VINYL BROMIDE

This substance was considered by previous Working Groups in February 1978 (IARC, 1979), June 1985 (IARC, 1986), March 1987 (IARC, 1987) and February 1998 (IARC, 1999). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

From IARC (1999) and IPCS-CEC (2002)
Chem. Abstr. Services Reg. No.: 593-60-2
Chem. Abstr. Name: Bromoethene
IUPAC Systematic Name: Bromoethylene
RTECS No.: KU8400000
UN TDG No.: 1085
EC Index No.: 602-024-00-2
EINECS No.: 209-800-6

1.1.2 *Structural and molecular formulae and relative molecular mass*

$$H_2C{=}CHBr$$

C_2H_3Br Relative molecular mass: 106.96

1.1.3 *Chemical and physical properties of the pure substance*

From IPCS-CEC (2002) and Lide (2005), unless otherwise specified

(a) Description: Colourless gas with a characteristic pungent odour; colourless liquid under pressure

(b) Boiling-point: 15.8 °C

(c) *Melting-point:* –139.5 °C
(d) *Density*: 1.522 at 20 °C
(e) *Solubility*: Insoluble in water; soluble in ethanol, ether, acetone, benzene and chloroform
(f) *Vapour pressure*: 119 kPa at 20 °C
(g) *Explosive limits*: Upper, 15%; lower, 9% by volume (National Library of Medicine, 1998)
(h) *Relative vapor density (air = 1)*: 3.7
(i) *Relative density (water = 1)*: 1.49
(j) *Flash-point*: Flammable gas
(k) *Auto-ignition temperature*: 530 °C
(l) *Octanol/water partition coefficient*: log P_{ow}, 1.57
(m) *Conversion factor*: $mg/m^3 = 4.37 \times ppm$[1]

1.1.4 *Technical impurities*

According to Ethyl Corporation (1980), hydroquinone methyl ether is used as an inhibitor (175–225 mg/kg) in vinyl bromide. Water (max. 100 mg/kg) and non-volatile matter (max. 500 mg/kg including the inhibitor) represent the major impurities.

1.1.5 *Analysis*

The Occupational Safety and Health Administration (1979) in the USA has developed a method (OSHA Method 8) to measure vinyl bromide with a detection limit of 0.2 ppm.

1.2 Production and use

1.2.1 *Production*

Vinyl bromide can be produced by the catalytic addition of hydrogen bromide to acetylene in the presence of mercury and copper halide catalysts or by partial dehydrobromination of ethylene dibromide with alcoholic potassium hydroxide (Ramey & Lini, 1971).

The Hazardous Substance Database indicated only one manufacturer of vinyl bromide in the USA in 2002 (National Toxicology Program, 2005). One plant in China reported a production capacity of 500 million tonnes per year in 2006 (Loyal Gain, 2006).

[1] Calculated from mg/m^3 = (molecular weight/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

1.2.2 *Use*

According to a notice in the Federal Register (Anon., 2002), vinyl bromide has been used predominantly in polymers in the production of fabrics and fabric blends that are used in nightwear (mostly for children) and home furnishings, in leather and fabricated metal products and in the production of pharmaceuticals and fumigants. Current applications of vinyl bromide include its use as an intermediate in the synthesis of pharmaceutical products, as a component of fire extinguishers in blends with compounds that contain fluorine, as a monomer in the formation of copolymers that possess flame-retardant properties and as a starting material for the preparation of vinylmagnesium bromide, which is a component of variety of other polymers (Far Research, 2000). According to the Chinese manufacturer Loyal Gain (2006), vinyl bromide is also used in the pharmaceutical industry in the production of the coenzyme Q_{10} and in the synthesis of organic bromo compounds.

1.3 Occurrence

1.3.1 *Natural occurrence*

Vinyl bromide is not known to occur naturally in the environment.

