VINYL ACETATE

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

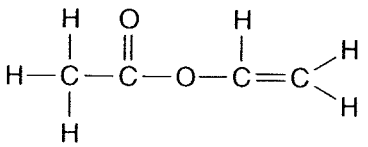
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 108-05-4
Deleted CAS Reg. Nos.: 61891-42-7; 82041-23-4
Chem. Abstr. Name: Acetic acid, ethenyl ester
IUPAC Systematic Name: Vinyl acetate
Synonyms: Acetoxyethene; acetoxyethylene; 1-acetoxyethylene; ethenyl acetate; ethenyl ethanoate; VA; VAC; VAM; vinyl A monomer

1.1.2 Structural and molecular formulae and relative molecular mass



$C_4H_6O_2$ Relative molecular mass: 86.09

1.1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Colourless liquid with an ether-like odour (Union Carbide Corp., 1981; Hoechst Celanese Corp., 1993)

(*b*) *Boiling-point*: 72.2 °C (Lide, 1993)

(*c*) *Melting-point*: –93.2 °C (Lide, 1993)

(*d*) *Density*: 0.9317 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [982]; grating [8112]), ultraviolet [1-29], nuclear magnetic resonance (proton [10245]; C-13 [1841]) and mass spectral data [136] have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Slightly soluble in water (20 g/L at 20 °C); soluble in acetone, benzene, diethyl ether, ethanol, chloroform and most organic solvents (Budavari, 1989; Lewis, 1993; Lide, 1993)

(*g*) *Volatility*: Vapour pressure, 100 mm Hg [13.3 kPa] at 23.3 °C (Lide, 1993); relative vapour density (air = 1), 3.0 (Hoechst Celanese Corp., 1993)

(*h*) *Stability*: Polymerizes in light to a colourless, transparent mass (Budavari, 1989)

(*i*) *Reactivity*: Vapour may react vigorously in contact with silica gel or alumina (Bretherick, 1985); can react with oxidizing materials (United States National Institute for Occupational Safety and Health, 1994a)

(*j*) *Octanol:water partition coefficient (P)*: log P, 0.73 (Hansch *et al.*, 1995)

(*k*) *Conversion factor*: $mg/m^3 = 3.52 \times ppm$[1]

1.1.4 Technical products and impurities

Various commercial grades of vinyl acetate are available, which differ in the amount and type of added inhibitor. Typically, 3–5 mg/L hydroquinone (see IARC, 1987b) are added if the chemical is to be stored for less than two months; for longer storage periods, 14–17 mg/L or even 20–30 mg/L hydroquinone are added. Typical specifications for vinyl acetate are: minimal purity, 99.9%; acidity (as acetic acid), 0.005% max.; acetaldehyde (see IARC, 1987c), 0.010% max. by weight; and water, 0.04% max. by weight (Union Carbide Corp., 1981; Hoechst Celanese Corp., 1993; Union Carbide Corp., 1994). Trade names for vinyl acetate include Vyac, Zeset T and RP 251.

1.1.5 Analysis

Selected methods for the analysis of vinyl acetate in various matrices are presented in Table 1.

1.2 Production and use

1.2.1 Production

The oldest process for producing vinyl acetate is the addition of acetic acid to acetylene, which was first accomplished by Klatte in 1912 in a liquid-phase process with a mercuric salt as a catalyst. The liquid-phase process was converted to a vapour-phase process, with a zinc salt as a catalyst, in Germany in the 1920s (Roscher *et al.*, 1983).

Production of vinyl acetate by the addition of acetic acid to ethylene (see IARC, 1994a) came into widespread use in the 1970s. Because ethylene is an inexpensive feed stock, essentially all manufacture since 1980 has been based on that compound (Daniels, 1983).

Both liquid-phase and vapour-phase processes are used. Liquid-phase processes, which were developed in Germany, Japan and the United Kingdom, involve palladium and copper salts as catalysts and production of vinyl acetate and acetaldehyde. The products are separated, and the acetaldehyde can be converted to acetic acid, which is fed back into the process. The vapour-phase process was developed independently by companies in Germany and the United States of America, and currently about 75% of world production is made by this technique (Roscher *et al.*,

[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

1983). The vapour-phase process differs from the liquid-phase in that very little acetaldehyde is formed. In Japan, most of the vinyl acetate produced by the vapour-phase process is used in the production of polyvinyl alcohol (see IARC, 1987d) via alcoholysis of polyvinyl acetate (see IARC, 1987e). The liberated acetic acid is then recycled for synthesis of the monomer (Daniels, 1983).

