FINAL

Report on Carcinogens Background Document for

Vinyl Bromide

Meeting of the
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee

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Public Health Services
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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

US Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary Statement

Vinyl Bromide

CASRN 593-60-2

Carcinogenicity

Vinyl bromide (VB) is *reasonably anticipated to be a human carcinogen* based on evidence of tumor induction at multiple organ sites in rats. Inhalation exposure of rats to VB resulted in increased incidences of hepatic hemangiosarcomas, Zymbal gland carcinomas, and liver neoplastic nodules and hepatocellular carcinomas (Benya *et al*. 1982, IARC 1986). The biological activity of VB is similar to that of its vinyl halide analogs, vinyl chloride (VC), a known human carcinogen (NTP 1998; IARC 1987), and of vinyl fluoride (VF), a probable human carcinogen (IARC 1995). A unique feature of VC carcinogenicity is the induction of rare hepatic hemangiosarcomas in animals and the causal association in epidemiological studies between VC exposure and excess risk of angiosarcoma of the liver (NTP 1998). VB appears to be a more potent inducer of liver angiosarcomas in rats than VC. The fact that VB and VF also induces rare hemangiosarcomas of the liver in rats and induced the formation of similar DNA adducts suggests a possible common mechanism of carcinogenicity for these three vinyl halides.

No studies on the potential carcinogenicity of VB in humans have been reported.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

VB is genotoxic in *Salmonella typhimurium* (IARC 1986) and *Drosophila melanogaster* (Ballering *et al*. 1996). VB also induces DNA damage in several organs of mice (Sasaki *et al*. 1998). The biotransformation pathway for VB is similar to that of VF and VC. All three compounds undergo cytochrome P-450 mediated oxidation to the corresponding haloethylene oxide (bromoethylene oxide, fluoroethylene oxide, and chloroethylene oxide). These intermediates may rearrange to the corresponding haloacetaldehydes (2-bromoacetaldehyde, 2-fluoroacetaldehyde, and 2-chloroacetaldehyde) which, in turn, are oxidized to haloacetic acids. The K_m for VB metabolism is about an order of magnitude lower than that for VC (Bolt *et al*. 1978), which implies that the greater carcinogenic potency of VB, may be related to kinetic differences in metabolism.

The metabolism of VB generates products that bind covalently to DNA and to protein; 2-bromoethylene oxide is the major DNA binding agent, and 2-bromoacetaldehyde is the major protein alkylating agent (Guengerich *et al*. 1981). After exposure to vinyl chloride, the major DNA adduct formed is 7-(2-oxoethyl)guanine (constituting approximately 98% of all adducts) (Bolt 1988). By analogy, the 7-position of guanine is considered to be the preferential site of DNA alkylation by bromoethylene oxide, the primary metabolite of VB biotransformation (Bolt 1988). Chloroacetaldehyde and bromoacetaldehyde can react with adenine or cytosine bases in DNA or RNA to produce cyclic etheno-DNA/RNA

adducts (1,N^6-ethenoadenosine and 3,N^4-ethenocytosine). Etheno-DNA adducts can cause miscoding as a consequence of their modification of base-pairing sites. Because the cyclic etheno-adducts have a longer half-life than 7-(2-oxoethyl)guanine, they have a greater potential to accumulate with chronic exposure (Swenberg *et al*. 1992).

No data are available that would suggest that mechanisms thought to account for tumor induction by VB in experimental animals would not also operate in humans.

Table of Contents

List of Tables

List of Figures

1 Introduction

Vinyl bromide (VB) was nominated for listing in the Report on Carcinogens (RoC) by the National Institute of Environmental Health Sciences (NIEHS) RoC Review Group (RG1) based on the 1999 International Agency for Research on Cancer IARC monograph (IARC 1999), which indicates that there is sufficient evidence in experimental animals for the carcinogenicity of VB and that it is *probably carcinogenic to humans* (Group 2A).

1.1 Chemical identification

VB is a member of the vinyl halide class. The vinyl halides are easily polymerized and copolymerized with various materials, such as acrylonitrile, vinyl acetate, and styrene, to form pliable, lightweight plastics or thermoplastic resins. Vinyl bromide (C_2H_3Br, mol wt 106.95, CASRN 593-60-2) also is known as bromoethylene, monobromoethylene, and bromoethene. It is a colorless gas at ambient temperature and pressure. VB has widespread industrial use, especially in the plastics industry. It is used in the production of polyvinyl bromide and other bromopolymers. A common intermediate in organic synthesis, it is used in the chemical, plastic and plastic products, leather and leather products, and metal fabrication industries. The structure of VB is illustrated in Figure 1-1.

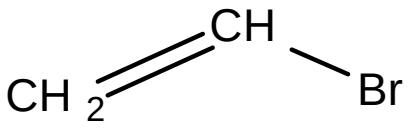

Figure 1-1. Structure of VB

1.2 Physical-chemical properties

VB is incompatible with strong oxidizing agents, copper, copper alloys, and plastics. It is a highly flammable gas under normal atmospheric conditions and a colorless liquid under pressure (IARC 1986). Its RTECS number is KU8400000. The physical and chemical properties of VB are summarized in Table 1-1.

Table 1-1. Physical and chemical properties of VB

Property	Information	Reference
Molecular weight	106.95	Budavari *et al*. (1996); CRC (1998)
Color	colorless	Budavari *et al*. (1996); CRC (1998)
Odor	characteristic pungent odor pleasant odor	IARC (1986) NIOSH (1994)
Physical state	flammable gas	Budavari *et al*. (1996); CRC (1998)
Melting point (°C)	- 139.5	Budavari *et al*. (1996); CRC (1998)
Boiling Point (°C) at 750 mm	15.8	Budavari *et al*. (1996); CRC (1998)
Flash point (°C)	5	Chemfinder (1999)

Property	Information	Reference
Specific gravity	1.4933	Chemfinder (1999)
Relative vapor density (air = 1)	3.8	Physchem (1999)
Vapor pressure (mm Hg)	1,033	HSDB 1996
Solubility in:		
Water at 20°C	insoluble	Budavari *et al*. (1996)
Chloroform	soluble	IARC (1986)
10% Ethanol	soluble	CRC (1998)
10% Ethyl Ether	soluble	CRC (1998)
10% Acetone	soluble	CRC (1998)
10 % Benzene	soluble	CRC (1998)

1.3 Identification of metabolites

The major metabolites of VB are bromoethylene oxide, bromoacetaldehyde, and bromoacetic acid. VB is initially oxidized by microsomal monooxygenase(s) to bromoethylene oxide (Bolt 1988; Ballering *et al*. 1996). The structure of bromoethylene oxide is illustrated in Figure 1-2.

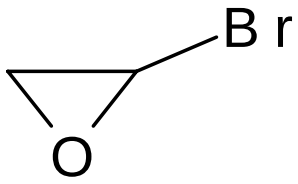

Figure 1-2. Structure of bromoethylene oxide

Bromoethylene oxide is deactivated by an epoxide hydrolase or gluthione transferase. It also may rearrange to form bromoacetaldehyde (Bolt 1988; Ballering *et al*. 1996). The structure of bromoacetaldehyde (C_2H_3BrO, mol wt 122.95, CASRN 17157-48-1) is shown in Figure 1-3.

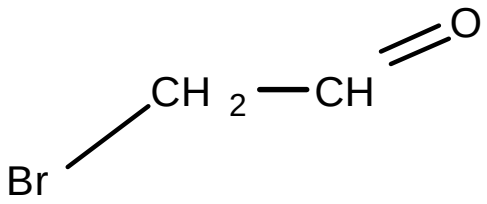

Figure 1-3. Structure of bromoacetaldehyde

Bromoacetic acid ($C_2H_3BrO_2$, mol wt 138.95, CASRN 79-08-3) is detected as a metabolite in VB-treated experimental animals. It probably is formed as a result of oxidation of bromoacetaldehyde (Bolt 1988; Ballering *et al*. 1996). The structure of bromoacetic acid is illustrated in Figure 1-4.

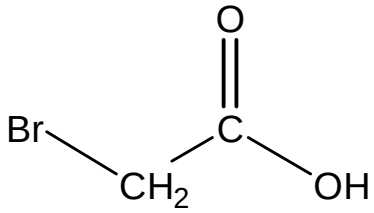

Figure 1-4. Structure of bromoacetic acid

2 Human Exposure

2.1 Use

VB is used predominantly as an intermediate in the production of polymers and copolymers. It is used in polymers as a flame retardant and in the production of monoacrylic fibers for carpet-backing material. As a comonomer with acrylonitrile, it is used in the production of fabrics and fabric blends used in sleepwear (mostly children's) and home furnishings. Copolymerized with vinyl acetate and maleic anhydride, VB is used to produce granular products. VC-VB copolymers are used for preparing films, for impregnating or laminating fibers, and as rubber substitutes. VB also is used in leather and fabricated metal products (HSDB 1996). Polyvinyl bromide, made from VB, is a polymer of little commercial value because it is unstable at room temperature. VB also is used in the production of pharmaceuticals and fumigants (IARC 1986).

2.2 Production

VB was first produced in the United States in 1968. In 1982, U.S. production was estimated to be 51 million lb (HSDB 1996). Currently, one producer, Monsanto Co., is identified by the U.S. Environmental Protection Agency (EPA) (TRI 1996). In 1994, U.S. EPA reported VB output levels to be < 1 million pounds and VB was not listed as a high production volume (HPV) chemical (U.S. EPA 1994).

2.3 Environmental exposure

2.3.1 Routes of exposure

The primary routes of potential human exposure to VB are inhalation and dermal contact. VB is not known to occur naturally in the environment. It is assumed that most, if not all, VB environmental exposure occurs as a result of industrial contamination (IARC 1986).

2.3.2 Industrial releases into the environment

In 1996, the most recent year for which information is available, only one facility reported environmental releases of VB. Monsanto Co. reported releasing a total of 5,840 lb of VB into the air, 240 lb in non-point source releases and 5,600 lb is point source releases (TRI 1996).

2.4 Occupational exposure

The National Institute for Occupational Safety and Health (NIOSH) has identified the following industries in which VB exposure occurs: chemicals and allied production, rubber and plastic production, leather and leather product production, and fabricated metal production for wholesale trade (NIOSH 1978).

The NIOSH National Occupational Exposure Survey (NOES) estimated that 1,821 workers potentially were exposed to VB from 1981 to 1983 (NIOSH 1990).

Median eight-hour time-weighted average (TWA) exposures were calculated for a VB manufacturing plant. They ranged from 0.4 to 27.5 mg/m^3 (0.1 to 6.3 ppm), depending upon jobs and areas surveyed. Personal air samples (one hour) were taken for various employees at this VB manufacturing plant. A plant operator was exposed to VB concentrations of 0.4 to 1.7 mg/m^3 (0.09 to 0.4 ppm), a laboratory technician to concentrations of 1.3 to 2.2 mg/m^3 (0.3 to 0.5 ppm),

and two loading crewmen to concentrations of 5.2 to 27.5 mg/m^3 (1.2 - 6.3 ppm) (Bales 1978, Oser 1980, both cited by IARC 1986).

2.5 Biological indices of exposure

No biomarkers of VB exposure are known. Air sampling is the method of choice for determining VB exposure levels. Table 2-1 identifies procedures used for VB air analysis.

Table 2-1. Methods for the analysis of VB in air

Sample preparation	Assay procedure	Limit of detection	Reference
Adsorb (charcoal tube); desorb (ethanol)	GC/FID	1.3 mg/m^3	Spafford and Dillon (1981); Taylor (1981)
Adsorb (charcoal tube); desorb (heat), purge (helium), dry (calcium sulphate tube), and adsorb (Tenax tube); desorb (thermal) and trap (liquid nitrogen); vaporize (heat) onto capillary GC column	GC/MS	8 ng/m^3	Pellizzari *et al.* (1978)
Adsorb (Tenax-GC); desorb (heat), purge (helium), trap (liquid nitrogen cooled nickel capillary); vaporize (heat) directly onto capillary GC column	GC/MS	250 ng/m^3	Pellizzari *et al.* (1978); Krost *et al.* (1982)

Source: IARC (1986).

GC: gas chromatography, FID: flame ionization detection, MS: mass spectrometry

2.6 Environmental fate

VB is found in nature as a result of industrial spills and discharges. About 99.8% of all polluting VB eventually dissipates in the air, and the rest contaminates water (U. S. EPA 1986). VB also may occur as a degradation product of 1,2-dibromoethane (HSDB 1996). Although VB concentrations were detected in the air in two communities of Arkansas with VB industries, exact levels were not reported (IARC 1986).

2.6.1 Air

Based upon the high vapor pressure of VB, it is most likely to exist in vapor phase in the atmosphere. VB is expected to react with hydroxyl radicals produced photochemically. Its major reactions are with the OH^- radical and ozone (O_3), which remove it from the air. The reported atmospheric lifetimes of VB range from less than one day to five days (HSDB 1996).

2.6.2 Water

VB is not prevalent in water, because it is water insoluble and highly volatile. VB has a half-life of less than two days in water (U. S. EPA 1986). Its volatilization half-life in a model river is estimated to be three hours (HSDB 1996). Bioaccumulation in aquatic organisms is thought to be insignificant, because the concentration of VB detected in fish tissues is not expected to exceed that of the habitat (U.S. EPA 1986). VB has a bioconcentration factor (BCF) of 9; a BCF greater than 1,000 is required for significant bioaccumulation in aquatic organisms (HSDB 1996).

2.6.3 Soil

VB has a high mobility in soil and only slightly adsorbs to suspended solids and sediments in water. When released into wet soil, VB rapidly evaporates or undergoes extensive leaching. Upon release into dry soil, VB rapidly evaporates (HSDB 1996).

2.7 Regulations

U.S. EPA regulates VB under the Clean Air Act (CAA), and the Occupational Safety and Health Administration (OSHA) regulates VB under the Hazard Communication Standard as a chemical hazard in laboratories. U.S. EPA regulations are summarized in Table 2-2, and OSHA regulations are summarized in Table 2-3.

Table 2-2. U.S. EPA regulations

U.S. EPA Regulations	
Regulatory action	**Effect of regulation and other comments**
40 CFR 63 – PART 63 – NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Codes: 7401 *et seq*.; CAA.	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the CAA.
40 CFR 63.800ff. – Subpart JJ – National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/07/95.	The provisions of this subpart apply to each facility that is engaged in the manufacture of wood furniture or wood furniture components and that is a major source as defined in 40 CFR 63.2. This subpart details which applications VB is prohibited from use. It also lists VB as a volatile, hazardous air pollutant.

Source: These regulations have been updated through the 1998 Code of Federal Regulations 40 CFR, July 1, 1996; 21 CFR, April 1, 1996; 29 CFR, July 1, 1996.

Table 2-3. OSHA regulations

OSHA Regulations	
Regulatory action	**Effect of regulation and other comments**
29 CFR 1910.1200—Sec. 1910.1200. Hazard Communication. Promulgated 62 FR 42018, 08/04/97.	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication program to include labels, material safety data sheets, and worker training.
29 CFR 1910.1450. Promulgated 1/31/90. Amended 58 FR 40191, 7/27/93. OSHA Act: Final rule for occupational exposure to hazardous chemicals in laboratories.	As select carcinogen (IARC Group 2A, *possibly carcinogenic to humans*), VB is included as a chemical hazard in laboratories. Employers are required to provide employee information and training and to provide Chemical Hygiene Plan.

Source: These regulations have been updated through the 1998 Code of Federal Regulations 40 CFR, July 1, 1996; 21 CFR, April 1, 1996; 29 CFR, July 1, 1996.

3 Human Cancer Studies

There are no reports of an association between exposure to VB and cancer in humans.

4 Studies of Cancer in Experimental Animals

An IARC Working Group reviewed studies of the carcinogenic potential of VB (IARC 1986, 1999). These reviews catalogued carcinogenesis studies conducted via inhalation, subcutaneous, and dermal routes of administration. The results of the reviews and evaluations are summarized in Section 4. A thorough search of the peer-reviewed scientific literature did not reveal any additional animal studies of the carcinogenic potential of VB.

4.1 Inhalation exposure

Rats exposed to VB by inhalation developed tumors at multiple sites. In this study, 9- to 10-week-old Sprague-Dawley rats (120 of each sex) were exposed to VB in air at concentrations of 10, 50, 250, or 1250 ppm (corresponding to 44, 219, 1093, or 5463 mg/m^3) six hours/day, five days/week, for 104 weeks. Hydroquinone methyl ether (0.02%, used as stabilizer), ethylene oxide (0.03%), acetylene (0.0007%), and aldehydes and ketones (0.008%) were present in the VB used. The animals in the highest dose group were sacrificed at 72 weeks because of 50% mortality (Benya *et al*. 1982, cited in IARC 1986).

VB caused statistically significant dose-related increases in the incidences of angiosarcomas of the liver and squamous cell carcinomas of the Zymbal gland in both sexes. In addition, the incidences of neoplastic nodules of the liver and hepatocellular carcinomas were significantly increased in males and females exposed to 250 ppm, but not in those exposed to 50 or 1250 ppm. Failure of the highest dose to increase the incidence of hepatocellular tumors was most likely a consequence of the reduced survival and early sacrifice of those animals. Tumor incidences in rats exposed to VB are summarized in Table 4-1.

Table 4-1. Tumor incidences in Sprague-Dawley rats exposed to VB by inhalation for up to 104 weeks

Tumor type	Tumor response/number examined				
	Inhalation concentration of vinyl bromide in air (ppm)[a]				
	0	10	50	250	1250
Males					
Liver: angiosarcoma	0/144	7/120*	36/120***	61/120***	43/120***
Liver: neoplastic nodules and hepatocellular carcinoma	4/143	5/103*	10/119*	13/120*	5/119*
Zymbal gland: squamous cell carcinoma	2/142	1/99	1/112	13/114**	35/116**
Females					
Liver: angiosarcoma	1/144	10/120***	50/120***	61/120***	41/120***
Liver: neoplastic nodules and hepatocellular carcinoma	7/142	18/101**	12/113	21/118**	9/112
Zymbal gland: squamous cell carcinoma	0/139	0/99	3/113	2/119	11/114***

Source: Benya *et al*. (1982, cited in IARC 1986)
[a]Logistic regression test for trend $^{*}P < 0.025$, $^{**}P < 0.005$, $^{***}P < 0.001$.

Based on the increased incidence of angiosarcomas of the liver and squamous cell carcinomas in both sexes of the rats in this study, IARC concluded that there is sufficient evidence of

carcinogenicity of VB in experimental animals and classified VB as *probably carcinogenic to humans* (Group 2A) (IARC 1986).

4.2 Dermal exposure

VB failed to induce skin tumors in mice when applied dermally (15 mg in 0.1 mL of acetone) three times a week for 60 weeks (Van Duuren 1977, cited by IARC 1986). There was no evidence of initiator activity when VB was tested in a two-stage skin carcinogenesis test. Groups of 30 ICR/Ha Swiss mice received a single topical treatment of VB (15 mg in 0.1 mL of acetone), followed by application three times a week for 60 weeks of 2.5 μg of 12-*0*-tetradecanoylphorbol-13-acetate (TPA) in 0.1 mL of acetone. Additional groups of 30 mice received a single application of 7,12-dimethylbenz[*a*]anthracene followed by treatment with TPA (positive controls), treatment with TPA only, or no treatment at all.

One of 30 mice dosed with VB followed by TPA had a skin papilloma at 412 days, and one skin carcinoma was observed in TPA-treated controls after 44 days. The positive control group had a high incidence of skin tumors (incidence not specified). No tumors were found in the untreated mice. Systemic carcinogenesis was not assessed. The IARC Working Group noted that because the skin application sites were not covered, the mice may have received less than the nominal dose, as VB is volatile (Van Duuren 1977, cited by IARC 1986).

4.3 Subcutaneous exposure

Female mice administered VB by subcutaneous injection, did not develop tumors at the injection site. Groups of female ICR/Ha Swiss mice were administered 25 mg VB in 0.5 mL trioctanoin once a week for 48 weeks and were observed for up to 420 days. No tumors were noted in VB-treated mice or in vehicle or untreated control mice. Systemic carcinogenesis was not assessed (Van Duuren 1977, cited in IARC 1986).

4.4 Summary

VB failed to induce skin tumors or to show any evidence of initiator activity when applied dermally, three times weekly for 60 weeks, to mice. Subcutaneously injected VB failed to induce injection-site tumors in female mice treated weekly for 48 weeks and observed for up to 420 days. (Systemic carcinogenesis was not assessed in these studies.) Rats exposed to VB by inhalation developed tumors at multiple sites, including angiosarcomas of the liver and squamous cell carcinomas of the Zymbal gland in both sexes. Hepatic neoplastic nodules and hepatocellular carcinomas also were significantly increased in males and females exposed to VB at a concentration of 250 ppm, but not at the highest concentration tested. Based on the increased incidence of angiosarcomas of the liver and squamous cell carcinomas in both sexes of the rats in this study, IARC concluded that there is sufficient evidence of carcinogenicity of VB in experimental animals and classified VB as *probably carcinogenic to humans* (Group 2A). The spectrum of these VB-induced neoplasms closely resembled that produced in Sprague-Dawley rats by inhalation exposure to vinyl chloride.

5 Genotoxicity

5.1 Prokaryotic systems

5.1.1 Induction of mutation in Salmonella typhimurium

A number of studies have shown that exposure to vapors of VB (0.2% to 20% v/v in air for various time periods) is mutagenic to *Salmonella typhimurium* strains TA1530 and TA100 in the presence or absence of a metabolic activation system (S9 liver homogenate from Aroclor-induced rats or phenobarbital-induced mice) (Bartsch 1976; Bartsch *et al*. 1976, 1979; Lijinsky and Andrews 1980, all cited in IARC 1986).

VB was assayed for mutagenicity with the ara forward-mutation test in *S. typhimurium,* with or without an exogenous metabolizing system (S9 rat liver homogenate) (Roldan-Arjona *et al.* 1991). Because VB is volatile, its bacterial mutagenic activity is difficult to assay by the standard plate incorporation or preincubation mutagenesis test. To avoid a false negative result, VB was tested in a liquid test (Hera and Pueyo 1986, cited in Roldan-Arjona *et al.* 1991). Bacteria were exposed in liquid for various time periods to VB at a concentration of 142 μmol/mL (corresponding to a minimum of 10 μL of VB). Under these test conditions, VB was mutagenic, and mutagenicity was enhanced by metabolic activation.

5.2 Lower eukaryotic systems

5.2.1 *Mutagenicity in* Drosophila melanogaster

The effect of VB in the *in vivo Drosophila melanogaster* w/w^+ eye mosaic assay was investigated by Vogel and Nivard (1993), who assessed damage to the somatic cells of *D. melanogaster* after exposure of larvae to concentrations of VB ranging from 0 to 64,000 ppm in air. VB was recombinagenic in the assay, as indicated in Table 5-1. A later study confirmed these results (Ballering *et al*. 1996).

