	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		?	?	T(-)
Mammals *(in vivo)*			?	
Humans *(in vivo)*				

T = cell transformation

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VINYL CHLORIDE (Group 1)*

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

Vinyl chloride causes angiosarcomas of the liver; it has also been associated with tumours of the brain and lung and of the haematopoietic and lymphatic systems in humans. Reports of increased incidences of tumours of the digestive system, urinary tract and breast (in women) are inadequate to evaluate the carcinogenicity of vinyl chloride for these sites[1].

* Categorized as Group 1 by the previous Working Group, and data on humans and on animals not reevaluated by the present Group.

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

Vinyl chloride is carcinogenic to mice, rats and hamsters after its administration orally or by inhalation, producing tumours at several sites, including angiosarcomas of the liver[1].

C. Evidence for activity in short-term tests (*sufficient*)

Vinyl chloride induced DNA damage in prokaryotes and in mammalian cells *in vitro*[2]. It was mutagenic to *Salmonella typhimurium* in the absence of an exogenous metabolic activation system[3] and to *Escherichia coli*, *Schizosaccharomyces pombe*[3] and *Saccharomyces cerevisiae*[4] but not to *Neurospora crassa*[3]. It was mutagenic to *Drosophila melanogaster*, inducing sex-linked recessive lethal mutations[3] and to hamster cells *in vitro*[5]. It induced chromosomal aberrations and sister chromatid exchanges in Chinese hamsters exposed *in vivo*[6]. It did not induce dominant lethal[3] or somatic mutations in mice[7]. Vinyl chloride alkylated the liver DNA of rats treated *in vivo*[8]. Chromosomal aberrations and sister chromatid exchanges were induced in workers exposed to vinyl chloride[3,10-12]. Most such data were obtained when exposure was to levels of 25 ppm. In follow-up studies, in which workers were exposed to levels that had been reduced to 15 ppm and lower, no aberration or sister chromatid exchange was reported[12,13]. Sister chromatid exchange incidence dropped to a normal level shortly after termination of exposure to higher levels; however, the incidence of chromosomal aberrations returned to normal only after two years[10]. [Thus, although sister chromatid exchanges were not observed in some studies, sampling may have occurred after the level returned to normal.]

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+	+		
Mammals *(in vivo)*	+	-	+	DL(-)
Humans *(in vivo)*			+	

DL = dominant lethal mutations

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VINYLIDENE CHLORIDE (Group 3)

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

In one epidemiological study of 138 workers exposed to vinylidene chloride (with no concomitant exposure to vinyl 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]. A study of 447 German and 182 foreign workers exposed to vinyl chloride

reported seven deaths from cancer, which was not in excess of expected values. 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. [The Working Group noted that this study has severe methodological weaknesses, e.g., no allowance for latency, no information on smoking habits, 76% loss from follow-up for the guest workers, young age structure of the cohort, and a reference category that can be considered valid only for the German workers.]

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

Vinylidene chloride was tested by oral administration to female rats and mice and to their offspring. In rats, liver and meningeal tumours, and in mice, liver and gastric tumours, were seen more frequently in treated than in control animals, although the differences were not statistically significant[3]. It was also tested in one experiment by inhalation in mice, rats and hamsters, inducing adenocarcinomas of the kidney in male mice and an increased incidence of mammary fibroadenomas and carcinomas in rats (although with no dose-response relationship). In hamsters exposed for 52 weeks, no tumour had occurred by 74 weeks, but the study was still in progress at the time of reporting[1].

C. Evidence for activity in short-term tests (*sufficient*)

Vinylidene chloride was mutagenic to bacteria in the presence of an exogenous metabolic activation system[1] and to yeast[1,4], but it was not mutagenic to V79 Chinese hamster cells *in vitro*[5]. It alkylated DNA in mammalian cells *in vitro*[8], and, at tumorigenic doses in mice, it produced minimal amounts of DNA alkylation and repair but massive amounts of tissue damage[6]. It did not induce dominant lethal mutations in mice[4]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		+		
Insects				
Mammalian cells (*in vitro*)	+	-		
Mammals (*in vivo*)				DL(-)
Humans (*in vivo*)				

DL = dominant lethal mutations

References

[1] *IARC Monographs*, *19*, 439-459, 1979

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

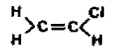
1.1 Synonyms and trade names

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_3Cl 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: Infra-red, 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 US 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 US for over fifty 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 UK (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 US 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 US 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 eight-hour time-weighted average of 2.6 mg/m^3 (1 ppm) in the workplace air in any eight-hour work shift of a forty-hour 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 minutes 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-hr) and ceiling concentrations (10- or 15-min), were as follows in 1977: Canada, 10 ppm (8-hr) and 25 ppm (15-min); Finland, 5 ppm (8-hr) and 10 ppm (10-min); Italy, 50 ppm (8-hr), although this is expected to change to 25 ppm (8-hr); Japan, expected to be 10 ppm; The Netherlands, 10 ppm (8-hr); Norway, 1 ppm (8-hr) and 5 ppm (15-min); Sweden, 1 ppm (8-hr) and 5 ppm (15-min); USSR, 12 ppm (Bertram, 1977). In France, the standards were reported to be 5 ppm for 1 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-hr); in Belgium, 5 ppm (1 week), ceiling 15 ppm; in the Federal Republic of Germany, the same as for France in existing factories, and 2 ppm (1 year) and ceiling 15 ppm (1-hr) for new factories; in the UK, 10 ppm (8-hr), ceiling 30 ppm max; and in Switzerland, 10 ppm (1 week, 8-hr day for 5 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 3 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/hr/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 UK 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 3 vinyl chloride plants in the US.