Table 1. Methods for the analysis of vinyl acetate

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on Carboxen-564; desorb with dichloromethane:methanol (95:5) solution	GC/FID	1.0 µg/sample	Eller (1994)
	Adsorb on Ambersorb XE-347; desorb with dichloromethane:methanol (95:5) solution	GC/FID	0.04 mg/m^3	US Occupational Safety and Health Administration (1990)
Water[a]	Purge (nitrogen); trap (Tenax-GC/OV-1/-silica gel); desorb as vapour (heat purging with nitrogen) directly onto gas chromatographic column	GC/MS	PQL	US Environmental Protection Agency (1986)

GC/FID, gas chromatography/flame ionization detection; MS, mass spectrometry; PQL, practical quantification limit: 50 µg/L in groundwater; 50 µg/kg in soil and sediment samples with low levels of vinyl acetate; 2.5 mg/L in water-miscible liquid waste samples; 6.25 mg/kg in soil and sediment samples with high levels of vinyl acetate; 25 mg/L in non-water-miscible waste samples

[a] This method is used to determine volatile organic compounds in a variety of solid wastes, regardless of water content, including groundwater, aqueous sludges, caustic liquors, acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils and sediments.

A third technique for producing vinyl acetate involves the reaction of acetaldehyde with acetic anhydride to yield ethylidene diacetate, which is pyrolytically cleaved to vinyl acetate and acetic acid (Leonard, 1970; Daniels, 1983).

Other methods for producing vinyl acetate include the reaction of vinyl chloride (see IARC, 1987f) with sodium acetate in solution in the presence of palladium chloride (Daniels, 1983), conversion of methyl acetate with carbon monoxide and hydrogen in the presence of catalysts to ethylidene diacetate and subsequent cleavage to vinyl acetate and acetic acid (Roscher *et al.*, 1983). Synthetic gas has been used as a feed for vinyl acetate (Mannsville Chemical Products Corp., 1982).

The total world capacity for production of vinyl acetate was about 1000 thousand tonnes in 1965. World production rose to 3000 thousand tonnes in 1982 (Roscher *et al.*, 1983) but had decreased to 2500 thousand tonnes by 1988. In that year, 530 thousand tonnes were produced in the Member States of the European Union, the main producers being France, Germany, Italy, Spain and the United Kingdom, and 460 thousand tonnes in Japan (Environmental Chemicals

Data and Information Network, 1993). In 1992, 1240 thousand tonnes were produced in the United States (Anon., 1993a).

Commercial production of vinyl acetate in the United States was first reported in 1928 (United States Agency for Toxic Substances and Disease Registry, 1992). Between 1960 and 1980, United States production rose from 114 to 850 thousand tonnes (Daniels, 1983). In 1992, 1200 thousand tonnes were produced, so that vinyl acetate ranked 40th among the 50 chemicals produced in the largest volumes (Anon., 1993b). Production of vinyl acetate in Japan in 1993 was about 530 thousand tonnes, about 44% of which was used to produce polyvinyl alcohol (Anon., 1993c).

Vinyl acetate is produced by six companies in Japan, five each in China and the United States, two companies each in Germany and the Russian Federation, and one company each in Brazil, Canada, France, Mexico, Poland, Romania, Spain, Thailand, the United Kingdom and Venezuela (Chemical Information Services, Inc., 1994).

1.2.2 Use

The only commercial use for vinyl acetate is in the preparation of polymers and copolymers (Daniels, 1983). In 1987, 55% of the vinyl acetate used in the United States was to produce polyvinyl acetate emulsions and resins for paints and adhesives; 20% was used in the production of polyvinyl alcohol, 5% for polyvinyl butyral, 10% for ethylene–vinyl acetate resins, 4% for polyvinyl chloride copolymers (see IARC, 1987g) and 5% for miscellaneous uses (United States Agency for Toxic Substances and Disease Registry, 1992).