Table 5-1. Mutagenicity of VB in the *Drosophila* w/w^+ eye mosaic assay

Conc. (ppm)	Eyes tested	Spots per 100 eyes tested			Average clone size	Clones per 10^4 cells	Activity
		S	L	Total			
0	700	2.86	0.57	3.4	2.4	2.1	—
4,000	250	5.20	1.60	6.8	3.6	6.1	weakly positive 0.085 ppm
8,000	500	3.80	1.20	5.0	2.8	3.5	inconclusive
32,000	500	6.40	1.60	8.0	3.6	7.2	weakly positive
64,000	166 [a]	11.45	4.22	15.7	5.3	20.8	positive

Source: Vogel and Nivard (1993).
Tested in C-4 strains: winscy, y, w females x w males; winscy, y, w/w females x y males.
[a] Reduced survival in relation to control.
L = large spots, clone size > 4 ommatidia.
S = small spots, clone size 1 –to 4 ommatidia.

VB at a concentration of 54,000 ppm in air induced sex-linked recessive mutations in the germ cells of male *D. melanogaster*. In addition to enhanced forward mutation rates (recessive lethal mutations), VB caused M_{exr-}/M_{exr+} hypermutability with *mus201* or *mei9* female genotypes (Ballering *et al.* 1996).

DNA sequence changes induced in the vermilion gene of *D. melanogaster,* following *in vivo* exposure of male flies to VB in air (27,000 ppm for 48 h) were investigated by Ballering *et al*. (1997). Because of low mutagenic activity of VB in nucleotide excision repair (NER^+) genotypes, vermilion mutants were isolated only from crosses of VB-treated males with NER^- females. A total of 14 mutants (5 from 391,039 F_1 females [mutation frequency (mf) = 0.13 x 10^4] and 9 from 125,000 F_2 offspring [mf = 0.72 x 10^{-4}]) were isolated, 3 of which carried large deletions (2 GC → AT transitions, 5 GC → TA transversions, 4 AT → TA transversions, and 3 intra-locus deletions).

In a 17 hour inhalation study, the genetic heterogenetic response of *D. melanogaster* to VB was investigated by Rodriguez-Arnaiz *et al.* (1993), in seven different strains (wild-type laboratory strains Leiden-S [LS], Oregon-K [OK], Berlin-K [BK], and 91-C and DDT-resistant strains 91-R, Hikone-R [HR], and Haag-79 [HG]) in combination with the w/w^+ eye mosaic assay for mitotic recombination. High exposure levels were required to see a significant number of spots in LS (2,000 to 64,000 ppm VB), OK (8,000 to 24,000 ppm VB), or BK (8,000 to 24,000 ppm). Mutation frequencies were highest in strains 91-C, HR, and HG, which were tested at 2,000 to 24,000 ppm VB. The highest concentration of VB (24,000 ppm) was toxic to strains HR and HG, and their mutagenic activity was lower at 24,000 ppm than at lower concentrations of VB at which they were tested. Induction rates were highest in 91-C and lowest in OK, with a 60-fold difference in response between these two strains. From highest to lowest induction rate, the strains responded in the following order: 91-C ≥ HG ~ HR > BK ~ LS ~ OK.

5.3 Mammalian systems *in vivo*

5.3.1 DNA damage

The alkaline single cell gel (SCG or Comet) assay was used to study the genotoxicity of VB in seven mouse organs: stomach, liver, kidney, bladder, lung, brain, and bone marrow (Sasaki *et al.* 1998). VB (2,000 mg/kg) dissolved in olive oil was administered orally to three groups of four male CD-1 mice. The animals were killed immediately (control) or 3 or 24 h after treatment, and necropsies of the seven organs were performed. DNA migration from the seven organs examined is presented in Table 5-2. VB induced DNA damage in all of the organs except bone marrow. The researchers observed no deaths, morbidity, distinctive clinical signs, or gross pathology. There were no microscopic signs of necrosis in the organs in which DNA damage was observed, implying that the DNA damage was not due to cytotoxicity (Sasaki *et al.* 1998).

Table 5-2. Migration of nuclear DNA from organs of mice orally administered 2,000 mg/kg of VB

Sampling time (h)		Migration (μm)						
		Stomach	Liver	Kidney	Bladder	Lung	Brain	Bone marrow
0	Mean	10.3	1.81	2.66	8.93	3.12	1.40	1.16
	SEM	0.88	0.50	0.29	0.75	0.17	0.48	0.76
3	Mean	28.2**	9.84***	8.62*	12.2	13.5***	2.66	0.70
	SEM	3.79	1.16	1.53	1.34	0.61	0.63	0.42
24	Mean	28.0**	8.36**	7.19	21.3**	6.73	11.8**	1.58
	SEM	3.51	1.05	1.48	3.02	1.54	2.12	0.24

Source: Sasaki *et al.* (1998)
SEM: Standard error of the mean. * $P < 0.05$. **$P < 0.01$. *** $P < 0.001$ (Dunnett test)

5.4 Summary

Like its structural analog VC, VB is mutagenic in *S. typhimurium* strains TA1530 and TA100 with or without metabolic activation. Exposure of *S. typhimurium* strains TA1530, TA1535, and G-46 to VB increased the number of histidine revertants/plate at rates 16, 12, or 5 times, respectively, the spontaneous mutation rate. The mutagenic response for strain TA1530 increased with metabolic activation by S9 liver fractions from rats or mice. Like VC, VB is clearly genotoxic (recombinagenic) to *D. melanogaster* in the *in vivo* w/w^+ eye mosaic assay. Both VC and VB are efficient clastogenic agents in *Drosophila* germ cells. VB and VC both can produce DNA and RNA adducts that are likely formed by their respective epoxide rearrangement products, bromoacetaldehyde and chloroacetaldehyde (as described in Section 6).

6 Other Relevant Data

6.1 Absorption and metabolism of VB

6.1.1 Absorption

VB is readily absorbed from the lungs of rats (Filser and Bolt 1979, 1981, Gargas and Andersen 1982, all cited in IARC 1986), and at equilibrium with inspired air, it exhibits an 11-fold bioaccumulation. Early evidence on VB metabolism indicated dose-related increases in plasma levels of nonvolatile bromide. Pretreatment of rats with phenobarbital accelerated the release of bromide from inhaled VB, suggesting a role for the cytochrome P-450 system (Van Stee *et al*. 1977, cited in IARC 1986).

6.1.2 Metabolism

The metabolic pathway in rats is saturable at inhalation exposure concentrations in excess of 250 mg/m^3 (55 ppm); however, the duration of exposure required for saturation was not reported (Van Stee *et al.* 1977, cited in IARC 1986). VB metabolism probably proceeds through epoxidation, with subsequent conjugation to macromolecules and other biologic compounds, similar to that seen for VC (Clayton and Clayton 1982).

The incidence of hepatic hemangiosarcoma in rats exposed to VB in air at a concentration of 10 ppm is 10%, compared with 1% in rats exposed to VC at 10 ppm (Maltoni *et al.* 1981). At a concentration of 50 ppm, the incidence of hemangiosarcoma is 36% in VB-exposed rats, compared with 7% in VC-exposed rats. The greater potency of VB in inducing hepatic hemangiosarcoma may be related to kinetic differences in the metabolism of the two compounds. The K_m for metabolism of VB is approximately an order of magnitude lower than that for VC (Bolt *et al.* 1982). Thus, VB may be metabolized to carcinogenic intermediates at a faster rate than VC.

The reactive metabolites of VB are produced in the hepatic microsomal fraction. When a mixture of VB and air was passed through a mouse liver microsomal system, a volatile alkylating metabolite was detected by trapping with 4-(4-nitrobenzyl)pyridine (Barbin *et al*. 1975; Bartsch *et al.* 1976, 1979, all cited in IARC 1986). VB incubated with liver microsomes from phenobarbital-treated rats alkylates the prosthetic group (heme) of cytochrome P-450. This alkylated moiety is the dimethyl ester of *N*-(2-oxoethyl)protoporphyrin IX (IARC 1986). A comparative study with isolated rat hepatocytes and hepatic sinusoidal cells revealed that metabolism of VB to reactive metabolites was confined primarily to hepatocytes (Ottenwalder and Bolt 1980).

The biotransformation of VB is similar to that observed for VC (IARC 1979; Guengerich *et al*. 1981, cited in Bolt 1988) and is summarized in Figure 6-1.

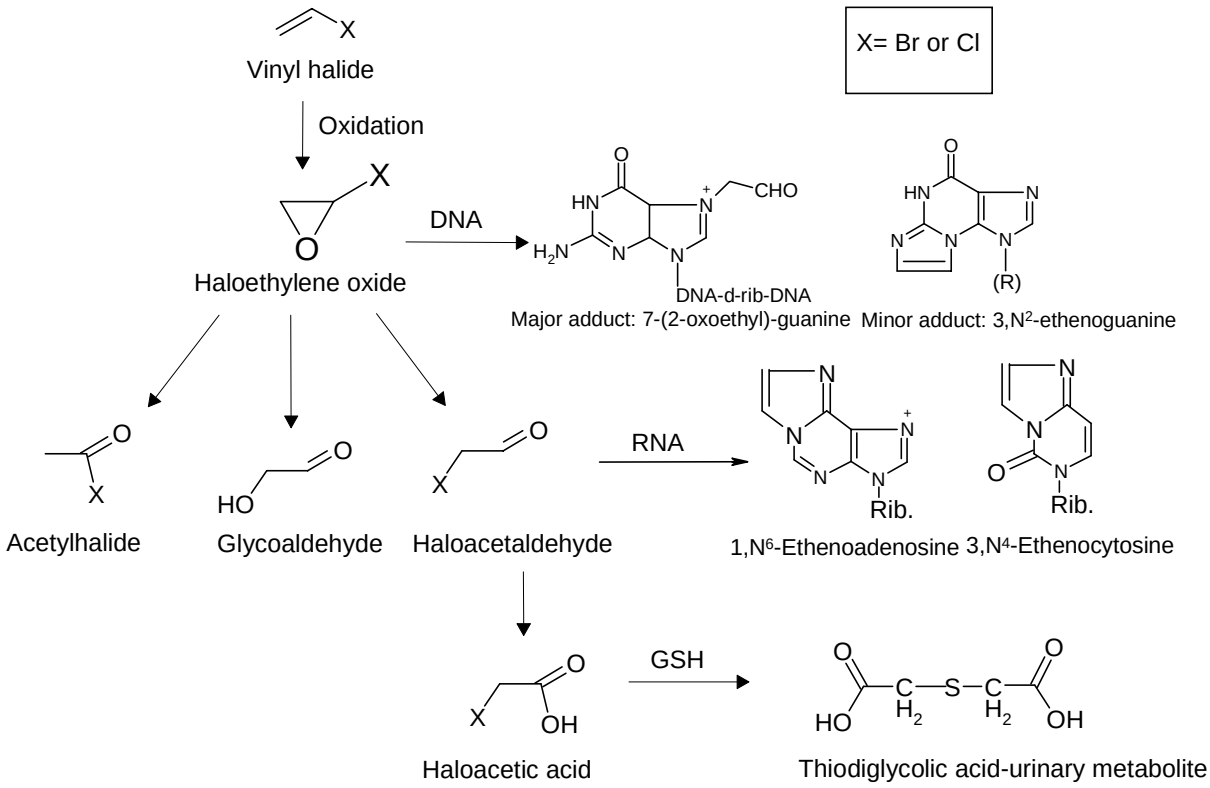

Figure 6-1. Proposed metabolic pathway of VB

Source: Bolt 1986, 1988 and Ballering *et al*. 1996

VB is initially oxidized by microsomal monooxygenase(s) to bromoethylene oxide (bromooxirane). The resulting bromooxirane is highly reactive and probably can bind to nucleic acids (Amdur *et al*. 1991). Bromoethylene oxide can be deactivated by epoxide hydrolase or by gluthione (GSH) transferase. It also can rearrange to bromoacetaldehyde, which in turn is oxidized to bromoacetic acid, with a subsequent secondary metabolism after reaction with GSH.

6.2 Alkylating properties and DNA binding

After *in vitro* incubation of DNA with VB, alkylation following VB metabolism is caused largely by an epoxide intermediate similar to that observed for VC (Guengerich *et al*. 1981, cited by Bolt *et al.* 1986). This mechanism was confirmed for VC by the observation that alkylation of guanine in DNA (at 7-N) occurred after exposure of rats to VC, but not after exposure to 2,2'-dichlorodiethyl ether, a metabolic precursor of chloroacetaldehyde (Gwinner *et al.* 1983, cited in Bolt 1988). Thus, under conditions of *in vivo* exposure to VB (or VC), bromoethylene oxide (or chloroethylene oxide) appears to be the primary DNA-reactive intermediate.

The metabolism of ^{14}C-labeled VB in rat liver microsomes, reconstituted cytochrome P-450 systems, and isolated hepatocytes leads to products that bind irreversibly to DNA and protein. A role for cytochrome P-450 was confirmed in inhibition and reconstitution experiments. The major form of cytochrome P-450 involved in VB metabolism is not either of the major isozymes induced by phenobarbital or beta-napthoflavone. 2-Bromoethylene oxide and 2-

bromoacetaldehyde were found to be the substrates for rat liver epoxide hydrolase and equine liver alcohol dehydrogenase, respectively. Alcohol dehydrogenase was more effective than epoxide hydrolase in inhibiting the binding of VB metabolites to protein in microsomal incubations. Epoxide hydrolase was more effective than alcohol dehydrogenase in inhibiting the binding of VB metabolites to calf thymus DNA. Similar results were observed for VB metabolites binding to DNA in a reconstituted enzyme system. Reduced glutathione blocked nonenzymatic binding of 2-bromo(1,2- [^{14}C])acetaldehyde to protein, but not DNA. Studies with isolated rat hepatocytes suggest that a significant portion of the total reactive metabolites can be released by these cells. In these systems, binding of metabolites of VB to DNA outside the hepatocytes could be partially blocked by epoxide hydrolase or by alcohol dehydrogenase. This implies that as targets farther away from sources of reactive species are considered, the stabilities of these species become important for reaction with nucleophilic sites (Guengerich *et al*. 1981, cited in Bolt 1988; Guengerich *et al*. 1991).

The role of human cytochrome P-450 IIE1 in the oxidation of a number of suspect carcinogens was examined by Guengerich *et al*. (1991). The results indicated that the P-450 IIE1 is a major catalyst for the oxidation of both VB and VC

The metabolic activation and macromolecular binding of VB is similar to that of VC (Barbin *et al*. 1975; Ottenwalder *et al*. 1979; Guengerich *et al*. 1981, all cited in Bolt *et al*. 1986; Bonse and Henschler 1976; Bolt *et al.* 1978; Bartsch *et al*. 1979; Bolt *et al*. 1981). Chloroethylene and bromoethylene oxides bind mostly to the N-7 site of deoxyguanosine. Bromoacetaldehyde binds to RNA to form 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine metabolites. These metabolites also are capable of alkylating nonspecific proteins, preferably those containing free sulfhydryls (Swenberg *et al*. 1992).

When rat liver microsomes, a NADPH-regenerating system, DNA, and ^{14}C-labeled VC are incubated, 1,N^6-ethenodeoxyadenosine, 3,N^4-ethenodeoxycytidine, and 7-(2-oxoethyl)guanine, (the product of the hydrolysis of 7-(2-oxoethyl)deoxyguanosine), are formed. These cyclic DNA adducts, as well as N^2,3-ethenoguanine, were detected in liver, lung, and kidney of rats exposed to VC (Swenberg *et al.* 1992).

Laib and Bolt (1977, cited in Bolt 1988) described the formation of labeled 1,N^6-ethenoadenosine in hepatic RNA of rats dosed with ^{14}C-labeled VC. Similar results were seen in *in vitro* experiments wherein RNA and rat liver microsomes were incubated together with the substrate. Later, 3,N^4-ethenocytidine was identified in RNA hydrolysates under similar conditions (Laib and Bolt 1978). Ottenwalder *et al*. (1979) studied RNA alkylation after administration of ^{14}C-labeled VB to rats and observed results similar to those for VC. 1,N^6-Ethenoadenosine and 3,N^4-ethenocytidine were detected in hepatic RNA of exposed rats. Adducts formed by vinyl halide metabolites, as demonstrated in studies of RNA alkylation by VB metabolites and by analogy with VC, are illustrated in Figure 6-1.

Guengerich *et al*. (1981, cited in Bolt *et al.* 1986) advanced the hypothesis, based on *in vitro* experimentation, that the product of epoxidation of VB, bromoethylene oxide, is the major alkylating agent at the DNA level. In addition, bromoacetaldehyde (the rearrangement product of bromoethylene oxide) has the potential to bind covalently to proteins.

6.3 Structure-activity relationship

The metabolism of VB probably proceeds through the same pathway as that of VC (*known to be a human carcinogen*) and the *probable human carcinogen*, vinyl fluoride (VF). VB is less rapidly metabolized in rats and mice than VF and VC (Bolt *et al*. 1982). The metabolic process appears to be saturable, as observed for VC (Bolt *et al.* 1981).

The spectrum of neoplasms produced by the three vinyl halides in rats and mice is strikingly similar. Table 6-1 summarizes the information available on carcinogenesis, mutagenesis, and pharmacokinetics for the three vinyl halides.

Table 6-1. Summary of carcinogenicity, mutagenicity, and pharmacokinetics of VF, VB, and VC

Study	VB	VF	VC
Animal carcinogenicity			
Types of tumors formed			
Hepatic hemangiosarcoma	rats[a]	rats, mice[b]	rat, mice[c]
Extrahepatic hemangiosarcoma	—	—	rats, mice[d]
Hepatocellular carcinoma	rats[a]	rats[e]	—
Hepatocellular adenoma	-	rats, mice[e]	rats[d]
Zymbal gland carcinoma	rats[a]	—	rats[d]
Bronchioalveolar adenoma and adenocarcinoma	—	rats, mice[e]	—
Harderian gland adenocarcinomas	—	mice[e]	-
Mammary gland adenocarcinomas	—	mice[e]	mice[d]
Oncogene activation			
Oncogenicity (formation of ATPase-deficient hepatic foci in newborn rats	positive[f]	positive[g]	positive[h]
Mutagenicity			
Prokaryotic cells *in vitro*	positive[i]	positive[j]	positive[d]
D. melanogaster in vivo	positive[k]	positive[l]	positive[d]
Mammalian cells *in vitro*	na	positive[m]	positive[d]
Mammalian bone marrow test *in vivo*	na	positive[n]	positive[o]
Pharmacokinetics			
Metabolism			
Metabolism by rat liver microsomes	na	V_{max} = 1.1 nmol/hr-mg protein[p]	V_{max} = 280.4 nmol/hr-mg protein[q]
Metabolism by mouse liver microsomes	na	V_{max} = 3.5 nmol/hr-mg protein[p]	na
Metabolism by human liver microsomes	na	V_{max} = 0.5-3.3 nmol/hr-mg protein[p]	na
Detection of free ions in urine	positive[r]	positive[r]	positive[r]
Detection of acetone in exhaled air in rats	positive[s]	positive[s]	positive[s]
Distribution (air partition coefficients)[p]			
Blood (rats)	4.05 ± 0.16	0.75 ± 0.09	1.68 ± 0.18
Liver (rats)	3.33 ± 0.38	0.83 ± 0.58	1.60 ± 0.17
Muscle (rats)	2.26 ± 0.13	0.54 ± 0.28	2.10 ± 0.45
Fat	49.2 ± 1.3	1.82 ± 0.15	20.0 ± 0.7

Study	VB	VF	VC
Alkylating properties			
Reactive intermediates and formation of DNA adducts	7-(2′-oxoethyl)guanine; N^2,3-ethenoguanine[t]	7-(2′-oxoethyl)guanine, N^2,3-ethenoguanine[u]	7-(2′-oxoethyl)guanine; N^2,3-ethenoguanine[v]; 3,N^4-ethenocytosine; 1,N^6-ethenoadenine[u]

—, Not reported; na, Not available.
[a]IARC 1986
[b]Bogdanffy *et al.* 1995, IARC 1995
[c]IARC 1979, NTP 1998
[d]IARC 1979
[e]Bogdanffy *et al.* 1995
[f]Bolt *et al.* 1979
[g]Bolt *et al.* 1981
[h]Laib *et al.* 1985
[i]IARC 1986, Roldan-Arjona *et al.* 1991
[j]Dupont de Nemours 1992a
[k]Vogel and Nivard 1993, Ballering *et al*. 1996.
[l]CMA 1988, IARC 1995
[m]Dupont de Nemours 1992b, IARC 1995
[n]Dupont de Nemours 1987, IARC 1995
[o]Richardson *et al.* 1983
[p]Cantonreggi and Keller 1997
[q]el Ghisassi *et al.* 1998
[r]Dilley *et al.* 1974
[s]Filser *et al.* 1982
[t]Bolt 1988
[u]Swenberg *et al.* 1995
[v]Swenberg *et al.* 1992

6.4 Summary

The available information on VB metabolism, DNA reactivity of its metabolites, and the spectrum of tumor induction in rats suggest that VB is a genotoxic carcinogen. The metabolism of VB probably proceeds through the same pathway as that of the known human carcinogen, VC, and the probable human carcinogen, VF. The metabolism of VC and VF results in the production of reactive metabolites that bind to proteins and nucleic acids. All three vinyl halide congeners are active in genotoxicity assays. Inhalation exposure to each congener produces a similar array of neoplasms and unequivocal carcinogenicity in rats and/or mice of both sexes.

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Appendix A: IARC. (1979). *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein. (Vinyl Bromide).* Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 19. Lyon, France. World Health Organization. pp. 367-375.

VINYL BROMIDE

1. Chemical and Physical Data

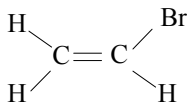
1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 593-60-2

Chem. Abstr. Name: Bromoethene

Bromoethylene

1.2 Structural and molecular formulae and molecular weight



C_2H_3Br Mol. wt: 106.9

1.3 Chemical and physical properties of the pure substance

From Weast (1976), unless otherwise specified

(a) Description: Gas (Hawley, 1971)

(b) Boiling-point: +15.8°C

(c) Melting-point: –139.5°C

(d) Density: d_4^{20}1.4933

(e) Refractive index: n_D^{20} 1.4410

(f) Spectroscopy data: Infrared, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(g) Solubility: Insoluble in water; soluble in ethanol, ether, acetone, benzene and chloroform

(h) Stability: Inflammable; polymerizes rapidly in light (Pollock & Stevens, 1965)

(i) Conversion factor: 1 ppm in air = 4.4 mg/m^3

1.4 Technical products and impurities

Vinyl bromide available commercially in the USA contains a minimum of 99.5% vinyl bromide, 175–225 mg/kg (ppm) of an undisclosed inhibitor and a maximum of 300 mg/kg (ppm) water.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Vinyl bromide was first prepared in 1835 by heating ethylene dibromide with alkali. It is prepared commercially in the USA by the reaction of acetylene with hydrogen bromide in the presence of a catalyst such as the halides of mercury, cerium or copper (Ramey & Lint, 1971). In Japan, it is prepared by the reaction of potassium hydroxide on ethylene dibromide.

Commercial production of vinyl bromide in the US was first reported in 1968 (US Tariff Commission, 1970). In 1975, two companies reported the manufacture of an undisclosed amount (US International Trade Commission, 1917).

It is produced commercially in Japan by one company.

(b) Use

Vinyl bromide is a reactive flame retardant used in small amounts as a comonomer with acrylonitrile and other vinyl monomers in modacrylic fibres (see also p. 86). Modacrylic fibres containing vinyl bromide are used in fabrics and fabric blends with polyesters for children's sleepwear and other clothing, home furnishings and industrial applications (LeBlanc, 1977).