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, Texas, area (where an estimated 40% of the US production capacity is located) in concentrations of 8 µg/m -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, California, 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, Delaware, 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 US (Shackelford & Keith, 1976). The highest concentration of vinyl chloride detected in finished drinking-water in the US 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 2 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 4 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 a 5-litre 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 4-5 times/week for 52 weeks. After 85 weeks from the initial treatment, 35, 39, 32 and 23 animals were still alive. At 120 weeks, 9 liver angiosarcomas, 2 Zymbal gland carcinomas and 3 nephroblastomas occurred in rats administered the 16.65 mg/kg bw dose; and 16 liver angiosarcomas, 2 nephroblastomas, 1 Zymbal gland carcinoma, and 1 thymic and 1 intra-abdominal angiosarcoma were found in the 50 mg/kg bw group. One intra-abdominal angiosarcoma was seen in the low-dose group, and 1 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 hours/day on 5 days/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, 8 pulmonary tumours and 3 lymphomas were observed (Maltoni, 1977; Maltoni *et al.*, 1974).

[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, 100; acetic aldehyde, 5; acetylene, 2; allene, 5; butane, 8; 1,3-butadiene, 10; chloroprene (see also, p. 131), 10; diacetylene, 4; vinyl acetylene, 10; propine, 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 hours/day on 5 days/week for 9 months and were observed for an additional 9 months. After 8 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 I). 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 I

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	Angiosarcomas	Adenocarcinomas
	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 3-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 hours/day on 5 days/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, 8 mice had angiosarcomas, mammary adenocarcinomas were found in 4 animals, 1 mouse had an angiosarcoma of the liver, 1 an adenoma of the kidney and 1 an angiosarcoma of brown fat. In the control group, 3/48 had tumours: 1 adenocarcinoma of the mammary gland, 1 dysgerminoma of the ovary and 1 reticulum-cell sarcoma of the spleen (Holmberg *et al.*, 1976).

Groups of 36 male and 36 female 2-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 hours/day on 5 days/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 3-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 hours/day on 5 days/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, 2 mucoepidermoid carcinomas, 1 papilloma); in addition, lung tumours developed in 7 rats and osteochondromas in 5. 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 hours/day on 5 days/week for 17 weeks. At 86 weeks, 18, 15, 37, 33, 16 and 9 animals were still alive in the 6 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 4 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 II). 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 hours/day on 5 days/week for 43 weeks, 30 (50%) developed Zymbal gland carcinomas, 13, liver angiosarcomas and 1, 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 hours/day on 5 days/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, 1 Zymbal gland carcinoma was found, whereas at a comparable time the Sprague-Dawley rats had developed 29 such tumours. In the Wistar rats, 1 nephroblastoma, 8 liver angiosarcomas and 1 brain neuroblastoma were found in the 10 000 ppm group; 3 nephroblastomas, 2 liver angiosarcomas and 1 brain neuroblastoma in the 6000 ppm group; 3 liver angiosarcomas in the 2500 ppm group; and 1 nephroblastoma and 4 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 hours/day on 5 days/week for 5, 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; 1 (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 5 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 hours/day on 5 days/week for 5 weeks, starting at the age of 13 weeks (120 rats/group) or 1 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 2-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 hours/day on 5 days/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 3 and 13 (Lee *et al.*, 1977).

In a report of a study in progress, 4 groups of 80 Sprague-Dawley male rats received either 5% ethanol in the drinking-water or drinking-water only for 4 weeks prior to beginning inhalation of 1560 mg/m^3 (600 ppm) vinyl chloride for 4 hours/day on 5 days/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 hours/day on 5 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 1 each treated with 50, 2500 and 10 000 ppm developed melanomas. In addition, 6 lymphomas and 35 forestomach papillomas and acanthomas were found in treated animals, and 2 and 2, respectively, in controls (Maltoni, 1977a; Maltoni *et al.*, 1974).

Rabbit: A group of 40 rabbits were exposed for 4 hours/day on 5 days/week for 12 months to air containing 26 g/m^3 (10 000 ppm) vinyl chloride. Between 9-15 months of exposure, 12 skin acanthomas and 6 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 s.c. 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, 2, 3 or 4 times in 2 months. One nephroblastoma and 1 s.c. 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: 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 hours/day by inhalation from the 12-18th 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), 1 s.c. angiosarcoma was observed in each group of offspring; 1 animal exposed *in utero* to 6000 ppm had a Zymbal gland carcinoma; and 3 animals exposed to 10 000 ppm had Zymbal gland carcinomas, and 1, 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) Experimental systems

Toxic effects

The 2-hour 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-hour 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 hours/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 3 consecutive days and exposed on day 4 by inhalation to 62.5 g/m^3 (24 000 ppm) vinyl chloride for 4 hours 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 hours significantly increased the hepatotoxic effects, as measured by sorbitol 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 hours/day for 3 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 hours/day on 5 days/week. The highest dose caused some acute deaths with toxic hepatitis and marked tubular necrosis in the renal cortex. From the 6th 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 hours, as a function both of concentration and duration of exposure (Watanabe *et al.*, 1976a).