Polyvinyl acetate is used as an intermediate in conversion to polyvinyl alcohol and acetals. The principal use of polyvinyl acetate is in adhesives for paper, wood, glass, metals and porcelain. It is also used in latex water paints, as a coating for paper, for textile and leather finishing, as a base for inks and lacquers, in heat-sealing films and in shatterproof photographic bulbs (Sax & Lewis, 1987; Rosato, 1993). Polyvinyl acetate has been used as an emulsifying agent in cosmetics, pesticide formulations and pharmaceuticals and as a food additive (Anon., 1992).

Polyvinyl alcohol is the synthetic, water-soluble plastic produced in the largest volume in the world. It is used in sizing for textile warp and yarn, in laminating adhesives, photosensitive films and cements and as a binder for cosmetics, ceramics, leather, nonwoven fabrics and paper. It is also used as an emulsifying agent, thickener and stabilizer (Sax & Lewis, 1987; Rosato, 1993).

Polyvinyl acetals result from the condensation of polyvinyl alcohol with an aldehyde. Commonly used aldehydes are formaldehyde (see IARC, 1995), acetaldehyde and butyraldehyde. Polyvinyl formal, polyvinyl acetal and polyvinyl butyral are mainly used in adhesives, paints, laquers and films. Polyvinyl butyral is used in sheet form as an interlayer in safety glasses and shatter-resistant acrylic protection in aircraft (Sax & Lewis, 1987).

Ethylene–vinyl acetate copolymers improve the adhesion properties of hot-melt and pressure-sensitive adhesives. They are also used in medical tubing, milk packaging and beer-dispensing equipment (Sax & Lewis, 1987; Rosato, 1993). Plastic containers with barrier layers

of ethylene–vinyl alcohol copolymers are replacing many glass and metal containers for packaging food (Rosato, 1993).

Polyvinyl chloride–acetate copolymers, compounded with plasticizers, are used for cable and wire coverings, in chemical plants and in protective garments (Rosato, 1993).

1.3 Occurrence

1.3.1 Natural occurrence

Vinyl acetate is not known to occur in nature.

1.3.2 Occupational exposures

The National Occupational Exposure Survey conducted between 1981 and 1983 indicated that 129 024 employees in the United States are potentially exposed to vinyl acetate. Vinyl acetate was found to be used in 27 industries with a total of 6264 facilities. The estimate is based on a survey of companies and did not involve actual measurements of exposure (United States National Institute for Occupational Safety and Health, 1994b). Data on occupational exposure to vinyl acetate are given in Table 2.

1.3.3 Air

Concentrations of 0.07–0.57 ppm [0.25–2 mg/m^3] were reported in ambient air in an area where several vinyl acetate manufacturers or process facilities were located (United States Agency for Toxic Substances and Disease Registry, 1992). An ambient air concentration of 0.5 μg/m^3 was detected near a chemical waste disposal site (Pellizzari, 1982). Vinyl acetate was monitored, but not detected, in the United States in 1990–91, in ambient air close to a furniture factory, in a paint incineration plant and in indoor air in an office and a machine shop (limit of detection, 2 ppb [7 μg/m^3] (Kelly *et al.*, 1993). At least 8.8 million pounds (4000 tonnes) of vinyl acetate were released to the environment from manufacturing and processing facilities in the United States in 1987 (United States Agency for Toxic Substances and Disease Registry, 1992).

1.3.4 Water

Vinyl acetate was detected at 50 mg/L in wastewater effluents from a polyvinyl acetate plant (Stepanyan *et al.*, 1970).

1.3.5 Other

Vinyl acetate was among the volatile chemicals released from food packaging during heating in a microwave oven, at concentrations of 0.01–0.88 μg/in^2 [0.002–0.14 μg/cm^2] (McNeal & Hollifield, 1993). A high rate of emission of vinyl acetate was found from new carpets that had a secondary backing of polyvinyl chloride (Hodgson *et al.*, 1993). Vinyl acetate has been detected in cigarette smoke at concentrations of 400 ng/cigarette (Guerin, 1980) and 0.5 μg/puff (Battista, 1976). Emissions of vinyl acetate from the combustion of pulverized coal were estimated to vary from 2.081×10^{-8} to 4.274×10^{-7} lb/10^6 Btu [0.009–0.18 mg/kJ] under different test conditions (Miller *et al.*, 1994).