In Japan, vinyl bromide is also used as a comonomer in modacrylic fibres, all of which are exported.

Vinyl bromide has been used to prepare polyvinyl bromide, but the polymer is unstable even at room temperature and, consequently, has been of little commercial significance (Ramey & Lini, 1971) (see however, section 3.1, p. 370).

The American Conference of Governmental Industrial Hygienists has proposed that an employee's exposure to vinyl bromide not exceed an 8-h time-weighted average of 22 mg/m^3 (5 ppm) in the workplace air in any 8-h work shift of a 40-h work week (Anon., 1977). This is a revision of their previous recommended threshold limit value for vinyl bromide, which was 1100 mg/m^3 (250 ppm) (American Conference of Governmental Industrial Hygienists, 1976).

2.2 Occurrence

Vinyl bromide is not known to occur as a natural product.

It has been detected as an impurity in commercial vinyl chloride (Kurosaki *et al*., 1968; Sassu *et al*., 1968).

2.3 Analysis

A sampling technique for air pollutants, including vinyl bromide, has been evaluated using different gas chromatographic packings. The compounds are desorbed thermally and analysed by gas chromatography using flame-ionization detection. The limit of detection is 4.4 μg/m^3 (1 ppb) (Russell, 1975).

Vinyl bromide in commercial vinyl chloride can be determined by gas chromatography and flame-ionization detection, with a limit of detection of several ppm (Sassu *et al*., 1968), or collected by preparative gas chromatography and identified by infra-red spectrophotometry, mass spectrometry, elemental analysis and measurement of its physical properties (Kurosaki *et al*., 1968).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(a) Skin application

Mouse: Vinyl bromide was tested as an initiator and as a complete carcinogen in a two-stage skin carcinogenesis study using groups of 30 female ICR/Ha Swiss mice, at a dose of 15 mg/animal in 0.1 mL acetone per application. When applied alone thrice weekly for 420 days, there were no skin tumours. When applied once only, followed by application of phorbol myristyl acetate (PMA) at 2.5 μg/0.1 mL acetone thrice weekly, 1/30 mice developed a skin papilloma at 412 days. One skin carcinoma occurred among 30 PMA-treated controls after 44 days. Untreated controls (160 animals) developed no skin tumours within 420 days. The positive

[1] The Working Group was aware of studies in progress to determine the carcinogenicity of vinyl bromide and polymerized vinyl bromide in rats by oral administration (IARC, 1978) and in mice and rats by inhalation exposure (Toxicology Information Program, 1976).

control group (7,12-dimethylbenz[*a*]anthracene followed by PMA) showed the expected high number of skin tumours (Van Duuren, 1977) [The Working Group noted that there was incomplete pathological examination of the animals].

A solution of polymerized vinyl bromide was also tested in groups of 30 female ICR/Ha Swiss mice. A dose of 0.1 mL of a commercial aqueous latex suspension was applied thrice weekly for 420 days; no skin tumours developed. When applied once only, followed by application of PMA at 2.5 μg/0.1 mL acetone thrice weekly, 1/30 mice developed a papilloma at 175 days. Untreated controls (160 animals) showed no skin tumours (Van Duuren, 1977) [The Working Group noted that there was incomplete pathological examination of the animals]

(b) Subcutaneous and/or intramuscular administration

Mouse: A group of 30 female ICR/Ha Swiss mice were injected with 25 mg/animal vinyl bromide in 0.05 mL trioctanoin once weekly for 48 weeks and observed up to 420 days. No local tumours were seen in treated mice, nor in 30 mice given 48 weekly injections of trioctanoin alone, nor in 60 untreated controls observed up to 420 days (Van Duuren, 1977) [The Working Group noted that there was incomplete pathological examination of the animals].

A group of 30 female ICR/Ha mice were injected once weekly for 48 weeks with 0.05 mL of a commercial polymerized vinyl bromide aqueous latex suspension and observed for 420 days. Nineteen mice developed sarcomas at the injection site. In a positive control group of 30 mice injected with β-propiolactone (0.3 mg/0.05 mL trioctanoin), the expected high incidence of tumours at the injection site was seen (18 sarcomas and three squamous-cell carcinomas). No local tumours were observed in 60 untreated mice or in 30 control mice injected with trioctanoin alone (Van Duuren, 1977) [The Working Group noted that there was incomplete pathological examination of the animals].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD_{50} of a 50% solution of vinyl bromide in corn oil in male rats was approximately 500 mg/kg bw. In acute inhalation studies, exposure of rats to 440 g/m^3 (100 000 ppm) resulted in deep anaesthesia and death within 15 min; but if exposure was terminated before death, all animals recovered and survived. Exposure to 220 g/m^3 (50 000 ppm) rendered rats unconscious in 25 min and was lethal after 7 h of exposure; slight liver and kidney damage were observed. No histopathological changes were found in rats exposed for 7 h to 110 g/m^3 (25 000 ppm) vinyl bromide (Torkelson, unpublished report cited in Leong & Torkelson, 1970).

In subacute inhalation studies, rats were exposed to 44 g/m^3 (10 000 ppm) vinyl bromide in air for 7 h a day on five days a week for four weeks; or rats, rabbits and monkeys were exposed to 1.1 or 2.2 g/m^3 (250 or 500 ppm) vinyl bromide for 6 h a day on five days a week for six months. No significant changes were detected in food consumption, haematology, gross pathology or histopathology. Non-volatile bromide levels in the blood increased with duration of exposure in all three species and were proportional to the concentrations of vinyl bromide inhaled (Leong & Torkelson, 1970).

Phenobarbital pretreatment of rats induced acceleration of vinyl bromide debromination in animals exposed to 2% (88 g/m^3; 20 000 ppm) vinyl bromide for 5 h a day, once, twice or for five or 10 consecutive days. Toxic injury to the liver observed during the first two days of exposure was reversed by day 5 (VanStee *et al*., 1977).

Aroclor 1254-pretreated rats exposed by inhalation for 4 h to 44 or 132 g/m^3 (10 000 or 30 000 ppm) vinyl bromide showed increases in serum alanine-α-ketoglutarate transaminase and serum sorbital dehydrogenase. The effect was more pronounced in fasted than in fed rats (Conolly & Jaeger, 1978; Conolly *et al*., 1977).

No data on the embryotoxicity or teratogenicity of this compound were available to the Working Group.

Metabolism

When a mixture of vinyl bromide in air was passed through a mouse-liver microsomal system, a volatile alkylating metabolite was formed, as demonstrated by trapping with 4-(4-nitrobenzyl)pyridine (Barbin *et al*., 1975; Bartsch *et al*., 1976, 1979).

Mutagenicity and other short-term tests

Exposure of *Salmonella typhimurium* TA1530 or TA100 to vapours of vinyl bromide in air caused mutagenic effects. The addition of 9000 × *g* liver supernatant fractions from phenobarbital-pretreated mice or from human liver biopsies enhanced the mutagenicity (Bartsch, 1976; Bartsch *et al*., 1976, 1979).

(b) Humans

No data were available to the Working Group.

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluations[1]

4.1 Experimental data

Vinyl bromide was tested in mice by skin application and by subcutaneous injection. No local tumours were produced.

Vinyl bromide was mutagenic in the only test system used.

A commercial suspension of polymerized vinyl bromide produced no skin tumours in mice when tested by skin application, but local sarcomas were produced following its subcutaneous injection.

4.2 Human data

No case reports or epidemiological studies regarding the carcinogenicity of vinyl bromide were available to the Working Group. The fact that workers are exposed to vinyl bromide indicates that it may be possible to identify occupational groups for epidemiological investigation.

4.3 Evaluation

The limited data from two studies in which vinyl bromide and polymerized vinyl bromide were tested for local (skin and subcutaneous) carcinogenesis in animals and the absence of human data preclude an evaluation of the carcinogenicity of these materials.

[1] Subsequent to the finalization of this evaluation by the Working Group in February 1978, the Secretariat became aware of an inhalation study in progress in male and female Sprague-Dawley rats which were exposed to vinyl bromide at concentrations of 5500, 1100, 220 and 44 mg/m^3 (1250, 250, 50 and 10 ppm) in air. Preliminary unpublished results after 18 months indicated an increase in the incidence of liver angiosarcomas (similar to those produced by vinyl chloride) at the three highest dose levels and an increase in the incidence of Zymbal gland carcinomas at the two highest dose levels (Huntingdon Research Center, 1978; National Institute for Occupational Safety and Health/Occupational Safety and Health Administration, 1978).

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Appendix B: IARC. (1986). *Some Chemicals Used in Plastics and Elastomers.* Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Vol 39. Lyon, France. World Health Organization. pp. 133-145.

VINYL BROMIDE

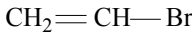
This substance was considered by a previous Working Group, in February 1978 (IARC, 1979). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 593-60-2
Chem. Abstr. Name: Ethene, bromo-
IUPAC Systematic Name: Bromoethylene
Synonym: NCI-C50373

1.2 Structural and molecular formulae and molecular weight



C_2H_3Br Mol. wt: 106.96

1.3 Chemical and physical properties of the pure substance

(a) Description: Gas under normal atmospheric conditions, colourless liquid under pressure; has a characteristic pungent odour (Ethyl Corp., 1980; Hawley, 1981)

(b) Boiling-point: 15.8°C (Weast, 1984)

(c) Melting-point: –139.5°C (Weast, 1984)

(d) Density: d_4^{20} 1.4933 (Weast, 1984); 1.522 at 20°C (Ethyl Corp., 1980)

(e) Spectroscopy data: Infrared (Pouchert, 1981 [56D]), nuclear magnetic resonance (Pouchert, 1983 [86C]) and mass spectral data (NIH/EPA Chemical Information System, 1983) have been reported.

(f) Solubility: Insoluble in water (Sax, 1984); soluble in ethanol, diethyl ether, acetone, benzene and chloroform (Grasselli & Ritchey, 1975; Weast, 1984)

(g) Volatility: Vapour pressure, 895 mm Hg at 20°C (Ramey & Lini, 1971); relative vapour density, 3.7 (Ethyl Corp., 1980)

(h) Stability: Polymerizes rapidly in sunlight (Buckingham, 1982); can react vigorously with oxidizing materials (Sax, 1984)

(i) Conversion factor: $mg/m^3 = 4.37 \times ppm$[a]

1.4 Technical products and impurities

Vinyl bromide is sold commercially in the USA in oxygen-free containers; shipping containers are normally under positive pressure because the vapour pressure of vinyl bromide is so high. In addition to precautions used to minimize contact with oxygen, peroxides and other free-radical initiators that cause polymerization, inhibitors are also added to the product.

Product specifications for polymerization-grade vinyl bromide are as follows: vinyl bromide content, 99.8 wt % min (exclusive of inhibitor); appearance, clear and free of suspended matter; water, 100 mg/kg max; nonvolatile matter (including inhibitor), 500 mg/kg max; inhibitor (hydroquinone methyl ether), 175-225 mg/kg (Ethyl Corp., 1980).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

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

[a] Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg)

Vinyl bromide was first produced in the USA in 1968, and in 1982 production exceeded 2.3 million kg (Benya *et al.*, 1982). At one time, two US firms were known to produce vinyl bromide (US Environmental Protection Agency, 1980), but in 1985 only one US producer was identified. No data were available on the quantities of vinyl bromide produced in 1983. In Japan, two major companies produced vinyl bromide in 1981, but production figures were not available.

(b) Use

Vinyl bromide is used as an intermediate in organic synthesis and in the manufacture of polymers, copolymers, flame retardants, pharmaceuticals and fumigants (Ethyl Corp., 1980).

There has been little interest in the homopolymer of vinyl bromide in view of its thermal and photolytic instability. Vinyl bromide is used primarily in polymers as a flame retardant in the production of modacrylic fibres for carpet-backing material. It has also been used in small quantities as a comonomer with acrylonitrile in the production of fabrics and fabric blends to be used in sleepwear (mostly for children) and home furnishings. It is also copolymerized with vinyl acetate and maleic anhydride to produce granular products. Vinyl bromide-vinyl chloride copolymers are used for preparing films, for laminating fibres and as rubber substitutes (Larsen, 1980). Vinyl bromide is also used in leather and fabricated metal products (National Institute for Occupational Safety and Health, 1978).

(c) Regulatory status and guidelines

Occupational exposure limits for vinyl bromide have been set by six countries by regulation or recommended guideline (Table 1).

The US National Institute for Occupational Safety and Health (1978, 1983) has recommended that exposure to vinyl halides be restricted to the lowest possible level, with the eventual goal of zero exposure.

2.2 Occurrence

(a) Natural occurrence

It is not known whether vinyl bromide occurs as a natural product.

(b) Occupational exposure

On the basis of results from the National Occupational Hazards Survey, a ‘probable estimate’ of 26 000 US workers potentially exposed to vinyl bromide was calculated (National Institute for Occupational Safety and Health, 1978).

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 lab technician to 1.3-2.2 mg/m^3 and two loading crewmen to 5.2 and 27.5 (1-h sample) mg/m^3 (Bales, 1978; Oser, 1980).

Table 1. National occupational exposure limits for vinyl bromide[a]

Country	Year	Concentration ($mg/m^{3)}$	Interpretation[b]
Australia	1978	1100	TWA
Belgium	1978	1100	TWA
Finland	1981	20	TWA
The Netherlands	1978	1100	TWA
UK	1985	20	TWA
USA			
ACGIH	1984	20	TWA
NIOSH	1984	4	TWA
OSHA	1978	4	TWA
		20	Ceiling

[a]From National Institute for Occupational Safety and Health (NIOSH) (1978); International Labour Office (1980); Työsuojeluhallitus (1981); NIOSH (1983); American Conference of Governmental Industrial Hygienists (ACGIH) (1984); Health and Safety Executive (1985)

[b]TWA, time-weighted average

(c) Air

Sampling conducted in and around two communities in Arkansas, USA, where bromine industries were sited led to the identification of vinyl bromide in air, but the actual levels detected were not reported (DeCarlo, 1979).

2.3 Analysis

Selected methods for the analysis of vinyl bromide in air are given in Table 2.

The analytical method of the US National Institute for Occupational Safety and Health for determination of vinyl bromide by gas chromatography/flame ionization detection has been validated over the range 1.3-56 mg/m^3 (Spafford & Dillon, 1981; Taylor, 1981). The estimated limit of detection for vinyl bromide by the gas chromatography/mass spectrometric method developed by Pellizzari *et al.* (1978) for environmental monitoring is 10^3-10^5 lower, although no specific range is given.

Table 2. Methods for the analysis of vinyl bromide in air

Sample preparation	Assay procedure[a]	Limit of detection	Reference
Adsorb (charcoal tube); desorb (ethanol)	GC/FID	1.3 mg/m^3	Spafford & Dillon (1981); Taylor (1981)
Adsorb (charcoal tube); desorb (heat), purge (helium), dry (calcium sulphate tube) and adsorb (Tenax tube); desorb (thermal) and trap (liquid nitrogen); vaporize (heat) onto capillary GC column	GC/MS	8 ng/m^3	Pellizzari *et al.* (1978)
Adsorb (Tenax-GC); desorb (heat), purge (helium), trap (liquid nitrogen cooled nickel capillary); vaporize (heat) directly onto capillary GC column	GC/MS	250 ng/m^3	Pellizzari *et al.* (1978) Krost *et al*. (1982)

[a]Abbreviations: GC/FID, gas chromatography/flame ionization detection; GC/MS, gas chromatography/mass spectrometry

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(a) Skin application

Mouse: A group of 30 female ICR/Ha Swiss mice received topical applications of 15 mg vinyl bromide [purity unspecified] in 0.1 mL acetone thrice weekly for 60 weeks. No skin tumour was observed. In a two-stage skin carcinogenesis study to test for initiating activity, further groups of 30 mice received a single application of vinyl bromide followed by thrice-weekly applications for 60 weeks of 2.5 μg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in 0.1 mL acetone, a single application of 7,12-dimethylbenz[*a*]anthracene followed by treatment with TPA (positive controls), treatment with TPA only, or no treatment at all (160 mice). One of 30 mice treated with vinyl bromide followed by TPA developed a skin papilloma at 412 days; one skin carcinoma occurred among the 30 TPA-treated controls

[1] The Working Group was aware of recently completed studies on repeated subcutaneous injection of vinyl bromide to mice (IARC, 1984).

after 44 days; no skin tumour developed in the 160 untreated controls within 420 days; and the positive-control group showed the expected high number of skin tumours (Van Duuren, 1977). [The Working Group noted that sites other than the skin were not examined, and that the test material was volatile.]

(b) Inhalation exposure

Rat: Groups of 120 male and 120 female Sprague-Dawley rats, nine to ten weeks of age, were exposed to 10, 50, 250 or 1250 ppm (44, 219, 1093 or 5875 mg/m^3) vinyl bromide (purity, 99.9%; 0.02% hydroquinone methyl ether as stabilizer, as well as 0.03% ethylene oxide, 0.0007% acetylene, 0.008% aldehydes and ketones) in air for 6 h per day on five days per week for 104 weeks, at which time they were sacrificed. In the group exposed to 1250 ppm, exposure was terminated at 72 weeks because about 50% of animals had died, and the remainder were sacrificed. A group of 144 male and 144 female rats served as untreated controls. Average survival time was not stated. Treatment-related increases in the incidences of liver angiosarcoma were observed in all treated 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 ($p < 0.001$ for all groups). In addition, increases were observed in the incidences of squamous-cell carcinoma of the Zymbal gland: males, 2/142, 1/99, 1/112, 13/114 ($p < 0.005$) and 35/116 ($p < 0.005$); females, 0/139, 0/99, 3/113, 2/119 and 11/114 ($p < 0.001$), neoplastic nodules and hepatocellular carcinoma: males, 4/143, 5/103, 10/119, 13/120 ($p < 0.025$)and 5/119; females: 7/142, 18/101 ($p < 0.005$),12/113, 21/118 ($p < 0.005$) and 9/112 in treated animals compared to controls (Benya *et al.*, 1982).

(c) Subcutaneous administration

Mouse: A group of 30 female ICR/Ha Swiss mice was injected subcutaneously with 25 mg/animal vinyl bromide in 0.05 mL trioctanoin once weekly for 48 weeks and observed up to 420 days. No local tumour was seen in treated mice, nor in 30 mice given 48 weekly injections of trioctanoin alone, nor in 60 untreated controls observed up to 420 days (Van Duuren, 1977). [The Working Group noted that examination of the animals for pathological lesions was limited to the injection site.]

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD_{50} of vinyl bromide given as a 50% solution in corn oil was approximately 500 mg/kg bw in male rats. No histopathological change was found in rats exposed for 7 h to 110 000 mg/m^3 (25 000 ppm) (Leong & Torkelson, 1970).

In subacute inhalation studies, rats were exposed to 44 000 mg/m^3 (10 000 ppm) vinyl bromide in air for 7 h per day on five days a week for four weeks; and rats, rabbits and monkeys were exposed to 1100 or 2200 mg/m^3 (250 or 500 ppm) vinyl bromide for 6 h a

day on five days a week for six months. No significant change was detected in food consumption, haematology, gross pathology or histopathology (Leong & Torkelson, 1970).

The hepatoxicity of vinyl bromide in rats is enhanced by pretreatment with polychlorinated biphenyls. Aroclor 1254-pretreated rats exposed by inhalation for 4 h to 44 000 mg/m^3 (10 000 ppm) vinyl bromide showed increases in serum alanine-α-ketoglutarate transaminase and serum sorbitol dehydrogenase, and histological signs of liver damage. The enhancement was more pronounced in fasted than in fed rats (Conolly & Jaeger, 1977; Conolly *et al.*, 1978).

Newborn Wistar rats exposed to 8800 mg/m^3 (2000 ppm) vinyl bromide for 8 h per day on five days per week for 8-15 weeks developed ATPase-deficient foci in the liver, but to an extent about ten-fold lower than was seen after similar exposure to vinyl chloride (Bolt *et al.*, 1979, 1982). [See also section 3.1.]

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

Inhalation pharmacokinetics of vinyl bromide have been studied in rats (Filser & Bolt, 1979, 1981; Gargas & Andersen, 1982). The compound was readily taken up by the lung and, at equilibrium, showed an 11-fold accumulation in the entire organism compared to the concentration in the gas phase. Metabolism was saturable at exposure concentrations of over 250 mg/m^3 (55 ppm) (Filser & Bolt, 1979) and was associated with the release of bromide into the plasma (Gargas & Andersen, 1982). Nonvolatile bromide levels in the blood increased with duration of exposure to vinyl bromide in rats, rabbits and monkeys (Leong & Torkelson, 1970).

It was reported in an abstract that pretreatment of rats with phenobarbital accelerated the release of bromide from vinyl bromide in animals exposed to 88 000 mg/m^3 (20 000 ppm) vinyl bromide for 5 h per day, once, twice or for five or ten consecutive days (Van Stee *et al.*, 1977).

When a mixture of vinyl bromide in air was passed through a mouse-liver microsomal system, a volatile alkylating metabolite was formed, as demonstrated by trapping with 4-(4-nitrobenzyl)pyridine (Barbin *et al.*, 1975; Bartsch *et al.*, 1976, 1979). Results of experiments *in vitro* indicate that the primary metabolite formed by mixed-function oxidases from vinyl bromide is 2-bromoethylene oxide, while the rearrangement product of the latter, 2-bromoacetaldehyde, might be the major alkylating agent bound to protein (Guengerich *et al.*, 1981). Irreversible protein binding of metabolites of [1,2-^{14}C]-vinyl bromide has been established both with rat-liver microsomes *in vitro* (Bolt *et al.*, 1978) and in rats *in viv*o (Bolt *et al.*, 1980).

A comparative study using isolated rat hepatocytes and hepatic sinusoidal cells revealed that the metabolism of vinyl bromide to reactive metabolites was confined primarily to hepatocytes (Ottenwälder & Bolt, 1980).

When incubated with liver microsomes from phenobarbital-treated rats, vinyl bromide alkylates the prosthetic group (haem) of cytochrome P-450. The alkylated moiety has been

identified as the dimethyl ester of *N*-(2-oxoethyl)protoporphyrin IX (Ortiz de Montellano *et al.*, 1982).

Incubation of [1,2-^{14}C]-vinyl bromide with rat-liver microsomes and RNA resulted in alkylation of RNA and formation of 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine. The same alkylation products occurred in the hepatic RNA of rats exposed to the radioactive compound (Ottenwälder *et al.*, 1979).

Like other halogenated C_1 and C_2 compounds that are transformed to reactive metabolites, vinyl bromide alters rat intermediary metabolism, leading to increased exhalation of acetone (Filser *et al.*, 1982).

Exposure of rats to 87 400 mg/m^3 (20 000 ppm) vinyl bromide for 4 h per day for ten days caused a decrease in hepatic cytochrome P-450 (Drew *et al.*, 1976).

Mutagenicity and other short-term tests

Vinyl bromide (0.2-20% v/v in air for various time periods) was mutagenic to *Salmonella typhimurium* TA1530 and TA100 in the presence or absence of a metabolic system (S9) from the liver of Aroclor-induced rats or phenobarbital-induced mice or humans (Bartsch, 1976; Bartsch *et al.*, 1976 (Abstract), 1979; Lijinsky & Andrews, 1980).