Vinyl chloride and two of its presumed metabolites, 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 hours/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 hours, 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 hours, respectively. ^{14}C-Radioactivity recovered from the carcass after 72 hours was 14 and 15%, respectively; no vinyl chloride *per se* was found in tissues. The proportions of 3 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 hours were 10, 11 and 2% of the 0.05, 1 and 100 mg/kg doses, respectively. Two of 3 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 i.v. 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 hours 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).

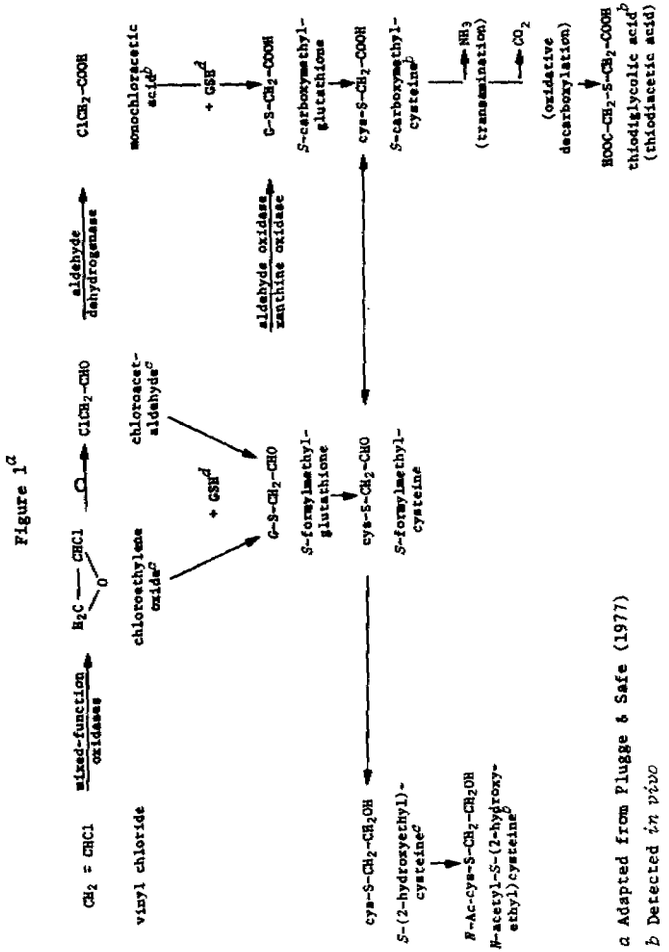
Vinyl chloride is metabolized by microsomal mixed-function oxidases to chloroethylene oxide, which can rearrange spontaneously to chloroacetaldehyde (Fig. 1). Although there is no direct evidence for this pathway *in vivo*, the following data are consistent with this hypothesis. Vinyl chloride in the 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*-acetyl-*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).

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).

Figure 1[a]



a Adapted from Plugge & Safe (1977)
b Detected *in vivo*
c Detected *in vitro*
d GSH = glutathione

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* G46, TA1530, TA1535 and TA100 in 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 x *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 hours/day for 5 days (Anderson *et al.*, 1976, 1977).

Exposure to vinyl chloride vapour in the presence of a 15 000 x *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* (Hussain & 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 7 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 (Jöhe & 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 1962-1969. 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 foetal 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 2 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 3 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

Chromosome 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 & 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 US.

[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 UK (Lee & Harry, 1974; Smith *et al.*, 1976b); the US (Block, 1974; Falk *et al.*, 1974a; Makk *et al.*, 1974); and Yugoslavia (Šarić *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 7 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 & Caffey, 1974) [Vital status was undetermined for 15% of the study cohort, and 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 5 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, 3 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 UK 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 reanalysing 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 5 or more years of employment and 10 years since onset of employment in departments or jobs with direct exposure to vinyl chloride at 1 of 4 vinyl chloride-polyvinyl chloride production plants in the US. 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 4 plants, 11 were angiosarcoma of the liver. Of 10 cases of brain cancer, 9 were classified histologically as glioblastoma multiforme, a cell type of brain cancer reported to be unusual in the US. Of the 14 cases of primary lung cancer, 5 were large-cell undifferentiated and 3 were adenocarcinoma.

In 771 workers employed in a Swedish vinyl chloride-polyvinyl chloride plant since its start in the early 1940's, a 4- to 5-fold 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 & Collier (1977) investigated the cancer mortality among 7561 males who were exposed to vinyl chloride in the manufacture of polyvinyl chloride in the UK 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 males 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 4 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 4-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 (Šarić *et al.*, 1976).