Table 2. Occupational exposure to vinyl acetate

Country	No. of plants	Job, task or industry	No. of samples	Air concentration (mg/m^3)		Reference
				Mean	Range	
USA (1969)	1	Vinyl acetate production	P (TWA)	NR	1.4–17	US National Institute for Occupational Safety and Health (1978)
USA	1	Vinyl acetate production and polymerization	40 (P)	0.7–106 (range of means)	0–173	Deese & Joyner (1969)
USA (1982)	1	Polymer adhesive manufacture	5 (P)	10.6	< 0.4–18	Boxer & Reed (1983)
USA (1980)	1	Latex paint manufacture	8 (P) 8 (A)		[< 6.7]–126 [< 4.2]–36.6	Belanger & Coy (1981)
Poland	1	Vinyl copolymer production	(A)		9.7–11.5	Jedrychowski *et al.* (1979)
		Vinyl acetate production	(A)		0.6–4.3	
		Polyvinyl acetate production	(A)		1.2–1.4	
USA (1979)	1	Polymerization	(P) (A)		0.4–4.3 0.35–19.4	Kimble *et al.* (1982)
Former Czechoslovakia	1	Vinyl acetate production	(A) (P)		2.5–416 3.3–388	Kollár *et al.* (1988)
Finland (1980–92)	NR	Various industries	119 (A and P)		All samples < 35	Finnish Institute of Occupational Health (1994)
USA	1	Polyvinyl acetate painters (airless spray equipment)	(A) (P)	< [35.2 µg/m³] < [774 µg/m³]		International Technology Corporation (1992)

P, personal sample; A, area sample; NR, not reported; TWA, time-weighted average

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for vinyl acetate in several countries are given in Table 3. Polyvinyl acetate, ethylene–vinyl acetate–vinyl alcohol copolymers, ethylene–vinyl acetate copolymers, vinyl acetate–vinyl chloride copolymers and vinyl acetate–crotonic acid copolymers have been approved for use by the United States Food and Drug Administration (1984) as components of surfaces in contact with food and beverages.

Table 3. Occupational exposure limits for vinyl acetate

Country	Year	Concentration (mg/m^3)	Interpretation
Australia	1991	30	TWA
		60	STEL
Belgium	1991	35	TWA
		70	STEL
Canada	1993	30	TWA
		60	STEL
Denmark	1991	30	TWA
Finland	1993	35	TWA
		70	STEL
France	1991	30	TWA
Germany	1993	35	TWA; justifiably suspected of having carcinogenic potential
Netherlands	1994	30	TWA
Poland	1991	10	TWA
Russian Federation	1991	10	STEL
Sweden	1993	18	TWA
		35	STEL
Switzerland	1994	35	TWA
		70	STEL
United Kingdom	1993	30	TWA
		60	STEL
USA			
ACGIH	1994	35	TWA; animal carcinogen
NIOSH	1994	15	TWA; ceiling

From ILO (1991); Arbetarskyddsstyrelsens (1993); Deutsche Forschungsgemeinschaft (1993); Environmental Chemicals Data and Information Network (1993); Työministeriö (1993); United Kingdom Health and Safety Executive (1993); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Arbeidsinspectie (1994); Schweizerische Unfallversicherungsanstalt (1994); United States National Institute for Occupational Safetry and Health NIOSH) (1994a). TWA, time-weighted average; STEL, short-term exposure limit

2. Studies of Cancer in Humans

2.1 Cohort study

Waxweiler *et al.* (1981) undertook a cohort study of 4806 men employed at a plant for the manufacture of synthetic chemicals in the United States between 1942 and 1973. Death certificates could not be found for 16 (3%) of the deceased. In comparison with national rates, the cohort had an excess risk for cancer of the respiratory system (42 observed; standardized mortality ratio, 1.5 [95% confidence interval, 1.1–2.0]). In a review of medical records, 45 men were found to have had lung cancer. Histological specimens were found for 27 of these men, and eight showed undifferentiated large-cell lung cancer. The exposure of the patients with lung cancer to 19 chemicals, including vinyl acetate, was examined. The group had an estimated cumulative dose of exposure to vinyl acetate below the estimated weighted mean expected for the members of the cohort with the same year of birth and age at commencement of work in the plant. The subgroup with undifferentiated large-cell lung cancer had had slightly higher cumulative exposure to vinyl acetate.