(b) Humans

Toxic effects

Short-term inhalation of high concentrations of vinyl bromide [levels not given] is reported to cause loss of consciousness. Skin and eye contact with liquid vinyl bromide produced irritation and caused a 'frost-bite' type of burn (Fawcett, 1976; Benya *et al.*, 1982).

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

No data were available to the Working Group.

Mutagenicity and chromosomal effects

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Vinyl bromide has been available commercially since 1968. Occupational exposure may occur during the production of vinyl bromide and its polymers.

4.2 Experimental data

Vinyl bromide was tested in female mice by skin application and by subcutaneous injection, and in rats by inhalation exposure. In the inhalation study in rats, there was a dose-related increase in the incidence of liver angiosarcomas and Zymbal gland carcinomas; an increased incidence of liver neoplastic nodules and hepatocellular carcinoma was also noted. In the limited studies in mice by skin application and subcutaneous administration, no local tumour was observed.

No data were available to evaluate the reproductive or prenatal toxicity of vinyl bromide to experimental animals.

Vinyl bromide was mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system.

Overall assessment of data from short-term tests: Vinyl bromide[a]

	Genetic activity			Cell transformation
	DNA Damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				
Degree of evidence in short-term tests for genetic activity: **Inadequate**				Cell transformation: No data

[a]The groups into which the table is divided and the symbols '+', '–'and '?'are defined in the Preamble; the degrees of evidence are also defined.

4.3 Human data

No data were available to evaluate the reproductive effects or prenatal toxicity of vinyl bromide to humans.

No case report or epidemiological study was available to evaluate the carcinogenicity of vinyl bromide to humans.

4.4 Evaluation[1]

There is *sufficient evidence*[2] for the carcinogenicity of vinyl bromide to experimental animals.

No data on humans were available.

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[1] For definition of the italicized term, see Preamble.

[2] In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they represented a carcinogenic risk to humans.

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Table 1. (contd)

Agent	Degree of evidence for carcinogenicity[a]		Overall evaluation[a]
	Human	Animal	
Treosulphan	S	ND	1
Trichlorfon[b] [*30*, 1983]	ND	I	3
1,1,1-Trichloroethane[b] [*20*, 1979]	ND	I	3
1,1,2-Trichloroethane[b] [*20*, 1979]	ND	L	3
Trichloroethylene	I	L	3
Trichlorotriethylamine hydrochloride[d] [*9*, 1975]	ND	I	3
T_2-Trichothecene[b] [*31*, 1983]	ND	I	3
Triethylene glycol diglycidyl ether[d] [*11*, 1976]	ND	L	3
2,4,5-Trimethylaniline[b] [*27*, 1982]	ND	L	3
2,4,6-Trimethylaniline[b] [*27*, 1982]	ND	I	3
4,5′,8-Trimethylpsoralen	I	I	3
Triphenylene[b] [*32*, 1983]	ND	I	3
Tris(aziridinyl)-*para*-benzoquinone (Triaziquone)	I	L	3
Tris(l-aziridinyl)phosphine oxide[d] [*9*, 1975]	ND	I	3
Tris(l-aziridinyl)phosphine sulphide (Thiotepa)[e]	I	S	2A
2,4,6-Tris(l-aziridinyl)-s-triazine[d] [*9*, 1975]	ND	L	3
1,2,3-Tris(chloromethoxy)propane[d] [*15*, 1977]	ND	L	3
Tris(2,3-dibromopropyl) phosphate[e]	I	S	2A
Tris(2-methyl-1-aziridinyl)phosphine oxide[d] [*9*, 1975]	ND	I	3
Trp-P-1 (3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole)[b] [31, 1983]	ND	S	2B
Trp-P-2 (3-Amino-l-methyl-5*H*-pyrido[4,3-*b*]indole)[b] [*31*, 1983]	ND	S	2B
Trypan blue[b] [*8*, 1975]	ND	S	2B
Uracil mustard	I	S	2B
Urethane[b] [*7*, 1974]	ND	S	2B
Vinblastine sulphate	I	I	3
Vincristine sulphate	I	I	3
Vinyl acetate[b] [*39*, 1986]	ND	I	3
Vinyl bromide[b,e] [39, 1986]	ND	S	2A
Vinyl chloride	S	S	1
Vinyl chloride-vinyl acetate copolymers[d] [*19*, 1979]	ND	I	3
4-Vinylcyclohexene[b] [*39*, 1986]	ND	L	3
Vinyl fluoride[b] [*39*, 1986]	ND	ND	3
Vinylidene chloride	I	L	3
Vinylidene chloride-vinyl chloride copolymers[d] [*19*, 1979]	ND	ND	3
Vinylidene fluoride[b] [*39*, 1986]	ND	I	3
N-Vinyl-2-pyrrolidone[d] [*19*, 1979]	ND	ND	3

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VINYL BROMIDE

Data were last reviewed in IARC (1986) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

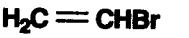
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 593-60-2
Chem. Abstr. Name: Bromoethene
IUPAC Systematic Name: Bromoethylene

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_2H_3Br Relative molecular mass: 106.96

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless gas with a characteristic pungent odour; colourless liquid under pressure (American Conference of Governmental Industrial Hygienists, 1992)

(*b*) *Boiling-point*: 15.8°C (Lide, 1997)

(*c*) *Melting-point*: –137.8°C (Lide, 1997)

(*d*) *Density*: 1.522 at 20°C (Lide, 1997)

(*e*) *Solubility*: Insoluble in water; soluble in acetone, benzene, chloroform and ethanol; very soluble in diethyl ether (American Conference of Governmental Industrial Hygienists, 1992; Lide, 1997)

(*f*) *Vapour pressure*: 119 kPa at 20°C; relative vapour density, 3.7 (American Conference of Governmental Industrial Hygienists, 1992)

(*g*) *Explosive limits*: Upper, 15%; lower, 9% by volume (United States National Library of Medicine, 1998a)

(*h*) *Conversion factor*: $mg/m^3 = 4.37 \times ppm$

1.2 Production and use

Information available in 1995 indicated that vinyl bromide was produced in three countries (Germany, Japan and the United States) (Chemical Information Services, Inc., 1995).

Vinyl bromide has been used as an intermediate in organic synthesis and in the manufacture of polymers, copolymers, flame retardants, pharmaceuticals and fumigants (American Conference of Governmental Industrial Hygienists, 1992).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997; United States National Library of Medicine, 1998b), approximately 1822 workers in the United States were potentially exposed to vinyl bromide (see General Remarks).

1.3.2 *Environmental occurrence*

Vinyl bromide may form in air as a degradation product of 1,2-dibromoethane. It may also be released to the environment from facilities which manufacture or use vinyl bromide as a flame retardant for acrylic fibres. Vinyl bromide has been qualitatively identified in ambient air samples (United States National Library of Medicine, 1998a)

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 22 mg/m^3 as the 8-h time-weighted average threshold limit value, with an animal carcinogen notation, for occupational exposures to vinyl bromide in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for vinyl bromide in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Vinyl bromide was tested for carcinogenicity in female mice by skin application and by subcutaneous injection, and in rats by inhalation exposure. In the inhalation study in rats, there was a dose-related increase in the incidence of liver angiosarcomas and Zymbal gland carcinomas; an increased incidence of liver neoplastic nodules and hepatocellular carcinoma was also noted. In the limited studies in mice by skin application and subcutaneous administration, no local tumour was observed (IARC, 1986).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

Vinyl bromide is readily absorbed upon inhalation by rats and showed an 11-fold accumulation within the rats compared with the concentration in gaseous phase. Metabolism is saturable at exposure concentrations greater than 250 mg/m^3. Following inhalation of vinyl bromide by rats, rabbits and monkeys, plasma levels of nonvolatile bromide increased with exposure duration, and more rapidly in phenobarbital-pretreated rats.

A volatile alkylating metabolite was formed in a mouse-liver microsomal system. The primary metabolite formed *in vitro* by mixed function oxidases is 2-bromoethylene oxide, which rearranges to 2-bromoacetaldehyde.

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 both with rat-liver microsomes *in vitro* and in rats in *vivo*. They can also alkylate the cytochrome P450 prosthetic group of phenobarbital-treated rat-liver microsomes. Exposure of rats to vinyl bromide causes a decrease in hepatic cytochrome P450 (IARC, 1986).

4.2 Toxic effects

4.2.1 *Humans*

Vinyl bromide inhalation is reported to cause loss of consciousness. It is a skin and eye irritant and causes a 'frost-bite' type of burn (IARC, 1986).

4.2.2 *Experimental systems*

Subacute inhalation studies performed with rats, rabbits and monkeys showed no significant haematological, gross pathological or histopathological change. Vinyl bromide is far less hepatotoxic than vinyl chloride in rats. However, its hepatotoxicity is enhanced in rats pretreated with polychlorinated biphenyls, as demonstrated by enzymatic and histological signs of liver damage. Like other halogenated compounds transformed to reactive metabolites, vinyl bromide alters rat intermediary metabolism, leading to acetone exhalation (IARC, 1986).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects (see Table 1 for references)

Vinyl bromide is mutagenic to *Salmonella typhimurium* and induced somatic mutations in *Drosophila melanogaster*. It is considered that vinyl bromide reacts with DNA to form various etheno-adducts which are the same as those formed by vinyl chloride (Bolt *et al.*, 1986).

Table 1. Genetic and related effects of vinyl bromide

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAF, *Salmonella typhimurium* BA13/BAL13, forward mutation, arabinoside resistance	+	+	15190	Roldán-Arjona *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1% in air	Lijinsky & Andrews (1980)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	+	+	0.2% in air	Bartsch *et al.* (1979)
DMM, *Drosophila melanogaster*, somatic mutation (*white/white*$^+$)	+		4000 ppm in air	Vogel & Nivard (1993)
DMM, *Drosophila melanogaster*, somatic mutation (*white/white*$^+$)	+		2000 ppm in air	Rodriguez-Arnaiz *et al.* (1993)

[a] +, positive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Occupational exposure may occur during the production of vinyl bromide and its polymers.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Vinyl bromide was tested in female mice by skin application and by subcutaneous injection, and in rats by inhalation exposure. In the inhalation study in rats, there was a dose-related increase in the incidence of liver angiosarcomas and Zymbal gland carcinomas; an increased incidence of liver neoplastic nodules and hepatocellular carcinoma was also noted.

5.4 Other relevant data

Vinyl bromide was mutagenic to *Salmonella typhimurium* and *Drosophila melanogaster*.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of vinyl bromide were available.

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

Overall evaluation

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

In making the overall evaluation, the Working Group took into consideration 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 P450-dependent pathway to their corresponding epoxides. For both vinyl chloride and vinyl bromide, the covalent binding of these compounds to DNA forms the respective 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.

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VINYL CHLORIDE, POLYVINYL CHLORIDE and VINYL CHLORIDE-VINYL ACETATE COPOLYMERS

Vinyl chloride

This substance was considered by a previous IARC Working Group, in June 1974 (IARC, 1974). Since that time new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.

A literature compilation (Warren *et al.*, 1978) and a review (Milby, 1977) are available.

1. Chemical and Physical Data

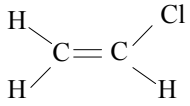
1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 75-01-4

Chem. Abstr. Name: Chloroethene

Chloroethylene; monochloroethylene; VC; VCM; Vinyl C monomer

1.2 Structural and molecular formulae and molecular weight



C_2H_3C1 Mol. wt: 62.5

1.3 Chemical and physical properties of the pure substance

From Weast (1976), unless otherwise specified

(a) Description: Colourless gas (Windholz, 1976)

(b) Boiling-point: –13.37°C

(c) Melting-point: –153.8°C

(d) Density: d_4^{20} 0.9106; vapour density, 2.2 (air = 1) (Anon., 1972)

(e) Refractive index: n_D^{20} 1.3700

(f) Spectrosocpy data: Infrared, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(g) Solubility: Slightly soluble in water (0.11 g/100 g at 25°C) (Hardie, 1964); soluble in ethanol; very soluble in ether, carbon tetrachloride and benzene

(h) Volatility: Vapour pressure is 2530 mm at 20°C (Hardie, 1964)

(i) Stability: Flash-point, –78˚ C (closed cup) (Hardie, 1964); polymerizes in light or in the presence of a catalyst (Windholz, 1976); on combustion it degrades to hydrogen chloride, carbon monoxide, carbon dioxide and traces of phosgene (O'Mara *et al*., 1971)

(j) Reactivity: On treatment with strong alkalis at high temperatures it loses hydrogen chloride (Miller, 1969).

(k) Conversion factor: 1 ppm in air = 2.6 mg/m^3

1.4 Technical products and impurities

Vinyl chloride is generally supplied as a liquid under pressure. Usually no inhibitor is added when it is to be shipped within the US. A typical analysis of a commercial US grade is as follows: water, 50 mg/kg (ppm); nonvolatile residue, 5 mg/kg (ppm); acetaldehyde, < 1 mg/kg (ppm); acetylene, < 1 mg/kg (ppm); iron, 0.1 mg/kg (ppm); hydrogen chloride, < 0.1 mg/kg (ppm); and hydrogen peroxide, 0.01 mg/kg (ppm).

In Japan, commercial vinyl chloride meets the following specifications: purity, 99.9% min; water, 200 mg/kg (ppm) max; hydrogen chloride, 1 mg/kg (ppm) max; iron, 1 mg/kg (ppm) max; and evaporation residue, 50 mg/kg (ppm) max. Chlorinated hydrocarbons may be present as impurities.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

The first synthesis of vinyl chloride appears to have been made in 1835 (Regnault, 1835). Addition of hydrogen chloride to acetylene, formerly the most

important route of synthesis, has been displaced by the halogenation of ethylene; over 95% of the vinyl chloride monomer produced in the USA and Japan in 1976 was made from ethylene. In this process, ethylene is reacted with hydrogen chloride and oxygen to give ethylene dichloride, which is subsequently cracked to produce vinyl chloride and hydrogen chloride.

Vinyl chloride has been produced commercially in the USA for over 50 years (US Tariff Commission, 1928). In 1976, nine companies reported the production of 2580 million kg (US International Trade Commission, 1977). US imports have been negligible; exports amounted to 291 million kg in 1976 (US Department of Commerce, 1977), and in 1977, exports were about 150 million kg to the following countries (% of total): Brazil (28), Canada (8), Colombia (11), Mexico (14), Norway (12) and Yugoslavia (14).

Total western European production in 1976 amounted to 3925 million kg, in the following countries (millions of kg): Belgium (490), the Federal Republic of Germany (990), Finland (25), France (620), Greece (25), Italy (690), The Netherlands (340), Spain (190), Sweden (95), Switzerland (30) and the United Kingdom (430). Exports from western Europe in that year were 44 million kg.

In Japan, commercial production of vinyl chloride began prior to 1946. In 1976, eighteen companies produced a total of 1281 million kg vinyl chloride; 115 million kg were exported.

(b) Use

About 96% of the 2274 million kg vinyl chloride used in the USA in 1976 was for the production of vinyl chloride homopolymer and copolymer resins. The remainder was used (essentially by one company internally) in the production of methyl chloroform and as a comonomer with vinylidene chloride in the production of resins. For a detailed description of the uses of vinylidene chloride-vinyl chloride copolymers, see p. 450.

The largest use for polyvinyl chloride resins is in the production of plastic piping and conduit. Other important uses are in floor coverings, in consumer goods, in electrical applications and in transport applications. For detailed descriptions of the uses of polyvinyl chloride and vinyl chloride-vinyl acetate copolymers, see pp. 406 and 414.

Hardie (1964) reported that vinyl chloride has been used as a refrigerant, as an extraction solvent for heat-sensitive materials and in the production of chloroacetaldehyde (an intermediate in the synthesis of sulphonamides); however no evidence was found that vinyl chloride is presently being used for these purposes.

Limited quantities of vinyl chloride were used in the USA as an aerosol propellant, but in 1974 it was banned from use in pesticide aerosol products (US Environmental Protection Agency, 1974a), in self-pressurized household containers,

and as an ingredient of drug and cosmetic products (US Consumer Product Safety Commission, 1974a,b).

Vinyl chloride was used in western Europe in 1977 in the production of polyvinyl chloride (95%) and for other uses, including the production of methyl chloroform (5%).

In Japan in 1976, vinyl chloride was used in the production of polyvinyl chloride (92–94%) and for other uses, such as in copolymers (6-8%).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employees's exposure to vinyl chloride not exceed an 8-h time-weighted average of 2.6 mg/m^3 (1 ppm) in the workplace air in any 8-h work shift of a 40-h work week. During any work shift an employee's exposure may not exceed a ceiling concentration limit of 13 mg/m^3 (5 ppm), averaged over any period of 15 min or less (US Occupational Safety and Health Administration, 1974).

The work environment hygiene standards for exposure to vinyl chloride in various countries, in terms of time-weighted averages (8-h) and ceiling concentrations (10- or 15-min), were as follows in 1977: Canada, 10 ppm (8-h) and 25 ppm (15-min); Finland, 5 ppm (8-h) and 10 ppm (10-min); Italy, 50 ppm (8-h), although this is expected to change to 25 ppm (8-h); Japan, expected to be 10 ppm; The Netherlands, 10 ppm (8-h); Norway, 1 ppm (8-h) and 5 ppm (15-min); Sweden, 1 ppm (8-h) and 5 ppm (15-min); USSR, 12 ppm (Bertram, 1977). In France, the standards were reported to be 5 ppm for one week, with a ceiling concentration of 15 ppm, in already existing factories, and 1 ppm and 5 ppm, respectively, for new factories; in Spain, no limits; in Denmark, 1 ppm (8-h); in Belgium, 5 ppm (one week), ceiling 15 ppm; in the Federal Republic of Germany, the same as for France in existing factories, and 2 ppm (one year) and ceiling 15 ppm (1-h) for new factories; in the United Kingdom, 10 ppm (8-h), ceiling 30 ppm max; and in Switzerland, 10 ppm (one week, 8-h day for five days) (Thomas, 1977).

In August 1977, the proposed European value was 3 ppm over one year for existing and future plants, with an 'alarm-value' of 15 ppm (Commission of the European Communities, 1977a).

The US Environmental Protection Agency has proposed new rules to reduce the national emission standard for vinyl chloride from 10 ppm to 5 ppm in order to reduce vinyl chloride emissions by one-half within three years of the actual rulemaking. This would result in hourly emissions (based on new average-sized plants) of 5.1 kg from an ethylene dichloride-vinyl chloride plant (instead of 10.3 kg); 9 kg from a dispersion process polyvinyl chloride plant (instead of 17.5 kg); and 13.5 kg from a suspension process polyvinyl chloride resin plant (instead of 16 kg) (US Environmental Protection Agency, 1977).

In the Federal Republic of Germany, the emission in the environment is limited to 3 kg/h/source or 150 mg/m^3/source, with a ground level of 0.3 mg/m^3 (99% confidence) in inhabited areas (Thomas, 1977).

The Commission of the European Communities has adopted a level of 1 mg/kg (1 ppm) as the amount of vinyl chloride which can be present in packaging and 0.01 mg/kg (ppm) in foodstuffs packed in polyvinyl chloride (Commission of the European Communities, 1977b, 1978). A maximum migration level of 0.05 mg/kg has been adopted in Belgium, Denmark, the Federal Republic of Germany, France, Italy, The Netherlands, Spain and Sweden (Thomas, 1977).

2.2 Occurrence

Vinyl chloride is not known to occur as a natural product.

The occurrence of vinyl chloride in ambient air near vinyl chloride and polyvinyl chloride plants, in water, and in food has been reviewed (US Environmental Protection Agency, 1975a,b).

(a) Occupational exposure

The air concentration of vinyl chloride in a polymerization reactor prior to ventilation is of the order of 7800 mg/m^3 (3000 ppm); during the scraping procedure, 130–260 mg/m^3 (50–100 ppm); and that close to the hands during scraping, 1560–2600 mg/m^3 (600–1000 ppm) (Cook *et al*., 1971). Between 1950 and 1959, concentrations up to 10.4 g/m^3 (4000 ppm) were found in one factory near the polymerization reactors (Ott *et al*., 1975). Air concentrations of vinyl chloride in working places in polyvinyl chloride-producing factories have been reported variously to range from 100–800 mg/m^3 (40–312 ppm), with peaks up to 87.3 g/m^3 (33 500 ppm) (Filatova & Gronsberg, 1957); from 112–556 mg/m^3 (43–214 ppm) (Anghelescu *et al*., 1969); and > 195 mg/m^3 (> 75 ppm) in a Yugoslav plant (Orusev *et al*., 1976). In a Russian synthetic leather plant, < 113.6 mg/m^3 (44 ppm) (Bol'shakov, 1969) and in three British cable factories, 0.4–0.9 mg/m^3 (0.15–0.35 ppm) (Murdoch & Hammond, 1977) were detected. In 1974, it was estimated that 20 000 US workers, past and present, had been exposed to vinyl chloride in manufacturing plants (Heath *et al*., 1975).

On a time-weighted average, the concentration of vinyl chloride monomer to which coagulator operators are exposed ranges from 130–650 mg/m^3 (50–250 ppm) (Baretta *et al*., 1969). However, in a more recent survey for the US National Institute for Occupational Safety and Health of three vinyl chloride plants it was reported that the time-weighted average exposure to vinyl chloride ranged from 0.2–70 mg/m^3 (0.07–27 ppm) (Milby, 1977). Barnhart *et al*. (1975) found < 0.03–15 mg/m^3 (< 0.01–5.89 ppm), 0.03–220 mg/m^3 (0.01–84.77 ppm) and 0.05–57 mg/m^3 (0.02–21.8 ppm) in three vinyl chloride plants in the USA.

In 1974, it was reported that polyvinyl chloride leaving certain manufacturing plants may have contained 200–400 mg/kg (ppm) vinyl chloride monomer; on

delivery to the customer, this level was about 250 mg/kg (ppm); and after processing, levels of 0.5–20 mg/kg (ppm) were reached, depending on the method of fabrication (Anon., 1974). Wilkinson *et al*. (1964) found 100 mg/kg (ppm) residual vinyl chloride monomer in polyvinyl chloride dispersions. However, new processing methods leave as little as 1-2 mg/kg (ppm) residual vinyl chloride in vinyl chloride resins (US Food and Drug Administration, 1975). Residual vinyl chloride in commercial food grade resins has been reduced by processing and stripping techniques to 115 μg/kg (ppb) for resin, less than 0.048 μg/kg (ppb) for compound and less than 0.043 μg/kg (ppb) for sheet polyvinyl chloride (Saggese *et al*., 1976). Industrial grade polyvinyl chloride-coated films used for food packaging were found to contain 5–71 μg/kg (ppb) of monomer (Gilbert *et al*., 1975) and plastic bottles up to 7.9 mg/kg (ppm) (Breder *et al*., 1975).

