dibromoethane is metabolized similarly in rodent species and in humans (although there may be varying potential for the production of active metabolites in humans, owing to genetic polymorphism), 1,2-dibromoethane is considered to be probably carcinogenic in humans, based on the results of studies in experimental species (IPCS, 1995, 1996). Similarly, IARC (1987) classified 1,2-dibromoethane in Group 2A (probably carcinogenic to humans).

Although most of the available bioassays for 1,2-dibromoethane are limited, particularly those in which the compound was administered by ingestion, these studies can nevertheless be used to calculate approximate estimates of the carcinogenic potency of 1,2-dibromoethane. In view of the serious limitations of the studies, however, these estimates must be considered imprecise and, therefore, provisional.

Lifetime low-dose cancer risks can be calculated by linearized multistage modelling of the incidences of haemangiosarcomas and tumours in the stomach, liver, lung and adrenal cortex (adjusted for the observed high early mortality, where appropriate, and corrected for the expected rate of increase in tumour formation in rodents in a standard bioassay of 104 weeks) of rats and/or mice administered 1,2-dibromoethane by gavage. The drinking-water concentrations that correspond to upper-bound excess lifetime cancer risks (for various tumour types) of 10^{-4}, 10^{-5} and 10^{-6} are 4–150 µg/litre, 0.4–15 µg/litre and 0.04–1.5 µg/litre, respectively.[4]

Because of the serious limitations of the critical studies, these concentrations are considered to be approximate estimates only, and hence the guideline value derived from them should be considered provisional. The provisional drinking-water guideline for 1,2-dibromoethane is 0.4 µg/litre, which corresponds to the lower end of the range (and thus is a more conservative estimate) of concentrations associated with an upper-bound excess lifetime cancer risk (for various tumour types) of 10^{-5}.

[4] Although the study in which animals were exposed to 1,2-dibromoethane in drinking-water was considered to be too limited to use as the basis for derivation of a guideline value (owing to high mortality at the only exposure level), drinking-water concentrations corresponding to risks of 10^{-4}, 10^{-5} and 10^{-6}, derived based on the results of this study, would be similar to the range presented here. Likewise, values derived on the basis of the exposure–response relationship observed for non-respiratory tract tumours in the study in which animals were exposed via inhalation are similar.

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