2.2 Case–control study

Ott *et al.* (1989) undertook a nested case–control study in a cohort of 29 139 men employed in two large chemical manufacturing facilities and a research and development centre in the United States, who had died in 1940–78 with non-Hodgkin's lymphoma, multiple myeloma, lymphocytic leukaemia or nonlymphocytic leukaemia as the underlying or contributing cause of death. Controls were frequency matched to the dead cases by date of hire and length of survival in a 5:1 ratio. Exposure to 21 chemicals was assessed on the basis of information about work activity, work area and production over time. Potential exposure to vinyl acetate was reported for seven of 52 men who had died with non-Hodgkin's lymphoma (odds ratio, 1.2), three of 20 with multiple myeloma (odds ratio, 1.6), two of 39 with non-lymphocytic leukaemia (odds ratio, 0.5) and two of 18 with lymphocytic leukaemia (odds ratio, 1.8).

3. Studies of Cancer in Experimental Animals[1]

3.1 Oral administration

Rat: Three groups of 20 male and 20 female Fischer 344 rats, seven to eight weeks of age, received 0, 1000 or 2500 mg/L vinyl acetate [purity unspecified] in the drinking-water on five days a week for 100 weeks and were observed for their lifetime (maximum, 130 weeks). The vinyl acetate solutions were prepared weekly; however, owing to the instability of vinyl acetate in water, the rats were estimated to have received only about half of the nominal dose. Survival did not differ significantly between the treated and control groups: the numbers of survivors at

[1] The Working Group was aware of studies in progress in which mice and rats were administered vinyl acetate in the drinking-water (IARC, 1994b).

130 weeks were 7/20 male controls, 8/20 at the low dose and 6/20 at the high dose; and 5/20 female controls, 11/20 at the low dose and 11/20 at the high dose. All animals were necropsied, and all major organs and lesions were examined histologically. Treated animals had increased incidences of liver neoplastic nodules (none in male controls, four at the low dose and two at the high dose; none in female controls or at the low dose and six at the high dose [$p = 0.01$, Fisher's exact test]); increased incidences of uterine adenocarcinomas (none in female controls, one at the low dose and five at the high dose [$p = 0.024$]); increased incidences of uterine polyps (none in controls, three at the low dose and five at the high dose) [$p = 0.024$]; and increased incidences of thyroid C-cell adenomas (none in female controls, two at the low dose and five at the high dose [$p = 0.024$]). No malignant neoplasm was found in the liver (Lijinsky & Reuber, 1983; Lijinsky, 1988). [The Working Group noted the small number of animals used and that the animals received less than the nominal doses of the compound.]

Newborn Wistar rats given 200 or 400 mg/kg bw vinyl acetate per day orally for three weeks had not developed hepatic enzyme-altered foci by 14 weeks, whereas newborn rats similarly treated with vinyl chloride or vinyl carbamate did (Laib & Bolt, 1986).

3.2 Inhalation

3.2.1 Mouse

Groups of 60 male and 60 female Swiss-derived Crl:Cd-1(ICR)BR mice, about seven weeks of age and weighing 22.4–35.5 and 16.0–28.5 g, respectively, were exposed by inhalation to 0, 50, 200 or 600 ppm [0, 176, 704 or 2112 mg/m^3] vinyl acetate (purity, > 99%) for 6 h per day on five days a week for about 104 weeks. The body weight gain of treated mice was consistently depressed, but the survival rates of treated and control groups were similar. All animals were subjected to complete necropsy, and all tissues from controls and animals receiving the high dose and respiratory tissues from animals at all doses were examined histologically. One squamous-cell carcinoma of the lung was found in a male at the high dose, and a single adenocarcinoma of the lung occurred in a male control. Non-neoplastic lesions related to treatment were seen in the respiratory tract and included atrophy of the olfactory epithelium accompanied by respiratory metaplasia and nonkeratinizing squamous metaplasia of the respiratory epithelium in the nasal cavities; tracheal epithelial hyperplasia was also seen (Bogdanffy *et al.*, 1994a).