1.3.2 *Occupational exposure*

Vinyl bromide has been available commercially since 1968. Occupational exposure may occur during the production of vinyl bromide and its polymers. According to the 1981–83 National Occupational Exposure Survey (NOES, 2002), approximately 1822 workers in the USA were potentially exposed to vinyl bromide (see General Remarks). Exposure to vinyl bromide was considered by CAREX but did not yield many exposed individuals (Kauppinen *et al.*, 2000). Other estimates of the number of workers exposed to vinyl bromide in Europe are available only from the Finnish Register of Occupational Exposure to Carcinogens which reported one individual who was notified as having been exposed to vinyl bromide in 2004 (Saalo *et al.*, 2006).

Median 8-h time-weighted average exposures at a vinyl bromide manufacturing plant ranged from 0.4 to 27.5 mg/m^3, depending on the job and area surveyed. Personal air samples showed that a plant operator was exposed to 0.4–1.7 mg/m^3, a laboratory technician to 1.3–2.2 mg/m^3 and two loading crewmen to 5.2 and 27.5 (1-h samples) mg/m^3 (Bales, 1978; Oser, 1980).

1.3.3 *Environmental occurrence*

Vinyl bromide may form in the air as a degradation product of 1,2-dibromoethane (IARC, 1999). It may also be released into the environment from facilities that manu-

facture or use vinyl bromide as a flame retardant for acrylic fibres. Vinyl bromide has been qualitatively identified in ambient air samples (National Library of Medicine, 1998).

1.4 Regulations and guidelines

No international guidelines for vinyl bromide in drinking-water have been established (WHO, 2006). Many countries, regions or organizations have established guideline values for vinyl bromide in the workplace (Table 1).

Table 1. Guidelines for levels of vinyl bromide in the workplace

Country/region or Organization	TWA	STEL	Carcinogenicity[a]	Notes
Australia	5		2	
Belgium	5			
Canada				
Alberta	0.5			Schedule 2
British Columbia	5		2[a]	ALARA substance
Ontario	0.5			
Quebec	5		A2	
Finland	1			
Ireland	0.5		Ca2	
Malaysia	0.5			
Netherlands	5			
New Zealand	5		A2	
Norway	1		Ca	
South Africa (DOL-RL)	5			
Spain	0.5		Ca2	
USA				
NIOSH (REL)			Ca	LFC
ACGIH	0.5		A2	

From ACGIH® Worldwide (2005)

ACGIH, American Conference of Governmental Industrial Hygienists; ALARA, as low as reasonably achievable; DOL-RL, Department of Labour - recommended limit; LFC, lowest feasible concentration; NIOSH, National Institute of Occupational Safety and Health; REL, recommended exposure limit; STEL, short-term exposure limit; TWA, time-weighted average

[a] 2, probable human carcinogen; 2[a], considered to be carcinogenic to humans; A2, suspected human carcinogen; Ca2, suspected human carcinogen; Ca, potential cancer-causing agent

The United Nations Committee on Transport of Dangerous Goods had classified vinyl bromide as Hazard class 2.1. (IPCS-CEC, 2002; UNTDG, 2005).

The classification expert group of the European Union (REACH) classified vinyl bromide as F+ (extremely flammable), T (toxic), with R (risk) phrases of 45 (causes

cancer) and 12 (extremely flammable) and S (safety) phrases of 53 (avoid exposure) and 45 (show label where possible; if you feel unwell, seek medical advice) (IPCS-CEC, 2002; ECB, 2004).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