(b) Air

It has been estimated that prior to 1975 vinyl chloride emissions from US polyvinyl chloride plants amounted to 110 million kg/year (US Environmental Protection Agency, 1975b) and that the average concentration of vinyl chloride in air around these plants was 44 μg/m^3 (17 ppb) (US Environmental Protection Agency, 1976). Vinyl chloride has been determined in the air in the Houston, TX, area (where an estimated 40% of the US production capacity is located) in concentrations of 8 μg/m^3–3.2 mg/m^3 (3.1–1250 ppb) (Gordon & Meeks, 1977) and in the ambient air near two vinyl chloride plants in the Long Beach, CA, area in concentrations of 0.26–8.8 mg/m^3 (0.1–3.4 ppm) (National Field Investigations Center, 1974). It has also been detected in the air in Delaware City, DE, in maximum concentrations of 3.9 mg/m^3 (1.5 ppm) with a mean of 2 mg/m^3 (0.8 ppm) (Lillian *et al*., 1975).

(c) Water

Vinyl chloride has been detected in effluent discharged by chemical and latex manufacturing plants and in raw water in the USA (Shackelford & Keith, 1976). The highest concentration of vinyl chloride detected in finished drinking-water in the USA was 10.0 μg/L (Safe Drinking Water Committee, 1977; US Environmental Protection Agency, 1975a).

In 1974, it was estimated that about 12.3 kg/day vinyl chloride were discharged in the waste-water effluent from two vinyl chloride plants in the Long Beach, California, area (National Field Investigations Center, 1974).

(d) Food

In May 1973, a branch of the US Treasury Department banned the use of polyvinyl chloride for the packaging of alcoholic beverages (Anon., 1973a), as a result of studies reported by the US Food and Drug Administration indicating that up to 20 mg/kg (ppm) vinyl chloride monomer were present in alcoholic beverages packaged in this material (Anon., 1973b). Vinyl chloride has been found in a variety of alcoholic drinks at levels of 0–2.1 mg/kg (ppm) (Williams, 1976a,b; Williams &

Miles, 1975) and in vinegars at levels of up to 9.4 mg/kg (ppm) (Williams & Miles, 1975).

It has been found in edible oils, in concentrations of 0.05–14.8 mg/kg (ppm) (Roesli *et al*., 1975; Williams, 1976a; Williams & Miles, 1975), and in butter and margarine, in concentrations of 0.05 mg/kg (ppm) (Fuchs *et al*., 1975), when these products were packaged and stored in polyvinyl chloride containers.

(e) Other

Vinyl chloride has been found in 2/7 new automobile interiors in concentrations of 1–3 mg/m^3 (0.4–1.2 ppm) (Hedley *et al*., 1976). In another study (Going, 1976), no concentrations above 10 ppb were found in 16 new or used automobiles or in four new or old mobile homes.

Vinyl chloride has been detected in domestic and foreign cigarettes and little cigars, in concentrations of 5.6–27 ng/cigarette, and in a marijuana cigarette at a level of 5.4 ng/cigarette (Hoffmann *et al*., 1976).

2.3 Analysis

A comprehensive critical review, containing over 100 references, of methods of sampling and analysis of vinyl chloride in the workplace atmosphere, ambient air, water, food, cigarette smoke and polyvinyl chloride is available (Egan *et al*., 1979). Methods of collection and analysis of vinyl chloride have also been reviewed (US Environmental Protection Agency, 1975b). A review of methods used to determine vinyl chloride in air, water, and water piping is available (Laramy, 1977).

A gas chromatographic method of analysis has been accepted by the US National Institute for Occupational Safety and Health for determining vinyl chloride in the workplace atmosphere, in the range of 0.008–5.2 mg/m^3 in 5-L air sample (National Institute for Occupational Safety and Health, 1977).

A gas chromatographic analytical method has been proposed by the Commission of the European Communities for determining vinyl chloride in foodstuffs and in vinyl chloride polymers and copolymers intended to come into contact with food (Commission of the European Communities, 1977b).

An official analytical method has been drafted in the Federal Republic of Germany for determining residual vinyl chloride in polyvinyl chloride. It is based on treatment of the polymer with *N,N*-dimethylacetamide, followed by gas chromatographic analysis of the solution with flame-ionization detection and has a limit of detection of 0.5 mg/kg (ppm) (Deutsche Industrie Normen Ausschuss, 1977).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1, 2]

(a) Oral administration

Rat: Groups of 40 male and 40 female 13-week-old Sprague-Dawley rats received gastric intubations of 0, 3.33, 16.65 or 50 mg/kg bw vinyl chloride dissolved in olive oil four to five times a week for 52 weeks. After 85 weeks from the initial treatment, 35, 39, 32 and 23 animals were still alive. At 120 weeks, nine liver angiosarcomas, two Zymbal gland carcinomas and three nephroblastomas occurred in rats administered the 16.65 mg/kg bw dose; and 16 liver angiosarcomas, two nephroblastomas, one Zymbal gland carcinoma, and one thymic and one intra-abdominal angiosarcoma were found in the 50 mg/kg bw group. One intra-abdominal angiosarcoma was seen in the low-dose group, and one Zymbal gland tumour occurred in the control group (Maltoni, 1977a; Maltoni *et al*., 1975).

(b) Inhalation and/or intratracheal administration

Mouse: Groups of 30 male and 30 female 11-week-old Swiss mice were exposed to concentrations of 130–26 000 mg/m^3 (50, 250, 500, 2500, 6000 or 10 000 ppm) vinyl chloride in air for 4 h per day on five days a week for 30 weeks. A total of 344 mice (176 males and 168 females) died within 61 weeks. At 81 weeks (end of experiment), 176 animals (3.5, 57, 66, 57, 70 and 70% in the different groups, respectively) had adenomas and/or adenocarcinomas of the lung, 60 animals (33, 32, 24, 30, 28 and 47%, respectively) had mammary adenocarcinomas and 47 animals (2, 19, 19, 20, 5 and 16%, respectively) had angiosarcomas of the liver. Except for lung tumours, which were not increased in the group treated with 50 ppm, a significantly higher number of neoplasms occurred in all treated groups. In 80 male and 70 female untreated controls, eight pulmonary tumours and three lymphomas were observed (Maltoni, 1977; Maltoni *et al*., 1974).

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[1] The Working Group was aware of studies in progress to assess the carcinogenicity of vinyl chloride in rats by administration in the drinking-water and by administration in the diet, and of complete but unpublished studies by inhalation in rats (IARC, 1978a).

[2] In all his experiments, Maltoni used vinyl chloride that contained the following impurities (mg/kg): water, l00; acetic aldehyde, 5; acetylene, 2; allene, 5; butane, 8; 1,3-butadiene, 10; chloroprene (see also, p. 131), 10; diacetylene, 4; vinyl acetylene, 10; propyne, 3; methyl chloride, 100.

Groups of 100 male and 100 female CDI Swiss/ChR mice (age unspecified) were exposed to 130, 520 or 6500 mg/m^3 (50, 200 or 2500 ppm) vinyl chloride in air (purity unspecified) for 7 h per day on five days a week for nine months and were observed for an additional nine months. After eight months' exposure, 49 treated animals died with tumours. A total of 42 pulmonary adenomas, 41 liver angiosarcomas and 11 mammary gland adenocarcinomas were observed (histological evaluation was carried out on grossly visible tumours only). A dose-related carcinogenic effect was evident (see Table 1). At 8 months, no tumours were observed in 200 controls (100 females and 100 males). The study was still in progress at the time of reporting (Keplinger *et al*., 1975).

Table 1

Incidence of tumours in mice exposed to vinyl chloride (purity unspecified) for 8 months[1]

Exposed groups	No. of mice with tumours at death			Type and location of tumour		
				Adenomas	Angiosar-comas	Adenocar-cinomas
	Male	Female	Total	lung	liver	mammary gland
50 ppm	1	3	4	2	2	2
200 ppm	3	12	15	12	11	3
2500 ppm	6	24	30	28	28	6
Control	0	0	0	0	0	0

[1]From Keplinger *et al*. (1975), preliminary results

Two groups each of 12 male and 12 female three-month-old NMRI outbred albino mice were exposed to either 130 or 1300 mg/m^3 (50 or 500 ppm) vinyl chloride in air for 6 h per day on five days a week. The 500 ppm group was exposed for 26 weeks only (due to the poor condition of the mice); the 50 ppm group was exposed for 52 weeks, at which time the experiment was terminated. In the low-dose group, 18/24 animals had developed tumours, including pulmonary adenomas in 13/24, angiosarcomas at various sites in 15/24 and a mammary carcinoma in 1 mouse. Inhalation of 500 ppm vinyl chloride for 26 weeks induced pulmonary adenomas in all mice; in addition, eight mice had angiosarcomas, mammary adenocarcinomas were found in four animals, one mouse had an angiosarcoma of the liver, one an adenoma of the kidney and one an angiosarcoma of brown fat. In the control group, 3/48 had tumours: one adenocarcinoma of the mammary gland, one dysgerminoma of the ovary and one reticulum-cell sarcoma of the spleen (Holmberg *et al*., 1976).

Groups of 36 male and 36 female two-month-old albino CD mice were exposed to 130, 650 and 2600 mg/m^3 (50, 250 and 1000 ppm) vinyl chloride (99.8% pure) in air for 6 h per day on five days a week for 52 weeks; at that time, 70, 52, 46 and 38 animals were still alive, respectively. A total of 12, 22 and 48 mice developed lung adenomas in the exposed groups, respectively; 1 lung adenoma was found in untreated control animals. In addition, angiosarcomas of the liver developed in 3, 23 and 31 treated mice, respectively, and angiosarcomas in other organs in 7, 5 and 9 mice. Mammary gland tumours were found in 9, 3 and 13 mice, respectively; most of these tumours metastasized to the lungs (Lee *et al*., 1977, 1978).

Rat: A group of 26 male three-month-old Ar/IRE Wistar rats were exposed to an atmospheric concentration of 3% v/v (equivalent to 78 g/m^3 or 30 000 ppm) commercial grade vinyl chloride (99% pure) for 4 h per day on five days a week for 12 months; the experiment was terminated at 54 weeks. Skin tumours developed in the submaxillary parotid region in all 17 surviving rats (14 epidermoid carcinomas, two mucoepidermoid carcinomas, one papilloma); in addition, lung tumours developed in seven rats and osteochondromas in five. No tumours were observed in 25 untreated controls killed at an unstated time (Viola *et al*., 1971) [Maltoni & Lefemine (1974) examined slides from this experiment and concluded that the skin tumours were Zymbal gland tumours and that the lung tumours were metastases from these].

Groups of 30 male and 30 female 21-week-old Sprague-Dawley rats were exposed by inhalation to 130–26 000 mg/m^3 (50, 250, 500, 2500, 6000 or 10 000 ppm) vinyl chloride in air for 4 h per day on five days a week for 17 weeks. At 86 weeks, 18, 15, 37, 33, 16 and 9 animals were still alive in the six groups. At 155 weeks (end of experiment), carcinomas of the Zymbal gland were found in 0, 1, 1, 3, 6 and 7 animals, respectively (1 in untreated controls), nephroblastomas in 1, 2, 0, 2, 1 and 1 animals, liver angiosarcomas in 0, 0, 1, 1, 1 and 0 animals and angiosarcomas at other sites in 2, 0, 1, 2, 1 and 1 (1 in controls). Brain neuroblastomas were seen in 0, 0, 0, 2, 2 and 6 animals, respectively (Maltoni, 1977a; Maltoni *et al*., 1974).

Groups of 64-96 13-week-old Sprague-Dawley rats were also treated for 52 weeks with the above concentrations of vinyl chloride in air. The following tumours developed in various organs by the end of the experiment, at 135 weeks: carcinomas of the Zymbal gland in 29/239 rats at the four highest dose levels, and nephroblastomas (26/257 rats) and angiosarcomas of the liver (47/357 rats) in all the treated groups (the numbers of rats given were those alive at 26 weeks); a total of 14 angiosarcomas was observed in organs other than the liver. The tumours of the liver and kidney metastasized to other organs. No such tumours were observed in 58 untreated controls alive at 26 weeks (see Table 2). In a group of 60 17-week-old Sprague-Dawley rats treated with 78 g/m^3 (30 000 ppm) vinyl chloride in air for 4 h per day on five days a week for 43 weeks, 30 (50%) developed Zymbal gland carcinomas, 13, liver angiosarcomas and one, a lung angiosarcoma within the 61 weeks of observation (Maltoni *et al*., 1974).

Table II[1]

Incidence of tumours in Sprague-Dawley rats exposed to vinyl chloride for 4 h per day on five days per week for 52 weeks and surviving up to 130 weeks

Concentration of vinyl chloride (ppm)	Total no. of animals at start	No. of animals alive at 26 weeks	No. of Zymbal gland tumours	No. of nephro-blastomas	No. of angio-sarcomas of the liver	No. of angio-sarcomas at other sites	No. of brain neuro-blastomas	No. of other tumours
10 000	69	61	16	5	9	3	7	11
6000	72	60	7	4	13	3	3	10
2500	74	59	2	6	13	3	5	7
500	67	59	4	4	7	2	0	8
250	67	59	0	6	4	2	0	7
50	64	59	0	1	1	1	0	10
Controls	68	58	0	0	0	0	0	10

[1]From Maltoni *et al*. (1974)

Wistar rats were also exposed by inhalation to 130–26 000 mg/m^3 (50, 250, 500, 2500, 6000 and 10 000 ppm) vinyl chloride in air for 52 weeks. After 136 weeks of observation, one Zymbal gland carcinoma was found, whereas at a comparable time the Sprague-Dawley rats had developed 29 such tumours. In the Wistar rats, one nephroblastoma, eight liver angiosarcomas and one brain neuroblastoma were found in the 10 000 ppm group; three nephroblastomas, two liver angiosarcomas and one brain neuroblastoma in the 6000 ppm group; three liver angiosarcomas in the 2500 ppm group; and one nephroblastoma and four liver angiosarcomas in the 500 ppm group (Maltoni, 1977a; Maltoni *et al*., 1974).

The effect of length of treatment by inhalation of vinyl chloride on the incidence of liver angiosarcomas was investigated. Groups of 60–120 Sprague-Dawley rats were given either 15.6 or 26 g/m^3 (6000 or 10 000 ppm) vinyl chloride in air for 4 h per day on five days a week for five, 17 or 52 weeks. The experiment was terminated at 155 weeks. Liver angiosarcomas developed in 13 (22%) and 9 (15%) of the 6000 and 10 000 ppm groups exposed for 52 weeks; one (0.6%) liver angiosarcoma was found in a rat exposed to 6000 ppm for 17 weeks and none in the 10 000 ppm group. No such tumours were induced in rats treated for five weeks (Maltoni, 1977b) [No information was given about tumours occurring at other sites].

The influence of age on the incidence of liver tumours was examined in Sprague-Dawley rats exposed to 15.6 or 26 g/m^3 (6000 or 10 000 ppm) vinyl chloride in air for 4 h per day on five days a week for five weeks, starting at the age of 13 weeks (120 rats/group) or one day (43 and 46 rats). The animals were observed for 135 weeks. One hepatoma was reported in the older rats treated with 10 000 ppm. In the newborn rats, 10 angiosarcomas and 13 hepatomas were observed in the 6000 ppm group, and 10 angiosarcomas and 15 hepatomas were found in rats treated with 10 000 ppm. No liver tumours were reported in the 249 untreated rats (Maltoni, 1977b).

Groups of 36 male and 36 female two-month-old CD rats were exposed to 0, 130, 650 and 2600 mg/m^3 (0, 50, 250 and 1000 ppm) vinyl chloride in air (99.8% pure) for 6 h per day on five days a week for 12 months, at which time the surviving animals (72, 70, 58 and 51) were killed. In rats treated with 250 and 1000 ppm, liver angiosarcomas occurred in 12 and 22 and lung angiosarcomas developed in three and 13 (Lee *et al*., 1977).

In a report of a study in progress, four groups of 80 Sprague-Dawley male rats received either 5% ethanol in the drinking-water or drinking-water only for four weeks prior to beginning inhalation of 1560 mg/m^3 (600 ppm) vinyl chloride for 4 h per day on five days a week for 12 months or air; ethanol-water was given until death or sacrifice. After 60 weeks from the first exposure to vinyl chloride, 55 rats had died or had been sacrificed; liver tumours were found in 21/28 (75%) in the vinyl chloride-ethanol group and 5/13 (38%) in the vinyl chloride only group (Radike *et al*., 1977).

Hamster: Groups of 32–35 male 11-week-old golden hamsters were exposed by inhalation to 130-26 000 mg/m^3 (50, 250, 500, 2500, 6000 and 10 000 ppm) vinyl chloride in air for 4 h a day on five days/week for 30 weeks. At 48 weeks from the initial treatment, 60/198 treated animals were still alive. At 109 weeks (end of treatment), 2 liver angiosarcomas were seen in hamsters treated with 500 ppm and 1 in those treated with 6000 ppm. Skin trichoepitheliomas developed in 22 treated hamsters (in 1-6 animals/group) and in 2/70 controls. Two animals treated with 6000 ppm and one each treated with 50, 2500 and 10 000 ppm developed melanomas. In addition, six lymphomas and 35 forestomach papillomas and acanthomas were found in treated animals, and two and two, respectively, in controls (Maltoni, 1977a; Maltoni *et al*., 1974).

Rabbit: A group of 40 rabbits were exposed for 4 h per day on five days a week for 12 months to air containing 26 g/m^3 (10 000 ppm) vinyl chloride. Between nine and 15 months of exposure, 12 skin acanthomas and six lung adenocarcinomas were seen. No similar tumours occurred in 20 controls after 15 months of observation (Caputo *et al*., 1974) [The Working Group noted the inadequacy of reporting].

(c) Subcutaneous and/or intramuscular administration

A group of 75 male and female 21-week-old Sprague-Dawley rats were given single subcutaneous injections of 4.25 mg/animal vinyl chloride in 1 mL olive oil. One nephroblastoma occurred in the treated animals (Maltoni, 1977a) [The Working Group noted that survival times and period of observation were not given].

(d) Intraperitoneal administration

Groups of 30 male and 30 female 13-week-old Sprague-Dawley rats received single injections of 4.25 mg/animal vinyl chloride in 1 mL olive oil, twice, thrice or four times in two months. One nephroblastoma and one subcutaneous angiosarcoma were found (Maltoni, 1977a) [The Working Group noted that survival times and period of observation were not given].

(e) Other experimental systems

Prenatal exposure

Rat: Two groups of 30 female Sprague-Dawley rats were given 15.6–26 g/m^3 (6000 or 10 000 ppm) vinyl chloride in air for 4 h per day by inhalation from the 12th to 18th day of pregnancy. Of the offspring, 17/32 and 23/54 had died by the 95th week after birth. After 143 weeks (end of experiment), one subcutaneous angiosarcoma was observed in each group of offspring; one animal exposed *in utero* to 6000 ppm had a Zymbal gland carcinoma; and three animals exposed to 10 000 ppm had Zymbal gland carcinomas, and one, a nephroblastoma. One female rat treated with 10 000 ppm developed a Zymbal gland carcinoma (Maltoni, 1974; Maltoni, 1977a).

3.2 Other relevant biological data

(a) Experimenta1 systems

Toxic effects

The 2-h LC_{50} of vinyl chloride for mice was 294 g/m^3 (113 000 ppm); for rats, 390 g/m^3 (150 000 ppm); for guinea-pigs, 595 g/m^3 (230 000 ppm); and for rabbits, 295 g/m^3 (113 000 ppm). Vinyl chloride gas had a narcotic effect on experimental animals, the most sensitive species being mice, followed by rats, guinea-pigs and rabbits. The death of animals was preceded by excitement, contractions and convulsions, accelerated respiration, followed by respiratory failure. Rabbits and guinea-pigs had more accentuated muscular contractions and convulsions than mice and rats. Microscopically, congestion of the internal organs with more intense damage to the lungs, liver and kidneys were found (Prodan *et al*., 1975a).

The hepatotoxicity of vinyl chloride has been shown to be increased after administration of cytochrome P-450 inducers such as phenobarbital, Aroclor 1254 and hexachlorobenzene (Ivanetich *et al*., 1977; Reynolds *et al*., 1975a,b). The extent of liver damage has been measured by the release of alanine-α-ketoglutarate, glutamic oxalacetic and glutamic pyruvic transaminases (Reynolds *et al*., 1975b, 1976) and of sorbitol dehydrogenase (Conolly & Jaeger, 1977) into the serum.

A single 6-h inhalation exposure to 130 g/m^3 vinyl chloride (50 000 ppm) produced acute liver injury in male Sprague-Dawley rats pretreated with phenobarbital or Aroclor 1254. The degree of injury, as indicated by elevation of serum levels of enzymes derived from the liver, correlated with the magnitude of induction of cytochrome P-450 and morphological changes in the endoplasmic reticulum (Reynolds *et al*., 1975a,b, 1976). Similar findings were reported in phenobarbital-pretreated male Holtzman rats (Jaeger *et al*., 1974) and in phenobarbital-treated male Charles River CD-1 rats that received 10 daily exposures for 6 h per day to 35 g/m^3 (13 500 ppm) vinyl chloride in air (Drew *et al*., 1975).

Cytochrome P-450 concentration decreased during in-vivo exposure or during in-vitro incubation of liver homogenate from phenobarbital or 3-methylcholanthrene-induced rats (Ivanetich *et al*., 1977; Reynolds *et al*., 1975c).

In an abstract, it was reported that male rats pretreated by gavage with Aroclor 1254 for three consecutive days and exposed on day 4 by inhalation to 62.5 g/m^3 (24 000 ppm) vinyl chloride for 4 h showed significant elevations of serum alanine-α-ketoglutarate transaminase and severe degeneration and necrosis of the liver (Conolly *et al*., 1977). Overnight fasting, which depletes hepatic glutathione, of Aroclor-pretreated male Holtzman rats before exposure to 26 g/m^3 (10 000 ppm) for 4 h significantly increased the hepatotoxic effects, as measured by sorbital dehydrogenase levels in the serum (Conolly & Jaeger, 1977).

Simultaneous exposure to 1.75 g/m^3 (671 ppm) vinyl chloride with 200 ppm vinylidene chloride prevented vinylidene chloride-induced hepatic injury in fasted male rats. However, pre-exposure to concentrations of vinyl chloride which depleted hepatic glutathione concentrations significantly enhanced early acute hepatotoxic response to vinylidene chloride in fed rats (Jaeger *et al*., 1975a,b).

Exposure of guinea-pigs to 260 g/m^3 (100 000 ppm) vinyl chloride for 2 h per day for three months resulted in marked growth disturbances and intense histopathological and histochemical lesions in the liver, kidneys, spleen and lungs. Interruption of the exposure resulted in a regenerative effect, denoting a certain degree of reversibility of the hepatorenal lesions. Large quantities of vitamin C reduced the gravity of the lesions caused by vinyl chloride (Prodan *et al*., 1975b).

Mice were exposed to 130, 650 or 2600 mg/m^3 (50, 250 or 1000 ppm) vinyl chloride for 6 h per day on five days a week. The highest dose caused some acute deaths with toxic hepatitis and marked tubular necrosis in the renal cortex. From the sixth month of treatment, all mice became lethargic, lost weight quickly and died. Only a few mice exposed to 50 ppm survived for 12 months (Lee *et al*., 1977).

The non-protein, free SH-groups of the liver are depleted in rats exposed to 390-5200 mg/m^3 (150-2000 ppm) vinyl chloride for 1–7 h, as a function both of concentration and duration of exposure (Watanabe *et al*., 1976a).