3.2.2 Rat

Groups of 60 male and 60 female Sprague-Dawley-derived Crl:Cd(SD)BR rats, about seven weeks of age and weighing 116–243 and 128–189 g, respectively, were exposed by inhalation to 0, 50, 200 or 600 ppm [0, 176, 704 or 2112 mg/m^3] vinyl acetate (purity, > 99%) for 6 h per day on five days a week for about 104 weeks. Body weight gain was consistently depressed in males and females at the high dose, but survival rates were similar in treated and control groups. Four of 59 females given the high dose had a squamous-cell carcinoma of the nasal cavity; no such tumour was seen in the other treated female rats or in 60 female controls [$p = 0.06$]. One of 59 males given the middle dose developed a nasal papilloma, two at the high dose developed squamous-cell carcinomas of the nasal cavity and one at the high dose had a carcinoma *in situ*;

four males at the high dose had nasal papillomas. The total number of nasal tumours (benign and malignant) in males at the high dose (7/59) was significantly greater than that in controls (0/59) ($p < 0.01$, Fisher's exact test). Non-neoplastic lesions related to treatment were seen in the respiratory tract and especially in the nasal cavity; the most consistent was thinning of the olfactory epithelium accompanied by basal-cell hyperplasia. No effects were seen in the nasal respiratory epithelium (Bogdanffy *et al.*, 1994a).

3.3 Exposure *in utero*

Rat: A total of 72 male and 144 female Sprague-Dawley-derived Crl:CD(SD)BR rats [age unspecified] were divided into four groups and received vinyl acetate (purity, > 99%) at 0, 200, 1000 or 5000 mg/L in the drinking-water daily. The solutions were prepared each day, and 5% was added to each dose in order to compensate for an observed degradation of 6–14% over 24 h. The average concentrations achieved over the entire study were 0, 208, 1019 and 5166 mg/L. Treatment commenced 10 weeks before mating; treatment of males was continued for an additional four weeks and that of females throughout mating, gestation and lactation. Two males of the F_0 generation in each group were paired with one female from the same group for up to 15 days. After weaning, groups of 60 male and 60 female F_1 pups were selected and were administered 0, 200, 1000 or 5000 mg/L vinyl acetate in the drinking-water daily (average daily consumption: 10, 47 or 202 mg/kg bw for males and 16, 76 or 302 mg/kg bw for females) for 104 weeks. Water consumption was decreased among rats given 1000 or 5000 mg/L, and both food consumption and body weight gain were decreased in the latter group. The percentages of rats still alive at the end of the study were 42% of male controls, 57% of those at 200 mg/L, 50% of those at 1000 mg/L and 64% of those at 5000 mg/L; and 55% of female controls, 49% at 200 mg/L, 40% at 1000 mg/L and 57% at 5000 mg/L. No increase in tumour incidence was observed that was related to treatment (Bogdanffy *et al.*, 1994b).

3.4 Carcinogenicity of metabolites

A previous working group concluded that there is *sufficient evidence* for the carcinogenicity of acetaldehyde to experimental animals (IARC, 1987b).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 *Experimental systems*

The elimination of vinyl acetate and formation of acetaldehyde were studied *in vitro* in a closed system comprising heparinized human blood and separated plasma and erythrocytes. The half-lives of vinyl acetate were 4.1 min in blood, 62 min in plasma and 5.5 min in erythrocytes. The esterase activity was shown to be sensitive to eserine and thus of the cholinesterase type; when carboxylesterase activity was inhibited, less effect was seen. Other reactions of vinyl acetate in blood, such as conjugation with reduced glutathione in erythrocytes, appeared to be of minor importance (Fedtke & Wiegand, 1990). In human lymphocytes cultured in whole blood and treated with 5.4 mmol[465 mg]/L vinyl acetate, the disappearance of parent compound and the formation of acetaldehyde were completed within 20 min (Norppa *et al.*, 1985).