Rat

Groups of 120 male and 120 female Sprague-Dawley rats, approximately 9–10 weeks of age, were exposed by inhalation to approximately 44, 220, 1100 or 5500 mg/m^3 ± 5% [10, 50, 250 or 1250 ppm ± 5%] vinyl bromide (purity ≥ 99.9%) for 6 h per day on 5 days per week for 104 weeks. A group of 144 males and 144 females served as untreated controls. The animals in the highest-dose group were killed at 72 weeks because of 50–60% mortality. Statistical significance was assessed by the χ^2 test. Tumour incidences in rats exposed to vinyl bromide are summarized in Table 2. Treatment-related increases in the incidence of liver angiosarcomas were observed in all exposed groups: males — 0/144 controls, 7/120 at 10 ppm ($p < 0.025$), 36/120 at 50 ppm ($p < 0.001$), 61/120 at 250 ppm ($p < 0.001$) and 43/120 at 1250 ppm ($p < 0.001$); females — 1/144, 10/120, 50/120, 61/120 and 41/120, respectively ($p < 0.01$ for all exposed groups). An increased incidence of Zymbal gland squamous-cell carcinomas also occurred in both sexes of exposed rats: males — 2/142 controls, 1/99 at 10 ppm, 1/112 at 50 ppm, 13/114 at 250 ppm ($p < 0.005$) and 35/116 at 1250 ppm ($p < 0.005$); females — 0/139, 0/99, 3/113, 2/119 and 11/114 ($p < 0.001$), respectively. Hepatic neoplastic nodules [hepatocellular adenomas] and hepatocellular carcinomas were also observed, the incidence of which was significantly increased in some but not all treatment groups. The incidence of benign and malignant hepatocellular liver tumours combined as 4/143 control, and 5/103, 10/119, 13/120 ($p < 0.025$) and 5/119 males treated with successively higher exposure levels; and 7/142 control, and 18/101 ($p < 0.005$), 12/113, 21/118 ($p < 0.005$) and 9/112 females, respectively. Failure of the highest dose to increase the incidence of hepatocellular tumours was most probably a consequence of the reduced survival and early termination of these animals. No exposure-related increased incidence of brain tumours was observed (Benya *et al.*, 1982).

Table 2. Tumour incidence in rats exposed to vinyl bromide by inhalation for up to 104 weeks

Tumour type	Rats with tumour/no. examined				
	Concentration (ppm) [mg/m^3]				
	0	10 [44]	50 [220]	250 [1100]	1250 [5500]
Males					
Liver					
Angiosarcoma	0/144	7/120[a]	36/120[b]	61/120[b]	43/120[b]
Neoplastic nodules and hepatocellular carcinoma	4/143	5/103	10/119	13/120[a]	5/119
Hepatocellular carcinoma	3/143	1/103	7/119	9/120	3/119
Zymbal gland					
Squamous-cell carcinoma	2/142	1/99	1/112	13/114	35/116[c]
Females					
Liver					
Angiosarcoma	1/144	10/120[d]	50/120[b]	61/120[b]	41/120[b]
Neoplastic nodules and hepatocellular carcinoma	7/142	18/101[c]	12/113	21/118[c]	9/112
Hepatocellular carcinoma	4/142	6/101	3/113	11/118[e]	4/112
Zymbal gland					
Squamous-cell carcinoma	0/139	0/99	3/113	2/119	11/114[b]

Adapted from Benya *et al*. (1982)
Statistical evaluation by χ^2 test
[a] $p < 0.025$
[b] $p < 0.001$
[c] $p < 0.005$
[d] $p < 0.01$
[e] $p < 0.05$

3.2 Dermal exposure

Mouse

A group of 30 female ICR/Ha Swiss mice [age unspecified] received dermal applications of 15 mg vinyl bromide [purity unspecified] in 0.1 mL acetone three times a week for 60 weeks. No skin tumours were observed. In a two-stage skin carcinogenesis study, groups of 30 female ICR/Ha Swiss mice received a single dermal application of 15 mg vinyl bromide in 0.1 mL acetone, followed by thrice-weekly applications of 2.5 μg of 12-*O*- tetradecanoylphorbol-13-acetate (TPA) in 0.1 mL acetone for 60 weeks. Additional groups of mice received TPA alone or no treatment. One of 30 mice treated with vinyl bromide followed by TPA had a skin papilloma at 412 days, and one of 30 mice treated with TPA alone had a skin carcinoma at 44 days. No tumours were found in 160

untreated mice. Systemic carcinogenesis was not assessed (Van Duuren, 1977). [The Working Group noted that the volatility of vinyl bromide would have led to very low doses in these studies of dermal application.]