Vinyl chloride and two of its presumed metabolizes, chloroethylene oxide and chloroacetaldehyde, depressed DNA synthesis in rat liver *in vivo* (Border & Webster, 1977).

Embryotoxicity and teratogenicity

Pregnant CF-1 mice were exposed by inhalation to 130 and 1300 mg/m^3 (50 and 500 ppm) vinyl chloride on days 6–15 of gestation, Sprague-Dawley rats to 1300 and 6500 mg/m^3 (500 and 2500 ppm) on days 6–15 of gestation, and New Zealand rabbits to 1300 and 6500 mg/m^3 (500 and 2500 ppm) on days 6–18 of gestation, for 7 h per day, with or without simultaneous exposure to 15% ethanol in the drinking-water. A significantly increased incidence of several skeletal anomalies was observed in offspring of mice that received vinyl chloride plus ethanol (John *et al*., 1977; Schwetz *et al*., 1975).

Absorption, distribution, excretion and metabolism

The in-vivo and in-vitro metabolism of vinyl chloride has been studied and reviewed (Antweiler, 1976; Bartsch & Montesano, 1975; Bonse & Henschler, 1976; Green & Hathway, 1975, 1977; Haley, 1975; Hefner *et al*., 1975; Malaveille *et al*., 1975; Müller & Norpoth, 1975; Müller *et al*., 1976; Plugge & Safe, 1977; Watanabe & Gehring, 1976; Watanabe *et al*., 1976b,c).

Low concentrations (130 mg/m^3, 50 ppm, for 65 min) of vinyl chloride are readily metabolized in rats exposed by inhalation and are converted into polar metabolites, which are predominantly excreted in the urine; a very small amount is expired in air as unchanged vinyl chloride (Hefner *et al*., 1975).

Following exposure of male rats by inhalation to 26 mg/m^3 (10 ppm) ^{14}C-vinyl chloride for 6 h, urinary ^{14}C-activity and expired vinyl chloride comprised 68 and 2%, respectively, of the recovered radioactivity; after exposure to 2600 mg/m^3 (1000 ppm) ^{14}C-vinyl chloride, the proportion of the radioactivity in the urine was lower and that expired as vinyl chloride higher, representing 56 and 12%, respectively. The pattern of pulmonary elimination of 10 and 1000 ppm vinyl chloride *per se* was described by apparently similar first-order kinetics, with half-lives of 20.4 and 22.4 min. respectively; the half-lives for the initial phase of excretion of ^{14}C-radioactivity in the urine were 4.6 and 4.1 h, respectively. ^{14}C-Radioactivity recovered from the carcass after 72 h was 14 and 15%, respectively; no vinyl chloride *per se* was found in tissues. The proportions of three urinary metabolites, *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, thiodiglycolic acid (thiodiacetic acid) and an unidentified metabolite, were not markedly influenced by the level of exposure (Watanabe *et al*., 1976b).

Following single oral administration of 0.05, 1 or 100 mg/kg bw ^{14}C-vinyl chloride to male rats, excretion in the urine was 59, 68 and 11%, respectively; the $^{14}CO_2$ in expired air accounted for 9, 13 and 3%, respectively; pulmonary elimination of unchanged vinyl chloride represented only 1–3% of the lower dose levels and 67% of the higher level. The pulmonary clearance of 0.05 and 1 mg/kg bw doses of vinyl chloride was monophasic, with half-lives of 53.3 and 57.8 min, respectively; it was biphasic after administration of 100 mg/kg bw, with half-lives of 14.4 and 40.8 min for the fast and slow phases, respectively. The percentages of the doses left in the carcass after 72 h were 10, 11 and 22 of the 0.05, 1 and 100 mg/kg doses, respectively. Two of three urinary metabolites were identified as *N*-acetyl-*S*-(2-hydroxyethyl)cysteine and thiodiglycolic acid; their proportions were not influenced by dose (Watanabe *et al*., 1976c). It has been suggested that the metabolism of vinyl chloride in rats following oral and inhalation exposure is a saturable process (Watanabe *et al*., 1976b,c).

The kinetic parameters and half-lives for the elimination of vinyl chloride from rats after inhalation and intravenous administration have also been reported by Withey (1976).

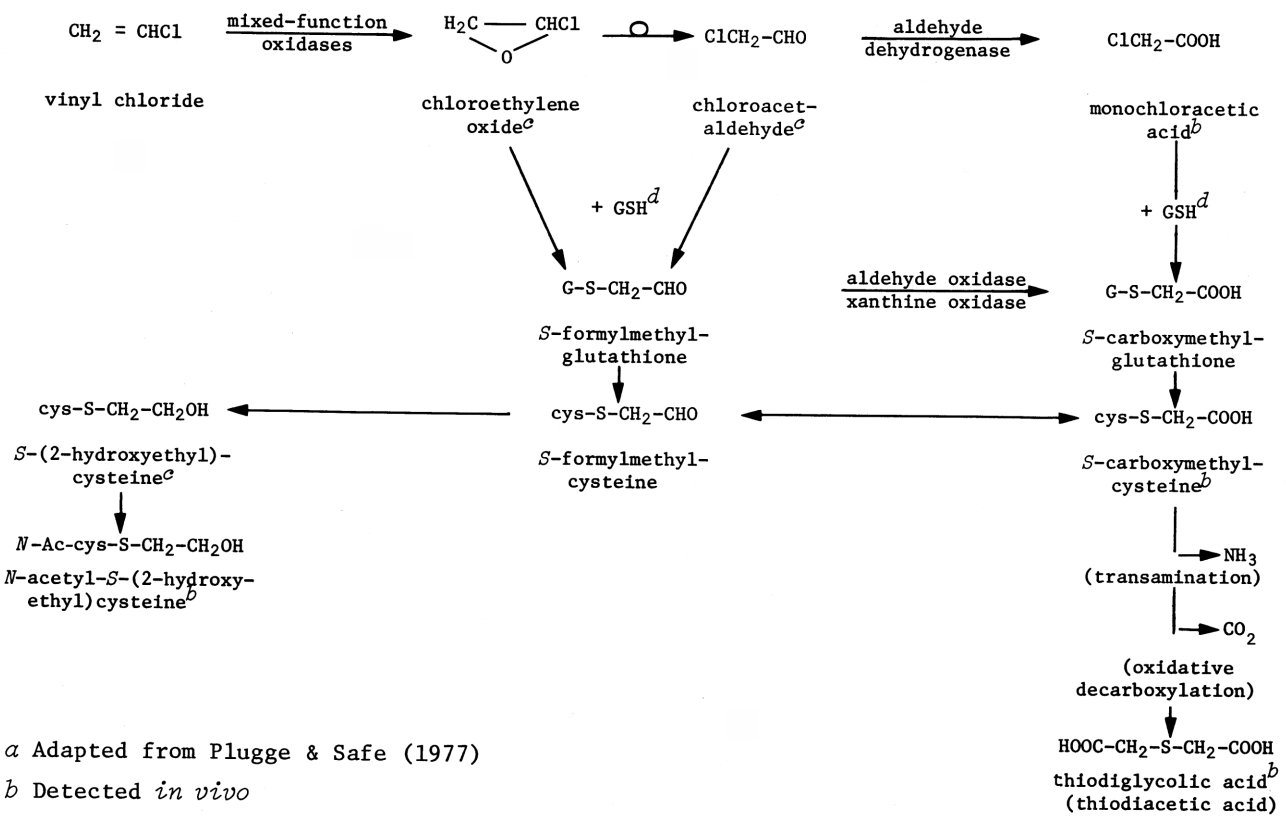
When rats were exposed to initial concentrations of less than 260 mg/m^3 (100 ppm) [1,2-^{14}C]-vinyl chloride, about 40% of that inspired was absorbed by the lung. Highest radioactivity levels were observed in the liver and kidney immediately after exposure. Most of the radioactive metabolites were excreted rapidly, largely by the kidneys: the radioactivity in the urine amounted to 70% within 24 hours. Some metabolites, however, remained in tissues (mostly in spleen, liver, kidneys) even 48 h after exposure (Bolt *et al*., 1976). Metabolites that were not excreted in urine were partly excreted via faeces and partly *via* expiration of $^{14}CO_2$ (Bolt *et al*., 1976; Green & Hathway, 1975).

Vinyl chloride is metabolized by microsomal mixed-function oxidases to chloroethylene oxide, which can rearrange spontaneously to chloroacetaldehyde (Fig. 1). Although there is no direct evidence for this pathway *in vivo*, the following data are consistent with this hypothesis. Vinyl chloride in the presence of a mouse liver microsomal fraction, rat liver homogenate, an NADPH generating system and oxygen yielded an alkylating intermediate which reacted with either 3,4-dichlorobenzenethiol (Göthe *et al*., 1974) or with 4-(4-nitrobenzyl)pyridine. The absorption spectra of the latter adduct was identical to those obtained with the product formed with synthetic chloroethylene oxide (Barbin *et al*., 1975; Bartsch *et al*., 1976). These studies indicate that the primary *in vitro* metabolite of vinyl chloride is chloroethylene oxide, which can rearrange to chloroacetaldehyde.

Metabolism of vinyl chloride occurs predominantly through the cytochrome P-450 system (Ivanetich *et al*., 1977; Reynolds *et al*., 1975c; Salmon, 1976). Inhibitors of microsomal mixed-function oxidases, such as 3-bromophenyl-4(5)-imidazole or 6-nitro-1,2,3-benzothiadiazole, reduced vinyl chloride metabolism *in vivo* (Bolt *et al*., 1976). Chloroethylene oxide, with a half-life of 1.6 min in aqueous solution at neutrality (Barbin *et al*., 1975), rearranges to chloroacetaldehyde (Bonse *et al*., 1975). Chloroacetaldehyde combines directly or enzymatically *via* glutathione *S*-transferase with glutathione to form *S*-formylmethylglutathione, which is excreted as *N*-acety1-*S*-(2-hydroxyethyl) cysteine (Green & Hathway, 1977) (Fig. 1). Chloroacetaldehyde can be oxidized to chloroacetic acid, which is either excreted as such or bound to glutathione to form *S*-carboxymethyl glutathione, which upon further enzymic degradation is excreted as thiodiglycolic acid (thiodiacetic acid) (Plugge & Safe, 1977).

Chloroacetic acid was metabolized in rats to two major urinary metabolites, *S*-carboxymethylcysteine and thiodiacetic acid (Yllner, 1971). *N*-Acetyl-*S*-(2-hydroxyethyl)cysteine (a major metabolite) (Green & Hathway, 1977; Watanabe *et al*., 1976b,c), *S*-(carboxymethyl)cysteine and *N*-acetyl-*S*-vinylcysteine have been shown to be metabolites of vinyl chloride in rats after oral administration (Green & Hathway, 1977) and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine after inhalation (Watanabe *et al*., 1976b); *S*-(2-chloroethyl)cysteine was also identified after oral administration of vinyl chloride to rats (Green & Hathway, 1975). As thiodiglycolic acid was obtained as a common metabolite in rats dosed separately with chloroacetaldehyde, chloroacetic acid or *S*-(carboxymethyl)cysteine, the identification of the same *S*-containing metabolite from vinyl chloride-treated animals gives further support to the hypothesis that chloroethylene oxide or chloroacetaldehyde are formed and react with glutathione (Green & Hathway, 1977).

Figure 1[a]



a Adapted from Plugge & Safe (1977)

b Detected *in vivo*

c Detected *in vitro*

d GSH = glutathione

Following oral administration of ^{14}C-vinyl chloride, $^{14}CO_2$ (Green & Hathway, 1975; Watanabe *et al*., 1976c), ^{14}C-labelled urea and glutamic acid were identified as minor metabolites (Green & Hathway, 1975).

In-vitro binding of ^{14}C-vinyl chloride was shown to be dependent on the thiol content of proteins (Bolt & Filser, 1977), and binding was dependent on the presence of NADPH, oxygen and microsomal enzymes (Kappus *et al*., 1976). It has been suggested that an epoxide of vinyl chloride is involved in the covalent binding reaction (Kappus *et al*., 1975). In the presence of a rat liver microsomal system, vinyl chloride binds to RNA *in vitro* (Kappus *et al*., 1975) and to RNA and DNA *in vivo* (Laib & Bolt, 1977).

Chloroacetaldehyde reacts with adenosine to give 1,N^6-ethenoadenosine (Barrio *et al*., 1972). Chloroethylene oxide and vinyl chloride, incubated in the presence of a mouse liver-microsomal preparation with adenosine *in vitro*, produced the same product (Barbin *et al*., 1975). Reaction of chloroacetaldehyde with cytidine gives 3,N^4-ethenocytidine (Barrio *et al*., 1972). 1,N^6-Ethenoadenosine was isolated after hydrolysis of polyadenosine that had been incubated with rat liver microsomes and ^{14}C-vinyl chloride or with liver RNA of rats treated with ^{14}C-vinyl chloride (Laib & Bolt, 1977). The corresponding etheno-derivatives of deoxyadenosine and deoxycytidine were identified in hydrolysis products obtained from calf thymus DNA treated with chloroacetaldehyde *in vitro* and from liver DNA of rats fed 250 mg/L vinyl chloride in their drinking-water (Green & Hathway, 1978).

The 2-hydroxyethyl derivatives of guanine, cysteine and histidine were identified after chemical reduction of the hydrolysis products of DNA and proteins isolated from the livers of mice treated with ^{14}C-vinyl chloride (Osterman-Golkar *et al*., 1977).

Mutagenicity and other short-term tests

The mutagenicity of vinyl chloride has been reviewed by Bartsch & Montesano (1975), Bartsch *et al*. (1976) and Fishbein (1976).

Vinyl chloride vapour induced reverse mutations of the base-pair substitution type in *Salmonella typhimurium* TA100, TA1530, TA1535 and G46in the presence of a 9000 x *g* supernatant from rat liver (Andrews *et al*., 1976; Bartsch *et al*., 1975; Garro *et al*., 1976; Malaveille *et al*., 1975; McCann *et al*., 1975; Rannug *et al*., 1974), mouse liver (Bartsch *et al*., 1975; Garro *et al*., 1976; Malaveille *et al*., 1975) and human liver biopsy specimens (Bartsch *et al*., 1975, 1979; Malaveille *et al*., 1975). Although vinyl chloride also induced mutations in the absence of a metabolic activation system, a much higher mutagenic response was observed when a 9000 x *g* supernatant from liver was added (Andrews *et al*., 1976; Bartsch *et al*., 1975; McCann *et al*., 1975).

Vinyl chloride in aqueous or methanolic solution was not mutagenic in the *Salmonella* test system (Bartsch *et al*., 1975; Rannug *et al*., 1974) but produced reverse mutations in *Escherichia coli* K12 (Greim *et al*., 1975), forward mutations

in *Schizosaccharomyces pombe* and mitotic gene conversions in *Saccharomyces cerevisiae* in the presence of a 9000 × *g* supernatant from mouse liver. Forward mutations in *S. pombe* were also induced in the host-mediated assay in mice (Loprieno *et al*., 1976, 1977).

Vinyl chloride as vapour or as ethanol solution was not mutagenic in *Neurospora crassa* in the presence or absence of a metabolic activation system (Drozdowicz & Huang, 1977).

In inhalation experiments in *Drosophila melanogaster*, vinyl chloride was mutagenic in the recessive lethal test (Magnusson & Ramel, 1976; Verburgt & Vogel, 1977) but not mutagenic in tests for dominant lethals, translocations and sex-chromosome loss (Verburgt & Vogel, 1977).

No dominant lethals were observed in male CD-1 mice after exposure by inhalation to 7.8, 26, or 78 g/m^3 (3000, 10 000 or 30 000 ppm) vinyl chloride in air for 6 h per day for five days (Anderson *et al*., 1976, 1977).

Exposure to vinyl chloride vapour in the presence of a 15 000 × *g* supernatant from phenobarbital-pretreated rat liver induced forward mutations in V79 Chinese hamster cells in terms of 8-azaguanine and ouabain resistance (Drevon *et al*., 1977).

The mutagenicity of several possible metabolites of vinyl chloride has also been examined. Chloroethylene oxide was the strongest mutagen among those tested in *S. typhimurium* TA1530 and TA1535 (Bartsch *et al*., 1975; Malaveille *et al*., 1975; Rannug *et al*., 1976), *E. coli* (Hussein & Osterman-Golkar, 1976), *S. pombe* (Loprieno *et al*., 1977), *S. cerevisiae* (Loprieno *et al*., 1977) and V79 Chinese hamster cells (Huberman *et al*., 1975). Chloroacetaldehyde was mutagenic in *S. typhimurium* TA1535, TA1530 and TA100 (Bartsch *et al*., 1975; Malaveille *et al*., 1975; McCann *et al*., 1975; Rannug *et al*., 1976) and V79 Chinese hamster cells (Huberman *et al*., 1975). Chloroethanol was a weak mutagen in *S. typhimurium* TA1530, TA1535 and TA100 (Bartsch *et al*., 1976; Malaveille *et al*., 1975; McCann *et al*., 1975; Rannug *et al*., 1976; Rosenkranz *et al*., 1974). Chloroacetic acid was not mutagenic in *S. typhimurium* TA1530, TA100 or TA1535 (Bartsch *et al*., 1975; Malaveille *et al*., 1975; McCann *et al*., 1975; Rannug *et al*., 1976).

1,2-Dichloroethane, a possible by-product of vinyl chloride production and a main component of waste products from vinyl chloride industries (EDC-tar), was mutagenic in *S. typhimurium* TA1535 (Rannug & Ramel, 1977) and in *S. typhimurium* TA100 (McCann *et al*., 1975) in the presence or absence of a liver microsomal metabolic activation system.

(b) Humans

Toxic effects

Exposure to vinyl chloride is associated with multiple systemic disorders, including a sclerotic syndrome, acro-osteolysis (sometimes associated with a Raynaud-like symptomatology), thrombocytopenia and liver damage, consisting of parenchymal damage, fibrosis of the liver capsule, periportal fibrosis associated with hepatomegaly, and splenomegaly (Lange *et al*., 1974a; Thomas *et al*., 1975).

Examination of 70 workers from a single polyvinyl chloride-producing factory showed a high frequency of signs and symptoms of vinyl chloride disease. Although skin and bone changes may disappear when the patient is removed from contact with vinyl chloride, the thrombocytopenia persists after termination of exposure (Veltman *et al*., 1975).

Non-cirrhotic portal fibrosis with associated portal hypertension was found in seven patients who had been involved in the production of vinyl chloride monomer for 4-15 years. An angiosarcoma developed in one patient, but fibrosis was a more common lesion and was considered to be probably not premalignant (Smith *et al*., 1976a).

Of 487 workers involved in polyvinyl chloride production, two cases presenting with thrombocytopenia were found to have portal hypertension due to periportal fibrosis, with oesophageal varices and splenomegaly (Williams *et al*., 1975, 1976).

Exposure to vinyl chloride was not only associated with circulatory and liver dysfunction and skin and bone disorders, but also deafness, vision failure and giddiness (Jühe & Lange, 1972).

Elevated carcino-embryonic antigen levels have been found in 48% of 200 polyvinyl chloride workers, as compared with 9% of a normal healthy population (Pagé *et al*., 1976). No evidence of an auto-immune disorder was found in 13 patients employed in polyvinyl chloride production who had symptoms of 'vinyl chloride disease' (Lange *et al*., 1974a); however, immunological data from 19/28 patients with vinyl chloride disease and in 2/30 workers exposed to vinyl chloride suggested an immune complex disorder (Ward *et al*., 1976).

A group of 168 workers (114 from one factory and 54 from another) were examined medically at various times during 1962–69. Manifestations of disorders of the nervous system were recorded commonly; hepatomegaly and splenomegaly occurred in 30% and 6% of workers; and some cases of anaemia and leucopenia were also observed. The incidence of Raynaud's syndrome fell from 6% in 1962 to 2.9% in 1966; this phenomenon cleared spontaneously upon removal of the subjects from exposure: these different incidence figures were associated with a 22-fold decrease in vinyl chloride levels during the period of the study. A much higher percentage of vasospastic changes was found in the two groups (66 and 55%, respectively), suggesting that vinyl chloride acts as an irritant in the reticuloendothelial system to produce reactive splenic enlargement (Suciu *et al*., 1975).

Reduced pulmonary function has been observed in workers exposed to vinyl chloride (Gamble *et al*., 1976; Miller *et al*., 1975). The prevalence of this impairment was similar in smokers and nonsmokers, suggesting that occupational or other environmental factors were operative (Miller *et al*., 1975).

Embryotoxicity and teratogenicity

A significant excess of fetal deaths was reported in women whose husbands were exposed to vinyl chloride: 15.8%, or 23, foetal deaths in 139 pregnancies, as compared with 8.8% (24/273) in the age-adjusted control group. This excess of foetal deaths was shown not to be a function of chronic abortions, i.e., the association was maintained after excluding pregnancies of women who had had more than two abortions (Infante *et al*., 1976a). The significance of this study was questioned because data collection methods were not specified and there was no statistical treatment of the data (Paddle, 1976). Subsequently, the data collection methods were described, showing that there had been no interviewer-respondent bias, and details of statistical analyses were specified (Infante *et al*., 1976b).

In a registry-based study, Infante (1976) reported that an excess of central nervous system defects, of deformities of the upper alimentary and genital tracts, and of clubfoot has been observed in stillborn and live children in three cities in Ohio in which vinyl chloride polymerization plants are located.

In hospital-based studies in newborns in Painesville (Ohio), where there are two polyvinyl chloride plants, and in Kanawha county (West Virginia), where there is one plant, excesses of anencephaly and spina bifida were reported, but no association was made with vinyl chloride (Edmonds, 1977; Edmonds *et al*., 1975, 1978).

Mutagenicity and other short-term tests

Chromosomal aberrations were found in workers occupationally exposed to vinyl chloride in the US (Ducatman *et al*., 1975; Heath *et al*., 1977), Sweden (Funes-Cravioto *et al*., 1975), the UK (Purchase *et al*., 1975), Belgium (Léonard *et al*., 1977), Hungary (Szentesi *et al*., 1976) and Norway (Hansteen *et al*., 1976). These aberrations were in most cases fragments, dicentrics and rings, and breaks and gaps.

3.3 Case reports and epidemiological studies[1]

In 1974, more than 40 years after the introduction of vinyl chloride into industry, Creech and Johnson (1974) first reported an association of exposure to this chemical with cancer in man. Three cases of liver angiosarcoma were reported in men who were employed in the manufacture of polyvinyl chloride resins (one had cleaned reactor vessels) in a single vinyl chloride polymerization plant in the USA.

[1] The Working Group was aware of a study in progress on the occupational and community carcinogenic risk of vinyl chloride (IARC, 1978b).

By reviewing medical records and pathological material and by systematic medical screening, the association between exposure to vinyl chloride and angiosarcoma of the liver has been reported from a number of other countries: Canada (Delorme & Thériault, 1978; Noria *et al*., 1976); Czechoslovakia (Lloyd, 1975); the Federal Republic of Germany (Lange *et al*., 1974b, 1975); France (Couderc *et al*., 1976; Ravier *et al*., 1975; Roche *et al*., 1978); Italy (Maltoni, 1974); Norway (Lloyd, 1975); Romania (Lloyd, 1975); Sweden (Byrén & Holmberg, 1975); the United Kingdom (Lee & Harry, 1974; Smith *et al*., 1976b); the USA (Block, 1974; Falk *et al*., 1974a; Makk *et al*., 1974); and Yugoslavia (Šarič *et al*., 1976). A review of 64 reported cases in various countries as of October 1977 is available (Spirtas & Kaminski, 1978).