The major metabolites of vinyl acetate *in vivo* are acetaldehyde (through an unstable vinyl alcohol) and acetic acid, which are formed by esterases, mostly in blood (Simon *et al.*, 1985a; Laib & Bolt, 1986). Disappearance of atmospheric vinyl acetate due to uptake and metabolism by male Wistar rats was measured in closed exposure chambers (Simon *et al.*, 1985a). The kinetics indicated that some aspects of the process must be saturable, since individual curves were composed of an apparent zero-order section at a higher concentration and a first-order section at a lower concentration. First-order kinetics applied up to about 200 ppm [704 mg/m^3]. Under these conditions, the total clearance (dose/area under the curve) from the gas phase was 30 000 ml/h per kg bw. This value is almost identical to the maximal ventilation rate in rats, 32 000 ml/h per kg bw (Guyton, 1947). The calculated rates of elimination due to metabolism indicated that vinyl acetate is metabolized in linear correlation with the atmospheric concentration up to 650 ppm [2288 mg/m^3], above which a saturation phenomenon occurs. In the closed exposure system, the concentration of acetaldehyde increased transiently as the vinyl acetate concentration declined. The kinetics of vinyl acetate appeared to be unaffected by prior treatment of the rats with diethyldithiocarbamate, indicating that monooxygenases may not be important in its metabolism; however, rat hepatic microsomes and plasma are particularly efficient in hydrolysing vinyl acetate to acetic acid. In a similar system, Fedtke and Wiegand (1990) found a half-life for vinyl acetate of < 1 min in rat blood and 1.2 min in rat plasma. The plasma hydrolytic activity was sensitive to phosphoric acid bis-4-nitrophenyl ester, a typical carboxylesterase inhibitor. It has been suggested (Norppa *et al.*, 1985) that some effects of vinyl acetate are due to acetaldehyde. No epoxide metabolite has been demonstrated (Simon *et al.*, 1985a).

The results of studies on DNA–protein cross-linking after exposure of rats to vinyl acetate and acetaldehyde have been presented in a series of reports (Kuykendall & Bogdanffy, 1992; Kuykendall *et al.*, 1993a,b [abstract]). The results, which include those for nasal tissues (which have high carboxylesterase levels), indicate that acetaldehyde is responsible for the cross-links; the other metabolite, acetic acid, was considered to be responsible for the cytotoxic response.

The kinetics of the hydrolysis of vinyl acetate in respiratory and olfactory nasal mucosa in rats and mice of each sex are similar (Bogdanffy & Taylor, 1993). The finding that metabolism occurs faster in olfactory then in respiratory mucosa may partially explain the distribution of nasal lesions induced by vinyl acetate, but these results do not explain the species difference in its carcinogenic effects.

Vinyl acetate is conjugated with glutathione *in vitro* in the presence of a rat liver supernatant (Boyland & Chasseaud, 1967), providing an explanation for the decreased levels of reduced glutathione seen after exposure to vinyl acetate *in vivo* (Boyland & Chasseaud, 1970; Holub & Tarkowski, 1982).

4.2 Toxic effects

4.2.1 Humans

Irritation of the eye and nose occurs at a threshold of 10–22 ppm [35–77 mg/m^3] (Deese & Joyner, 1969). Throat irritation occurred at 200 ppm (704 mg/m^3) and eye irritation at 72 ppm (253 mg/m^3) (United States National Institute for Occupational Safety and Health, 1978). Dermal contact may cause skin irritation and blister formation.

4.2.2 Experimental systems

Groups of four male and four female rats were exposed by inhalation to various concentrations of vinyl acetate for 6 h per day for 15 days. Rats exposed to 2000 ppm [7040 mg/m^3] experienced eye and nose irritation and respiratory difficulty and had reduced body weight gain. At autopsy, large numbers of macrophages were seen in the lung. Rats exposed to 630 or 250 ppm [2220 or 880 mg/m^3] had reduced weight gain. The lowest dose, 100 ppm [350 mg/m^3] induced no signs of toxicity (Gage, 1970).