3.3 Subcutaneous administration

Mouse

Groups of 30 female ICR/Ha Swiss mice [age unspecified] received weekly subcutaneous injections of 0 or 25 mg vinyl bromide [purity unspecified] in 0.05 mL trioctanoin for 48 weeks and were observed for up to 420 days. No tumours were reported in vinyl bromide-treated mice or in vehicle or in 60 untreated controls. Systemic carcinogenesis was not assessed (Van Duuren, 1977).

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The limited available data on absorption, distribution, metabolism and excretion of vinyl bromide in experimental systems have been reviewed previously (IARC, 1986, 1999). The following section summarizes the salient features of the studies that were reviewed at that time, as well as significant new information on the metabolism and pharmacokinetics of vinyl bromide in experimental animals.

Vinyl bromide is readily absorbed upon inhalation by rats (IARC, 1986). The blood:air partition coefficient of vinyl bromide in rats is 4.05, which is about 2.5-fold and fivefold greater than the values for vinyl chloride and vinyl fluoride, respectively (Cantoreggi & Keller, 1997). Similarly, the tissue solubility (particularly the affinity for adipose tissues) and the volume of distribution of vinyl bromide are greater than those for vinyl chloride and vinyl fluoride (Cantoreggi & Keller, 1997).

Vinyl bromide is metabolized in a similar manner to vinyl chloride and vinyl fluoride, and it is a substrate for human cytochrome P450 (CYP) 2E1. Guengerich *et al*. (1991) reported that the rate of metabolism of vinyl bromide was identical to that of vinyl chloride (0.027 nmol/min.nmol CYP), using purified human liver CYP2E1. In this study, the in-vitro formation of 1,N^6-ethenoadenosine that resulted from bromoethylene oxide was also demonstrated (Guengerich *et al*., 1991). Bromoethylene oxide can be

deactivated by epoxide hydrolase and glutathione-*S*-transferases, or can re-arrange to bromoacetaldehyde (National Toxicology Program, 1999).

The metabolism of vinyl bromide in rats is saturable at exposure concentrations greater than 235 mg/m^3 [55 ppm] (Filser & Bolt, 1979). Following inhalation of vinyl bromide by rats, rabbits and monkeys, plasma levels of non-volatile bromide increased with duration of exposure, and were formed more rapidly in hepatic CYP-induced rats (IARC, 1986).

In rats, the conversion of vinyl bromide to reactive metabolites occurs primarily in hepatocytes. Irreversible binding of such metabolites to proteins and RNA has been established with rat liver microsomes *in vitro* as well as in rats *in vivo* (Bolt *et al*., 1980). These metabolites can also alkylate the CYP prosthetic group of phenobarbital-treated rat liver microsomes. Further, the exposure of rats to high concentrations of vinyl bromide has been shown to cause a decrease in hepatic CYP (IARC, 1986).

4.2 Genetic and related effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

(a) DNA adducts

Vinyl bromide metabolites bind covalently to DNA and proteins; 2-bromoethylene oxide is the major DNA-binding moiety and 2-bromoacetaldehyde is the major protein-binding metabolite (Guengerich *et al*., 1981). The major adduct that results from exposure to vinyl bromide is *N*-7-(2-oxoethyl)guanosine (Bolt *et al*., 1981). Bromoacetaldehyde and bromoethylene oxide can react with adenine or cytosine bases to produce the cyclic etheno adducts 1,N^6-ethenoadenosine and 3,N^4-ethenocytosine, which can cause mis-coding by modifying base-pairing sites (Bolt, 1988). Cyclic etheno adducts have a longer half-life than *N*-7-(2-oxoethyl)guanine and, therefore, may have a greater potential to accumulate with long-term exposure (Swenberg *et al*., 1992).