No history of acro-osteolysis and no evidence of exposure to hepatotoxic materials other than vinyl chloride was reported in a clinical review of seven cases of liver angiosarcoma among US vinyl chloride polymerization workers (Heath *et al*., 1975). In a pathological evaluation of cases of liver angiosarcoma among exposed US vinyl chloride workers, it was concluded that these tumours were often multicentric: angiosarcomas were also detected in the wall of the duodenum, in the heart and kidney, and in other organs (Thomas & Popper, 1975).

The cancer risk among a cohort of males in the US who had at least one year of occupational exposure to vinyl chloride was studied. When compared with the US male population, an excess of cancer of the digestive system, of the liver (primarily angiosarcoma), of the respiratory system, of the brain and of unknown sites, as well as lymphomas was observed in those members of the study cohort with the greatest estimated exposure to vinyl chloride (Tabershaw & Gaffey. 1974) [Vital status was undertermined for 15% of the study cohort, only 50% had 15 or more years since onset of exposure to vinyl chloride].

In a proportional-mortality analysis of 161 deceased workers in two US plants producing and polymerizing vinyl chloride, a 50% excess of deaths due to all cancers was reported. Sites of cancer with the greatest excess were liver and biliary tract, brain, digestive tract and lung (Monson *et al*., 1974). Falk *et al*. (1974b) questioned the authors' conclusion, on the grounds that not all deaths studied were among workers in activities directly related to vinyl chloride production or polymerization and that the study failed to include deaths among workers who had terminated employment prior to retirement or death.

The cancer mortality experience of 257 US workers (255 were traced), each of whom had been occupationally exposed to vinyl chloride for at least five years and observed after 10 years from onset was studied using union seniority and company employment records. Among 24 deaths from all causes, a 2.3-fold excess was observed in deaths from cancer; of the 24 deaths, three were due to haemangiosarcoma of the liver (Nicholson *et al*., 1975).

No excess of total or cause-specific mortality was reported in a study of 2100 male workers in the United Kingdom exposed to vinyl chloride for periods of up to 27 years; in addition, the authors reported a decreasing risk of mortality with increasing duration of exposure to vinyl chloride (Duck *et al*., 1975). Wagoner *et al*. (1976) challenged the conclusions of the study on the grounds of analytical shortcomings. After reanalyzing the data, the authors (Duck & Carter, 1976) reported an increased risk of cancer of the digestive system 15 years after initial exposure to vinyl chloride.

The cancer mortality of 594 US workers exposed occupationally to vinyl chloride and to lesser amounts of vinylidene chloride (see p. 439) and other compounds (such as methyl methacrylate, see p. 187, and acrylonitrile, see p. 73) was studied. Although no angiosarcomas were found (no deaths due to any liver cancer), an excess of all malignancies combined was reported among those workers classified as having been highly exposed to vinyl chloride when compared with all other exposure categories. However, the number of workers in the lower exposure categories who were exposed for more than 10 years was small, resulting in part from the fact that workers first took jobs in the dry end of the polymerization process where exposures to vinyl chloride were low; many employees who remained with the units and established seniority would subsequently have moved to the higher exposure areas (Ott *et al*., 1975).

The incidence of abnormal sputum cytology among workers in the vinyl chloride-polyvinyl chloride industry in Italy was much higher than expected, even when compared with a population of heavy smokers who did not work in chemical industries (Maltoni, 1976).

Waxweiller *et al*. (1976) studied the cancer mortality experience of 1294 individuals with five or more years of employment and 10 years since onset of employment in departments or jobs with direct exposure to vinyl chloride at one of four vinyl chloride–polyvinyl chloride production plants in the USA. When compared with the US white male population, an excess of cancer was found in four organ systems: brain and central nervous system, respiratory system, hepatic system, and lymphatic and haematopoietic systems. This excess of organ-specific cancer was restricted to those workers with 15 or more years since onset of vinyl chloride exposure. For all malignant neoplasms combined, the standard mortality ratio was 184; for the brain and central nervous system, 498; for the respiratory system, 194; for the hepatic system, 1606; and for the lymphatic and haematopoietic system, 176. Of 14 histologically confirmed cases of biliary and liver cancer among workers from these four plants, 11 were angiosarcoma of the liver. Of 10 cases of brain cancer, nine were classified histologically as glioblastoma multiforme, a cell type of brain cancer reported to be unusual in the USA. Of the 14 cases of primary lung cancer, five were large-cell undifferentiated and three were adenocarcinoma.

In 771 workers employed in a Swedish vinyl chloride-polyvinyl chloride plant since its start in the early 1940s, a four- to fivefold excess of cancer of the liver and pancreas was found. Although the risks of cancer of the brain and of the lung were also increased, they were not statistically significant (Byrén *et al*., 1976).

Whereas no excess mortality from lung cancer was demonstrated among currently employed individuals 15 years after initial occupational exposure to vinyl chloride, a 56% excess of lung cancer was observed among those individuals who had terminated employment less than 15 years since initial exposure; this excess was found for each duration of exposure (Fox & Collier, 1976).

Fox and Collier (1977) investigated the cancer mortality among 7561 men who were exposed to vinyl chloride in the manufacture of polyvinyl chloride in the United Kingdom at some time between 1940 and 1974. An excess mortality from liver cancer was reported for each group of workers, whether exposure was thought to be high, medium or low; however, the authors reported no evidence of an excess mortality from cancers other than of the liver. Relatively few subjects had long-term exposure to vinyl chloride, and even in cases in which men had completed 20 years of employment, the follow-up period was judged to be too short to evaluate the carcinogenic effect of vinyl chloride.

A study was reported of cancer mortality among 7021 men employed in the production and polymerization of vinyl chloride in the Federal Republic of Germany. When compared with the national male population, an excess of cancers was found for four organs: liver, brain, lung and lymphatic organs. This excess of organ-specific cancer was shown to increase with duration of exposure (von Reinl *et al*., 1977).

The risk of cancer mortality was investigated among residents 45 years of age and older in three US communities with vinyl chloride polymerization facilities. Among males, the death rate from central nervous system cancer was higher than that for the state as a whole. No excess mortality from leukaemia and aleukaemic leukaemia or from lymphoma was found (Infante, 1976).

The incidence of liver and lung cancer was studied for a four-year period in a city in Yugoslavia with a factory in which vinyl chloride was polymerized and polyvinyl chloride processed. Polyvinyl chloride workers were included in the study. Except for liver angiosarcoma, no association was found between cancer incidence and place of work or residence (Šarič *et al*., 1976).

Polyvinyl chloride

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 9002-86-2

Chem. Abstr. Name: Chloroethene homopolymer

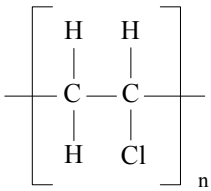
Atactic poly(vinyl chloride); chloroethylene polymer; poly(chloroethylene); poly(vinyl chloride); poly(vinylchloride); polyvinyl-chloride; PVC; vinyl chloride homopolymer; vinyl chloride polymer

Airex; AL 30; AL 31; Armodour; Aron compound HW; Astralon; Bakelite OYNV; Bakelite QSAH 7; Bakelite QYAC 10; Bakelite QYJV 1; Bakelite QYOH-1; Bakelite QYSJ; Bakelite QYSL 7; Bakelite QYTO 7; Bakelite UCA 3310; Benvic; Blacar 1716; Bolatron 6200; Bonloid; Breon; Breon 107; Breon 113; Breon 121; Breon 125/10; Breon 151; Breon 4121; Breon 111EP; Breon 112EP; Breon P 130/1; Breon S 110/10; Breon S 125/12; C 65; Caliplast; Carina S 70-01; Carina S 70-71; Chemosol; Chlorostop; Cobex (polymer); Contizell; Corvic 55/9; Corvic 65/50; Corvic 206573; Corvic 20560600; Corvic 20650600; Corvic C 65/02; Corvic D 55/9; Corvic D 57/15; Corvic D 57/17; Corvic D 60/11; Corvic D 65; Corvic D 65/02; Corvic D 65/8; Corvic D 75/10; Corvic D 6518; Corvic H 55/34; Corvic P 65/50; Corvic P 65/54; Corvic P 65/55; Corvic R 65/81; Corvic S 46/70; Dacovin; Dacovin 2082; Danuvil 70; Darvic 110; Darvis Clear 025; Daycell; Decelith H; Denka Vinyl SS 80; Denka Vinyl SS-Y; Diamond Shamrock 40; Diamond Shamrock 71; Diamond Shamrock 450; Diamond Shamrock 7602; DN 4; DN 5; Dorlyl; Durofol P; Dynadur; E 62; E 66; Ekavyl SD 2; Ekavyl SDF 58; Ekavyl SK64; Ekavyl SK66; E 66P; 103EP8; E-PVC; Escambia 2160; Escambia 2200; Europhan; Exon 605; Exon 640; Exon 654; Exon 965; Exon 9269; Exon 9290; Exon 9269A; FC 4648; Flocor; Genotherm; Genotherm N; Genotherm UG 200; Geon 51; Geon 59; Geon 72; Geon 101; Geon 103; Geon 110X233; Geon 120X241; Geon 121; Geon 124; Geon 126; Geon 128; Geon 131; Geon 151; Geon 85542; Geon 101EP; Geon 102EP; Geon 103EP; Geon 103EP8; Geon 103EPF7; Geon 135J; Geon 121L; Geon Latex 151; Guttagena; Halvic 223; Halvic 229; HC 825; Hi-S Film No. 111L; Hishirex 502; Hishirex 502Z; Hispavic 229; Hostalit; Hostalit E; Hostalit P 7078; Hostalit PVP 3475; Hostalit PVP 5470; Hostalit S; Hostalit S 4070; HX-M; Igelite F; Igelite P; Improved Wilt Pruf; Kanevinyl PSH 10; Kanevinyl PSL 81; Kanevinyl S 1001; Kanevinyl S 1007; KhS 010; KhSE 3; Klegecell; Kohiner R 687; KR 800;

Kureha S 901; L 5; Lak Kh SL; Lonza 380 ES; Lonza G; Lucoflex; Lucovyl BB 800; Lucovyl BB 8010; Lucovyl GB 1150; Lucovyl GB 9550; Lucovyl GS 1200; Lucovyl GS 8001; Lucovyl PB 1302; Lucovyl PE; Lucovyl PE 1100; Lucovyl PE 1290; Lucovyl PE 1311; Lucovyl PE 1355; Lucovyl RB 8010; Lutofan; Marvinal; Marvinol; Marvinol 14; Marvinol 53; Marvinol 57; Marvinol 7000; Marvinol VR 50; Marvinol VR 53; Mirrex MCFD 1025; Movinyl 100; Mowilith F; Myraform; NIKA-TEMP; Nikavinyl SG 700; Nipeon A 21; Nipol 576; Nipolit CM 081; Nipolit SK; Nipolit SK 081; Nipolit SL 082; Nipolit SM 092; Nipolit SV 13081; Norvinyl; Norvinyl P 2; Norvinyl P10; Norvinyl S 1-70.; Norvinyl S 1-80; Norvinyl S 3-68; Novon 712; Ongrovil S 165; Ongrovil S 470; Opalon; Opalon 410; Opalon 440; Opalon 610; Opalon 630; Opalon 650; Opalon 660; Opalon R 7611; Ortodur; P 400 (vinyl polymer); Pantasote R 873; Pattina V 82; Pevikon D 61; Pevikon KL 2; Pevikon PE 709; Pevikon PE 712; Pevikon PS 690; Pevikon R 23; Pevikon R 25; Pevikon R 45; Pevikon R 341; Pevikon S 602; Pliovic D 100X; Pliovic DB 80V; Pliovic K 906; Pliovic K 90E; Pliovic S 50; POK 60; Polivinit; Polwinit; Polyco 2622; Polytherm; Porodur; Prototype III Soft; PVKhL 4; PVKhS 60; PVKh-S 60; PVKh-S 65; PVKh-S 63Zh; QSAH 7; QSAN 7; Quirvil; Quirvil 278; QYSA; Ravinil R 100/65D; Rucon B 20; Ryurene S 800B; S 61; S 65 (polymer); S 70; S 901; Scon 5300; Sicron; Sicron 530; Sicron 540; Sicron 548; Sicron 548FM; SKhV 71; S-Lon; SM 200; Solvic; Solvic 223; Solvic 229; Solvic 239; Solvic 334; Solvic 340; Solvic 406; SP 60; SP 60 (chlorocarbon); SR11; Sumilit EXA 13; Sumilit PXA 13; Sumilit PX-A; Sumilit PX-N; Sumilit PXNH; Sumilit PX-NL; Sumilit SX 11; Sumilit SX 13; Sumilit S χ-D; Sumilit SX 7G; Sumilit VS

9200; Sumitomo PX 11; SV 55; SX 11; SX 7G; SX 8T; Takilon; Technopor; Tenneco 1742; TK 1000; Tocryl C 440; Trovidur; Trovidur N; Trovithern HTL; TS 1100; U 1; U 1 (polymer); Ultron; VA 15; VC 100; VC 410; Veron P 130/1; Vestolit B 7021; Vestolit GH; Vestolit S 60; Vestolit S 6554; Vestolit S 6857; Vestolit S 7054; Vestolit S 7554; Vestolit S 8054; Vinika KR 600; Vinika KR 800; Vinika 37M; Vinika 35R; Vinikulon; Viniplast; Viniplen P 73; Viniplen P 74; Viniplen P 73E; Viniplen P 73EM; Vinnol E 75; Vinnol H 100/65; Vinnol H 100/70; Vinnol H 60d; Vinnol H 70D; Vinnol H 100/70d; Vinnol H 75F; Vinnol P 70; Vinnol P 70E; Vinnol P 100/70e; Vinnol Y; Vinoflex; Vinoflex P 313; Vinylchlon 4000LL; Vinylite QYJV; Viplast RA/F; Volgovinyl E 62; Volgovinyl E 62P; Volgovinyl E 66P; VSKh-S; Vygen 85; Vygen 110; Vygen 120; Vygen 313; Welvic G 2/5; Welvic PRIO 953; Welvic PRO 686; Welvic R 7/622; Welvic RI 7/316; Welvic RIO 715; Wilt Pruf; Winidur; X-AB; Yugovinyl

1.2 Structural and molecular formulae and molecular weight



$(C_2H_3Cl)_n$ Mol. wt: 60 000–150 000 (average)

1.3 Chemical and physical properties of the polymer

From Windholz (1976), unless otherwise specified

(a) Description: White or colourless granules (Hawley, 1971)

(b) Density: 1.406

(c) Refractive index: n 1.54

(d) Solubility: Solvents for unmodified polyvinyl chloride (PVC) of high molecular weight are: cyclohexanone, methyl cyclohexanone, dimethyl formamide, nitrobenzene, tetrahydrofuran, isophorone and mesityl oxide. Solvents for lower polymers are: di-*n*-propyl ketone, methyl amyl ketone, methyl isobutyl ketone, acetonylacetone, methyl ethyl ketone, dioxane and methylene chloride.

(e) Stability: PVC is unstable to heat and light in the absence of added stabilizers. Thermal decomposition products can include ethylene, benzene, toluene (Eckardt & Hindin, 1973), 1,3,5-trichlorobenzene (Tsuge, 1969) and naphthalene (Dyer & Esch, 1976).

1.4 Technical products and impurities

A wide variety of vinyl chloride homo- and copolymers are available, with varying properties designed for specific applications. Consequently, the specifications vary widely.

PVC resins for the production of rigid plastics are processed essentially without plasticizer: the polymer may be a homopolymer or a copolymer made with low levels of comonomer such as vinyl acetate or ethylene. The comonomers are used to aid in the processing of the resulting polymer.

Most of the flexible and semi-rigid PVC plastics contain plasticizers at a level of 10–100% of the resin weight. The plasticizers most commonly used are dialkyl phthalates (e.g., dioctyl phthalate). Other compounding materials (such as pigments, fillers and light- and heat-stabilizers) are also used.

PVC dispersion or paste resins are used in the form of plastisols (PVC resin dispersed in plasticizer). In Europe, significant amounts of PVC are used in the form of latexes; in the USA very little of the latex form is used.

For concentrations of unreacted vinyl chloride monomer in various PVC samples, see p. 382.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

A method for the synthesis of PVC was reported in 1872 (Baumann, 1872) Commercial homopolymers of vinyl chloride were introduced in 1933 (Darby & Sears, 1968). Vinyl chloride polymer is currently produced by one of four processes: suspension, emulsion, bulk or solution polymerization. In the USA in 1976, over 80% of homopolymers and copolymers were produced by the suspension polymerization process.

In 1976, 22 US companies reported production of 2065 million kg PVC resins of all types (US International Trade Commission, 1977); approximately 230 million kg of the total were copolymers. US exports of uncompounded PVC resins in 1977 were about 72 million kg, and exports of compounded PVC (excluding any additives in compounded products) were approximately 39 million kg. These exports went primarily to Belgium (13%), Brazil (12%), Canada (21%), Iran (6%), New Zealand (7%) and Venezuela (13%). US imports of PVC resins are negligible (approximately 1% of domestic production).

Total western Europe production in 1976 amounted to 3745 million kg. The major producers were the following countries (production in millions of kg): Austria (40), Belgium (200), the Federal Republic of Germany (1020), Finland (35), France (615), Greece (25), Italy (675), The Netherlands (290), Norway (55), Portugal (15), Spain (215), Switzerland (30), Sweden (110) and the United Kingdom (415). Exports from western Europe in that year were 1050 million kg and imports 690 million kg.

PVC was first produced commercially in Japan prior to 1946. In 1976, nineteen companies produced a total of 1044 million kg; 121 million kg were exported, and 15 million kg imported.

(b) Use

Use of PVC resins in the USA in 1976 was as follows: building and construction industries (49%), consumer goods (15%), electrical applications (8%), packaging (9%) and transportation (7%), with miscellaneous uses accounting for the remainder. Since 1968, the major uses have been in the building and construction industries, in consumer goods, packaging and electrical wire insulation.

In building and construction, PVC resins are used in piping and conduits (including water pipes), in flooring, in windows and other rigid structures, in pipe fittings, in sidings and as swimming-pool liners. They are used in such consumer products as upholstery, wall coverings, garden hoses and appliances and also in gramophone records, stationery supplies, footwear, toys, outerwear and sporting

goods. Electrical applications consist primarily of wire and cable insulation. The major uses of PVC in packaging are in plasticized film, bottles and bottle-cap liners and gaskets; however, in the USA, its use for packaging of alcoholic beverages has been banned because of migration of vinyl chloride monomer into the alcohol. Major uses in transport include upholstery and seat covers, automotive tops and automotive floor mats.

In 1975, 27 million kg PVC were used in Europe and 14 million kg in the US Ain plastic materials for medical applications, including external tubing and catheters; in sheet form for splints; and in shunts, balloons, blood storage bags, cannulae, surgical drapes and packaging containers for parenteral substances (Halpern & Karo, 1977).

The 1977 western Europe use pattern for PVC was as follows: piping and fittings (24%), rigid and flexible films (20%), profiles (12%), cable (10%), artifical leather cloth (8%), bottles (7%), gramophone records (3%) and other uses (16%).

In Japan in 1976, it was used as follows: piping (31%), film (17%), sheet (14%), extrusions and artifical leather (12%), wire/cable (11%) and other, including flooring (15%).

The US Food and Drug Administration permits the use of PVC as a component of the following products when they are intended for use in contact with food: (1) adhesives; (2) resinous and polymeric coatings; (3) paper and paperboard (in contact with dry food only); and (4) semi-rigid and rigid acrylic and modified acrylic plastics. The amount present may not exceed that which is reasonably required to produce the intended effect (US Food and Drug Administration, 1977).

An estimated 700 000 to 2 million workers are employed in the production of PVC in the USA (Infante, 1977).

2.2 Occurrence

PVC is not known to occur as a natural product.

It has been estimated that prior to 1975 more than 22.7 million kg, may have been discharged into the environment in the USA. These losses occurred as particulates in air emissions, suspended solids in water effluents, and components of solid wastes (US Environmental Protection Racy, 1974b). Workers in the USSR have been exposed to PVC dust in the production of block polymer (Filatova *et al*., 1974).

The disposal of PVC by ocean dumping, as solid waste, as landfilling and by incineration has been reviewed (US Environmental-Protection Agency, 1974b,c).

2.3 Analysis

No information was available to the Working Group on methods for determining PVC residues in foods or other parts of the environment.

A rapid and simple way of identifying fifteen packaging films, including PVC, has been described in which the films were treated with ten different solvents and the solubility and physical appearance of the film at room temperature and at the boiling-points of the solvents were noted (Van Gieson, 1969).

Plastics, including PVC, have been identified by measurement of the pH of an aqueous solution of the pyrolysis products, followed by thin-layer chromatography, and by reaction of PVC with pyridine (Braun & Nixdorf, 1972).

PVC has been separated from plasticizers, stabilizers, modifiers, fillers, pigments and other inorganic additives by gel permeation chromatography or sequential solvent extraction. The resulting additive-free fraction has been analysed by chlorine analysis, infrared spectroscopy, molecular-weight determination by viscosity measurements and thermal gravimetry and differential thermal analysis (Brookman, 1974).

Pyrolysis–gas chromatography has been proposed to identify PVC in polymers used in medical applications (Nematollahi *et al*., 1970), in three commercial polymers (in this case, pyrolysis–gas chromatography was used in combination with thermogravimetric analysis and differential thermal analysis) (Boettner *et al*., 1969), and among some chlorine-containing polymers (Tsuge *et al*., 1969). Pyrolysis-gas chromatography has also been used to identify polymers, including PVC, among 37 commercial polymers (Okumoto & Takeuchi, 1972), in plastics and rubbers (Fischer, 1967) and in adhesives used in building (in this case, pyrolysis–gas chromatography was used in combination with thermogravimetry, differential thermogravimetry and differential thermal analysis) (Rona, 1971).

Thin-layer chromatography of pyrolysis products has been used to identify high polymers, including PVC (Pastuska, 1969).

Thermogravimetry and infrared spectral analysis have been used to determine PVC in floor tiles (Powell, 1974).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

Subcutaneous or intraperitoneal administration

Rat: A group of 45 adult Wistar rats were given subcutaneous implants in the abdominal wall of squares or discs of a commercial PVC known to contain some additives; the implants were 0.04 mm thick and 15 mm wide. At the appearance of the first tumour, 44 animals were still alive. Seventeen (38.6%) malignant tumours (fibrosarcomas and one liposarcoma) developed at the site of film implantation, with a latent period of 189–727 days; a similar but perforated film did not produce local tumours in 27 rats at risk. No local tumours were found in a group of 50 rats given a subcutaneous implant of cotton (Oppenheimer *et al*., 1952, 1955). With a pure PVC film of 0.03 mm thickness, four malignant tumours were obtained after 533 days in a similar group (Oppenheimer *et al*., 1955) [The Working Group noted that the reporting of this experiment was preliminary and that final results were never forthcoming].