(b) Mutations and other related effects

Vinyl bromide has been shown to be mutagenic in *Salmonella typhimurium* (Lijinsky & Andrews, 1980) and in a recessive lethal mutation test with post-meiotic male germ cells of *Drosophila melanogaster* (Ballering *et al*. 1996). Two GC→AT transitions, five GC→TA and four AT→TA transversions were observed (Ballering *et al*., 1997; Nivard & Vogel, 1999).

The comet assay was used to assess the genotoxicity of vinyl bromide in the stomach, liver, kidney, bladder, lung, brain and bone marrow of male CD-1 mice. The compound

(at 2000 mg/kg bw) induced statistically significant DNA damage in all organs except the bone marrow (Sasaki *et al*., 1998).

4.3 Mechanisms of carcinogenesis

The metabolism of vinyl bromide is similar to that of vinyl chloride and vinyl fluoride. Vinyl bromide is metabolized to bromoethylene oxide and bromoacetaldehyde by human CYP2E1. In-vitro studies have shown that these intermediates, in the presence of adenosine, form 1,N^6-ethenoadenosine. The same promutagenic adduct is formed with chloroethylene oxide, the primary intermediate of vinyl chloride metabolism. It is one of the adducts that are implicated in the mutagenicity and carcinogenicity of vinyl chloride.

5. Summary of Data Reported

5.1 Exposure data

Vinyl bromide is a flammable gas that is produced in a limited number of countries. It is used predominantly for the manufacture of polyvinyl bromide and to a smaller extent as a flame retardant in a large variety of industrial and consumer products. Workers may be exposed during the manufacture of vinyl bromide monomer and during production of the polymer.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

In a study of inhalation exposure in both sexes of rats, vinyl bromide caused a significant increase in the incidence of angiosarcomas of the liver, hepatocellular adenomas and carcinomas, and squamous-cell carcinomas of the Zymbal gland.

In limited studies in female mice, vinyl bromide neither induced nor initiated skin tumours after dermal application and did not cause injection-site tumours after repeated subcutaneous injection.

5.4 Mechanistic and other relevant data

Vinyl bromide is readily absorbed upon inhalation. It is a substrate for human cytochrome P450 2E1 and is metabolized by this enzyme in a manner similar to that of

vinyl chloride and vinyl fluoride. A study in rats has shown that the metabolism of vinyl bromide is saturable at exposure concentrations greater than 55 ppm (~240 mg/m^3).

Bromoethylene oxide and bromoacetaldehyde are known metabolites of vinyl bromide that can form DNA adducts that are similar to those formed by metabolites of vinyl chloride. These include *N*7-(2-oxoethyl)guanosine (the major adduct) and the cyclic adducts, ethenodeoxyadenosine and ethenodeoxycytidine, which can cause miscoding by modifying base-pairing sites. Vinyl bromide caused DNA damage in mice treated *in vivo*, and has been shown to be mutagenic in bacteria and in *Drosophila*.

6. Evaluation and Rationale

6.1 Carcinogenicity in humans

There is *inadequate evidence* in humans for the carcinogenicity of vinyl bromide.

6.2 Carcinogenicity in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of vinyl bromide.

6.3 Overall evaluation

Vinyl bromide is *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

In making the overall evaluation, the Working Group took into consideration the fact that all available studies showed a consistently parallel response between vinyl bromide and vinyl chloride. In addition, both vinyl chloride and vinyl bromide are activated via a human cytochrome P450 2E1-dependent pathway to their corresponding epoxides. For both vinyl chloride and vinyl bromide, the covalent binding of these compounds to nucleosides/DNA yields pro-mutagenic etheno adducts. The weight of positive evidence for both compounds was also noted among the studies for genotoxicity, although the number and variety of tests for vinyl bromide were fewer. For practical purposes, vinyl bromide should be considered to act similarly to the human carcinogen, vinyl chloride.

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