Groups of 35 (male and female) Wistar rats were given a subcutaneous implant into the abdomen of PVC film 4 × 5 × 0.16 mm. A group of 25 control rats received an implant of glass of similar size. After 300 days, 30 and 20 animals were still alive in the two groups, respectively; all surviving rats were killed 800 days after implantation. One sarcoma and one fibroma were found after 580 days in the PVC-treated rats, whereas no local tumours developed in the control group (Russell *et al*., 1959).

A group of 80 outbred albino rats [sex unspecified] received implants [of unstated size] of PVC film by laparotomy to surround the kidney. The animals were sacrificed at 3, 10, 15, 30, 90, 195, 285, 300 and 380 days after the implantation. Of rats that survived 285–375 days, 6/16 developed fibrosarcomas at the site of implantation (Raikhlin & Kogan, 1961).

In rats implanted in the kidney with either PVC capsules, whole PVC films or perforated PVC films, 5/16, 2/5 and 1/5 sarcomas were observed (Kogan & Tugarinova, 1959).

[1] The Working Group was aware of a study in progress to assess the carcinogenicity of PVC powder by inhalation exposure and intrapleural administration to rats (IARC, 1978a).

3.2 Other relevant biological data

(a) Experimental systems

Rats and guinea-pigs exposed continuously to PVC dust for 24 h per day for periods varying from two to seven months were found to have extensive lung damage (Frongia *et al*., 1974).

The growth of granulation tissue around PVC particles implanted into the muscles of rabbits has been reported (Guess & Stetson, 1968). Severe fibroblastic reactions were found in rats (Calnan, 1963) and dogs (Harrison *et al*., 1957) which received PVC sponge implants into the subcutaneous tissue of the anterior abdominal wall.

Ingested and rectally absorbed PVC particles (5–110 μm) were found to be transported by both the lymphatic and the portal system from the intestinal wall of rats, guinea-pigs, rabbits, chickens, dogs and pigs (Volkheimer, 1975).

In rats, inhalation of fumes from heated PVC produced interstitial oedema, as well as focal bronchial and intra-alveolar haemorrhage in the lungs of some animals (Cornish & Abar, 1969).

No data on the embryotoxicity, teratogenicity, metabolism or mutagenicity of this compound were available to the Working Group.

(b) Humans

Workers exposed to PVC dust during the manufacture of articles made from PVC showed alterations in the respiratory organs (e.g., changed bronchovascular pattern, increased pulmonary ventilation at rest) (Vertkin & Mamontov, 1970).

Pneumoconiosis due to inhalation of PVC dust was suggested following pulmonary biopsies in a male patient who had inhaled PVC dust for one year and exhibited granulomatous lesions due to foreign bodies. The severity of the disease was shown by the observed dyspnoea, secondary polyglobulia and reduced respiratory function (Szende *et al*., 1970).

Fibrotic lung changes and altered pulmonary function tests have been reported in 96 workers exposed to PVC dust; the changes were more pronounced in those with long exposure (Lilis *et al*., 1976; Waxweiler *et al*., 1976).

Reduced pulmonary function and an enhancement of pulmonary function defects associated with an increased risk of respiratory impairment were noted in a number of nonsmoking workers exposed to an occupational environment contaminated with vinyl chloride fumes and PVC dust (Miller, 1975; Miller *et al*., 1975).

In 15 polyvinyl production workers employed in 'PVC-processing industries', where stabilizers, colours and bulk materials were added to and mixed with the basic PVC powder, the following pathological findings were reported: in seven, slight to moderate thrombocytopenia; in seven, increased bromosulphalein retention; in six, reticulocytosis; in one, leucopenia; and in one, slight splenomegaly. Neither scleroderma-like skin changes nor Raynaud's syndrome were observed (Lange *et al*., 1975). A large proportion of abnormal liver function tests and platelet counts were found in a group 37 PVC process workers: 20% had abnormal alkaline phosphatase, 60% normal lactic dehydrogenase, 30% abnormal serum glutamic-oxaloacetic transaminase, 10% abnormal serum glutamic-pyruvic transaminase, and 35% abnormal platelets (Wegman, 1975).

Cases of 'meat-wrappers' asthma' have been reported, in which meat wrappers developed respiratory symptoms when exposed to fumes of PVC film sealed and cut with a hot wire. The identity of the causative agent(s) has not been established (Brooks & Vandervort, 1977; Falk & Portnoy, 1976; Polakoff *et al*., 1975; Sokol *et al*., 1973).

During the period 1970–75, 175 fire-fighters experienced respiratory distress due to the toxicity of hydrogen chloride gas released from the combustion of PVC plastics (Dyer & Esch, 1976). Carbon monoxide, hydrochloric acid and phosgene (Cornish & Abar, 1969; Dyer & Esch, 1976) have been reported as the major PVC pyrolysis products of toxicological importance, although more than 75 components have been identified following the thermal degradation of PVC (Dyer & Esch, 1976).

The few cases of dermatitis that have been reported are believed to be caused by sensitivity to plasticizers in polyvinyl plastics (Morris, 1953).

3.3 Case reports and epidemiological studies[1]

A proportional mortality study was carried out using death certificates from 1970–72 of 707 male plastic workers (extruding, moulding, cutting, turning or otherwise machining plastics, and including PVC fabricating). A statistically significant excess of stomach cancer mortality was found (24 observed versus 16.4 expected, $p < 0.05$) (Baxter & Fox, 1976) [The study is limited by the use of proportionate mortality methodology and by the fact that not all deaths studied were among workers engaged in activities directly involving PVC].

[1] The Working Group was aware of a study in progress on workers exposed to PVC (IARC, 1978c)

In a cross-sectional mortality study of 4341 deaths during 1964–73 among current and former employees of 17 PVC fabricators, an excess in total cancer mortality, particularly that of the digestive system, was reported among both white men and white women. The risk of cancer of the breast and urinary organs was also reported to be in excess among white women (Chiazze *et al*., 1977) [The study is limited by the use of proportionate mortality methodology and by the fact that not all deaths were among workers engaged in activities directly involving PVC].

Casterline *et al*. (1977) reported a case of a 22-year-old man who developed a squamous-cell carcinoma of the buccal mucosa as a result of a habit, acquired at the age of eight years, of chewing plastic materials containing PVC. No prior history of mouth or lip lesions, of smoking tobacco or drinking alcohol, or of occupational exposure to vinyl chloride was noted.

Vinyl chloride–vinyl acetate copolymers

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 9003-22-9

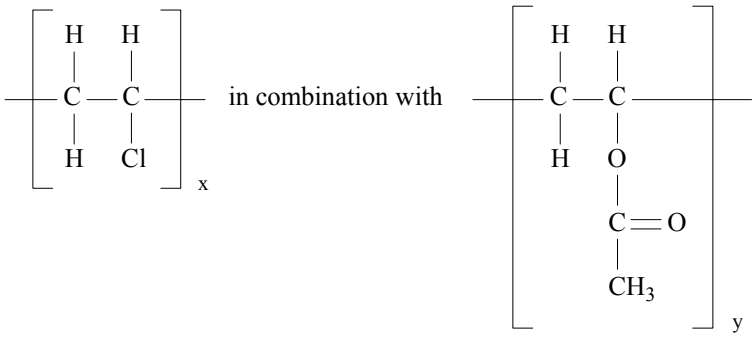
Chem. Abstr. Name: Acetic acid ethenyl ester polymer with chloroethene

Acetic acid vinyl ester polymer with chloroethylene; chloroethylene–vinyl acetate polymer; polyvinyl chloride–polyvinyl acetate; vinyl acetate–vinyl chloride copolymer; vinyl acetate–vinyl chloride polymer; vinyl chloride–vinyl acetate polymer

A 15; A 15 (polymer); A 15-0; A 15S; Bakelite LP 70; Bakelite VLFV; Bakelite VMCC; Bakelite VSJD 10; Bakelite VYHD; Bakelite VYHH; Bakelite VYNS; Bakelite VYNW; Breon 351; Breon 425; Breon AS 60/41; Corvic 51/83; Corvic 236581; Corvic R 46/88; Denkalac 41M; Denka Vinyl MM 90; Diamond Shamrock 744; Diamond Shamrock 7401; Exon 450; Exon 454; Exon 470; Exon 481; Exon 760; Flovic; Geon l00x150; Geon 130xl0; Geon 135; Geon 351; Geon 400x47; Geon 421; Geon 427; Geon 434; Geon 103EP-J; Geon 440L2; Geon 450x150PN; Geon 150XML; Geon 103ZX; Hostalit PVP; Leucovyl PA 1302; Lucovyl GA 8502; Lucovyl MA 6028; Lucovyl PA 1208; Marvinol VP 56; 50ME; Norvinyl P 6; Opalon 400; Pevikon

C 870; Pliovac AO; Pliovic AO; PVC Cordo; Resin 4301; Rhodopas 6000; Rhodopas AX; Rhodopas AX 30/10; Rhodopas AX 85/15; Sarpifan HP 1; Solvic 523KC; Solvic PA 513; Solvic 513PB; Sumilit PCX; Tennus 0565; VA 3 (copolymer); VAGD; VH 10/60; Vilit 40; Vinnol H 10/60; Vinnol H 15/45; Vinnol H 40/60; Vinylite VGHH; Vinylite VYDR; Vinylite VYDR 21; Vinylite VYFS; Vinylite VYHD; Vinylite VYHH; Vinylite VYNS; Vinylite VYNW; Vinyon; VTVF; VMCC; VYHH; VYNS; VYNW

1.2 Structural and molecular formulae and molecular weight



$(C_2H_3Cl)_x$–$(C_4H_6O_2)_y$ Mol. wt: ~100 000

1.3 Chemical and physical properties of the copolymers

(a) Description: White powder

(b) Stability: Sensitive to excessive exposure to heat and light in the absence of added stabilizers. Hydrogen chloride gas is a decomposition product of degradation.

1.4 Technical products and impurities

Low levels of vinyl acetate are copolymerized with vinyl chloride obtain resins with specific properties. Depending upon the use, the vinyl acetate level may vary from 2–20%, with an average of 11–12%. As described in the monograph on polyvinyl chloride, p. 405, various additives are used to aid in processing the resins.

No detailed information on the possible presence of unreacted monomers in the copolymers was available to the Working Group.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Vinyl chloride–vinyl acetate copolymers were introduced commercially in 1934 (Darby & Sears, 1968). Most of these copolymers are manufactured by free radical-initiated suspension and emulsion polymerization techniques; solution polymerization is used for the manufacture of some special coating resins. In the USA, over 80% of vinyl chloride–vinyl acetate copolymer resins are made by suspension processes.

In 1976, five US companies produced 230 million kg vinyl chloride–vinyl acetate copolymer resins.

Western European production in 1977 was 200 million kg.

About 30 Japanese companies produced a total of 6 million kg of these copolymers in 1976.

(b) Use

In the USA, the major use for vinyl chloride–vinyl acetate copolymers is in the production of vinyl asbestos flooring tiles (a declining market) and gramophone records. Other applications include injection moulding, rigid sheet production and coatings.

Copolymers containing about 13% vinyl acetate are used for floor tiles and gramophone records; others with lower levels of vinyl acetate are used for sheet extrusion and injection moulding. The resins used for soluble coating resins contain from 4–10% vinyl acetate and may be further modified. Solutions of these copolymers in solvents such as cyclohexane and tetrahydrofuran are used in coatings of tin cans and metals, and for maintenance coatings.

In western Europe vinyl chloride–vinyl acetate copolymers were used in 1977 in gramophone records (50%), vinyl asbestos flooring tiles (35%), film (10%) and coatings (5%).

The US Food and Drug Administration permits the use of vinyl chloride–vinyl acetate copolymers as components of the following products when they are intended for use in contact with food: (1) adhesives; (2) resinous and polymeric coatings, including those for polyolefin films; (3) paper and paperboard; (4) semirigid and rigid acrylic and modified acrylic plastics. The amount present may not exceed that which is reasonably required to produce the intended effect (US Food and Drug Administration, 1977).

2.2 Occurrence

Vinyl chloride–vinyl acetate copolymers are not known to occur as natural products.

2.3 Analysis

Pyrolysis–gas chromatography has been used to identify vinyl acetate–vinyl chloride copolymers in paints and plastics (May *et al*., 1973) and polymeric materials, including these copolymers, in 37 commercial polymers, (Okumoto & Takeuchi, 1972). Combined pyrolysis–gas chromatography, thermogravimetry, differential thermogravimetry and differential thermal analysis have been used to identify polymers, including vinyl acetate–vinyl chloride copolymers, in adhesives used in building (Rona, 1971).

The vinyl resin content of vinyl floor tiles, including vinyl acetate–vinyl chloride copolymers, has been determined by thermogravimetric and infrared spectrophotometry (Powell, 1974).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Subcutaneous and/or intramuscular administration

Mouse: A group of 82 (male and female) 1.5–2-month-old CBA/H-T6 mice received a subcutaneous implant of a piece of 15 × 22 × 0.2 mm film made of vinyl chloride–vinyl acetate copolymer. Sarcomas at the site of implantation developed in 65% of males within 9–12 months and in almost all the females after 7–12 months. A control group of 80 mice with no implants developed no subcutaneous tumours (Brand *et al*., 1967a,b, 1975).

Groups of 30 male and 46 female six-week-old CBA mice were given subcutaneous implants of vinyl chloride–vinyl acetate copolymer powder (particle size, 50–100 μm), corresponding by weight to two films of 15 × 22 × 0.2 mm, and were observed until death. No treatment-related tumours were reported; however, one sarcoma found in a female was attributable to clumping of the powder (Brand *et al*., 1975).

Groups of 9–124 male and female mice of 18 strains were given subcutaneous implants of 15 × 22 × 0.2 mm or 7 × 15 × 0.2 mm vinyl chlorid–-vinyl acetate copolymer films to test strain differences in response. The incidence of tumours was 90–100% in CBA/H and CBA/H-T6 female mice, AKR/J males, BALB/cJ and BALB/cWat females, C57BL/10ScSn females and (C57BL/10ScSn × CBA/H)F_1 males and females. No tumours were induced in males of strain I/LnJ or strain SJL/J. The tumour incidence in other strains was intermediate, the males being less sensitive than females, except for AKR mice (Brand *et al*., 1977).

3.2 Other relevant biological data

(a) Experimental systems

An aqueous dispersion of a vinyl chloride–vinyl acetate copolymer administered orally at a dose of 10 mL per day to rats or rabbits decreased the reticulocyte count and caused changes in the blood serum protein fractions and histological changes in the stomach and liver. Inhalation of the dry residue at concentrations of 4.2 mg/m^3 in air decreased body-weight gain and caused pneumonia and peribronchitis. Application of this preparation to the skin decreased reticulocyte and leucocyte counts and haemoglobin levels (Ivanova & Shamina, 1973).

In rats, inhalation of fumes from heated vinyl chloride–vinyl acetate copolymer produced focal oedema and intra-alveolar haemorrhages of the lung (Cornish & Abar, 1969).

No toxic effects were reported in male and female Wistar albino rats following daily intakes of 0.61 or 5.75 g/kg bw vinyl resin (copolymer of 95% vinyl chloride and 5% vinyl acetate) for two years (Smyth & Weil, 1966).

No data on the embryotoxicity, teratogenicity, metabolism or mutagenicity of this compound were available to the Working Group.

(b) Humans

Two cases of dermatitis have been reported in people wearing Elastiglass garters (vinyl chloride–vinyl acetate copolymer) (Zeisler, 1940).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Vinyl chloride was tested in rats by oral, subcutaneous and intraperitoneal administration and in mice, rats and hamsters by inhalation exposure. Following oral and inhalation exposure, vinyl chloride was carcinogenic in all three species, producing tumours at different sites, including angio-sarcomas of the liver. Vinyl chloride was carcinogenic in rats following prenatal exposure. A dose-response effect has been demonstrated.

The results of subcutaneous and intraperitoneal injection studies in rats are incomplete and cannot be evaluated.

Vinyl chloride is mutagenic.

Polyvinyl chloride was tested in rats by subcutaneous and intraperitoneal implantation; local sarcomas were induced, the incidence of which varied with the size and form of the implant.

Vinyl chloride–vinyl acetate copolymers were tested in mcie by subcutaneous implantation as films or powder; local sarcomas were induced following implantation of films.

4.2 Human data

Vinyl chloride is manufactured on a vast scale, and exposure involves workers in the production, polymerization and processing industries. Also, large sections of the general population may have some exposure to vinyl chloride, particularly through direct or indirect contact with polymer products.

Several independent but mutually confirmatory studies have shown that exposure to vinyl chloride results in an increased carcinogenic risk in humans, involving the liver, brain, lung and haemo-lymphopoietic system.

In one epidemiological study, an excess of foetal mortality was reported among wives of workers who had been exposed to vinyl chloride, indicating a possible mutagenic effect in human germ cells. Several investigations have detected an increase in chromosomal aberrations in lymphocytes of workers exposed to vinyl chloride. Increased rates of birth defects among children of parents residing in communities where vinyl chloride–polyvinyl chloride or other chemical processing plants are located have been reported in several other studies. These suggest teratogenic and/or mutagenic effects of vinyl chloride in humans.

In two proportionate mortality studies, in which death certificates of workers who had been involved in the fabrication of plastics, including polyvinyl chloride, were analysed, there appeared to be an increased proportion of cancer of the digestive system in both sexes and possibly of the urinary system and of the breast in women.

4.3 Evaluation

Vinyl chloride is a human carcinogen. Its target organs are the liver, brain, lung and haemo-lymphopoietic system. Similar carcinogenic effects were first demonstrated in rats and were later confirmed in mice and hamsters. Although evidence of a carcinogenic effect of vinyl chloride in humans has come from groups occupationally exposed to high doses of vinyl chloride, there is no evidence that there is an exposure level below which no increased risk of cancer would occur in humans.

Epidemiological reports regarding clastogenic effects among vinyl chloride-exposed workers and a single study of increased foetal mortality among the wives of workers who had been exposed to vinyl chloride suggest that vinyl chloride could be mutagenic to humans. Additional support for this suggestion derives from experimental evidence of its mutagenicity.

Studies which indicate increased rates of birth defects among the children of parents residing in communities where vinyl chloride production and polymerization plants are located indicate the necessity for further investigation of the teratogenicity of vinyl chloride and its polymers in both animals and humans.

The available studies on polyvinyl chloride, which indicate an elevated proportion of digestive system cancer in male and female workers and possibly of cancers of the breast and urinary organs in female workers involved in the fabrication of plastics, including polyvinyl chloride, are insufficient to evaluate the carcinogenicity of this compound.

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Appendix F: IARC. (1987). *Overall Evaluations of carcinogenicity: An Updating of the IARC Monographs. Volumes 1 to 42.* Monographs on the Evaluation of the Carcinogenicity. Suppl. 7. Lyon, France. World Health Organization. pp. 373-376.

Vincristine sulphate induced micronuclei in bone-marrow cells of mice and hamsters treated *in vivo*. Conflicting results were obtained for induction of sister chromatid exchanges in human lymphocytes *in vitro*. It induced aneuploidy in and transformation of Syrian hamster embryo cells, but it did not transform mouse C3H 10TI/2 cells. It did not induce chromosomal aberrations, sister chromatid exchanges or unscheduled DNA synthesis in rodent cells *in vitro*. It induced mutation in mouse lymphoma cells but not in other rodent cells. It did not induce sex-linked recessive lethal mutations in *Drosophila* and was not mutagenic to bacteria[2].

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VINYL CHLORIDE (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Vinyl chloride has been associated with tumours of the liver, brain, lung and haematolymphopoietic system[1]. A large number of epidemiological studies[2-12] and case reports[13-25] have substantiated the causal association between vinyl chloride and angiosarcoma of the liver. Several studies also confirm that exposure to vinyl chloride causes other forms of cancer, i.e., hepatocellular carcinoma[13,19,23,26], brain tumours[11,27], lung tumours[12,28-30] and malignancies of the lymphatic and haematopoietic system[11,29,31]. Exposure to polyvinyl chloride dust was associated with an increased incidence of lung tumours in one study; the authors suggested that trapped vinyl chloride monomer was responsible[30]. Melanoma occurred in excess in one study[12] but has not been mentioned in others. Slightly elevated risks for gastric[29] and gastrointestinal cancer (other than liver cancer)[32] were indicated in some studies, but these were not confirmed in others.

B. Evidence for carcinogenicity to animals (*sufficient*)

Vinyl chloride administered orally or by inhalation to mice, rats and hamsters produced tumours in the mammary gland, lung, Zymbal gland and skin and angiosarcomas of the liver[1]. Similar findings were made in more recent studies[33-39]. In one, a combination of oral administration of ethanol and inhalation of vinyl chloride resulted in more liver tumours (including angiosarcomas) than after treatment with vinyl chloride alone[40].

C. Other relevant data

Chromosomal aberrations were induced in peripheral blood lymphocytes of workers exposed to vinyl chloride at levels of 5-500 ppm (13-1300 mg/m^3). Two studies reported negative results for sister chromatid exchanges in exposed workers, while in another study a weakly positive response was found[41].

Vinyl chloride induced chromosomal aberrations, sister chromatid exchanges and micronuclei in rodents exposed *in vivo* but did not induce mutation in the mouse spot test or dominant lethal mutations in rats or mice. It alkylated DNA in several tissues of mice and rats exposed *in vivo*. Vinyl chloride induced sister chromatid exchanges in human lymphocytes *in vitro*. It induced mutation in Chinese hamster cells and unscheduled DNA synthesis in rat hepatocytes *in vitro* and induced transformation of BALB/c $3T^3$ cells and virus-infected Syrian hamster cells. It induced sex-linked recessive lethal mutations, but not aneuploidy, heritable translocations or dominant lethal mutations in *Drosophila*. It was mutagenic to plants and to *Schizosaccharomyces pombe* but not to other fungi; it induced gene conversion in yeast. It caused DNA damage and mutation in bacteria. Vinyl chloride bound covalently to isolated DNA in the presence of a metabolic system[41].

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VINYLIDENE CHLORIDE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one epidemiological study of 138 US workers exposed to vinylidene chloride, no excess of cancer was found, but follow-up was incomplete, and nearly 40% of the workers had less than 15 years' latency since first exposure[1]. In a study in the Federal Republic of Germany of 629 workers exposed to vinylidene chloride, seven deaths from cancer (five bronchial carcinomas) were reported; this number was not in excess of the expected value. Two cases of bronchial carcinoma were found in workers, both of whom were 37 years old, whereas 0.07 were expected for persons aged 35-39 years[1,2]. The limitations of these two studies do not permit assessment of the carcinogenicity of the agent to humans. No specific association was found between exposure to vinylidene chloride and the excess of lung cancer noted previously in a US synthetic chemicals plant[1].

B. Evidence for carcinogenicity to animals (*limited*)

Vinylidene chloride was tested for carcinogenicity in mice and rats by oral administration and by inhalation, in mice by subcutaneous administration and by topical application, and in hamsters by inhalation. Studies in mice and rats by oral administration gave negative results. In inhalation studies, no treatment-related neoplasm was observed in rats or hamsters. In mice, a treatment-related increase in the incidence of kidney adenocarcinomas was observed in male mice, as were increases in the incidences of