Mice exposed to vinyl acetate at 1500 ppm [5280 mg/m^3] for 6 h per day on five days per week for 28 days had hyperplasia and metaplasia of the upper and lower respiratory tract (Clary, 1988).

As reported in an abstract, groups of 10 male and 10 female rats and mice were exposed by inhalation to 50, 200 or 1000 ppm [176, 704 or 3520 mg/m^3] for 6 h per day on five days per week for three months. Rats at 1000 ppm showed respiratory distress and reduced body weight. Mice showed respiratory distress at 200 and 1000 ppm, reduced body weight at 1000 ppm and rhinitis, nasal mucosal metaplasia, tracheal metaplasia and bronchitis/bronchiolitis, mainly at 1000 ppm. Animals of both species had increased lung weights [presumably at all doses] (Owen, 1983).

Rats exposed to 10, 100 or 500 mg/m^3 vinyl acetate for 5 h per day on five days per week for 10 months showed dose-related reductions in body weight and reticulopenia. Squamous metaplasia of the bronchi was seen at all doses, and fatty degeneration of the hepatic parenchyma, proliferation of smooth endoplasmic reticulum and changes in biliary canaliculi were noted at the two higher doses (Czajkowska *et al.*, 1986).

Groups of 60 male and 60 female rats and mice were exposed to vinyl acetate by inhalation for 104 weeks at doses of 0, 50, 200 or 600 ppm [0, 176, 704 or 2112 mg/m^3] (Bogdanffy *et al.*, 1994b). Ten animals per group were allowed to recover for 15 (males) or 16 (females) weeks after termination of exposure at 70 weeks. Weight gain was depressed in all groups receiving 600 ppm and in mice at 200 ppm. Animals that were allowed to recover showed improvement in weight gain, except for female rats at 600 ppm. No haematological changes were consistently related to treatment; a decrease in blood glucose in females at 600 ppm was the only change in

clinical chemistry observed. Increased lung weights were observed in both species, especially at 600 ppm, and all treated rats [not clear whether males and females or only females] had increases at the time of terminal sacrifice; the changes in lung weights were associated with bronchial exfoliation, macrophage accumulation, fibrous plaques and buds and bronchial/bronchiolar epithelial disorganization. Histopathological changes were observed in the nasal cavity; the main non-neoplastic effects in the olfactory epithelium of both species were epithelial atrophy, regeneration, basal-cell hyperplasia and epithelial nest-like infolds. No non-neoplastic changes were seen in the respiratory epithelium of rats, but squamous metaplasia was seen in mice.

In rats and mice that received vinyl acetate in the drinking-water at concentrations of 200, 1000 or 5000 ppm [mg/L], no obvious toxic effects were noted (Clary, 1988).

Groups of 60 male and 60 female rats were exposed to vinyl acetate in drinking-water at concentrations of 0, 200, 1000 or 5000 ppm [mg/L] (v/v) for 104 weeks, after exposure of their F_0 parents to vinyl acetate for 10 weeks before mating. Decreased body weights and decreased food and water consumption were recorded in animals at 5000 ppm; water consumption was reduced in rats at 1000 ppm. No other compound-related effects on chemical, haematological or pathological end-points were observed (Bogdanffy *et al.*, 1994a).

4.3 Reproductive and prenatal effects

4.3.1 Humans

No data were available to the Working Group.

4.3.2 Experimental systems

Male and female rats were given 0, 200, 1000 or 5000 ppm [mg/L] vinyl acetate in the drinking-water over two generations. The F_1 generation of male and female controls and those at 5000 ppm were then cross-mated. Signs of general toxicity were observed in the F_0 and F_1 generations at 5000 ppm, and several reproductive paramaters were altered (decreased fertility and mating performance); however, the responses were inconsistent across generations. The no-observed adverse effect level was considered to be 1000 ppm (Mebus *et al.*, 1995).

Developmental toxicity was studied in rats exposed in the drinking-water to up to 5000 ppm [mg/L] or by inhalation to up to 1000 ppm [3520 mg/m^3] for 6 h per day on days 6–15 of gestation. Administration in the drinking-water induced no maternal or developmental toxicity. After exposure by inhalation, evidence was found of maternal toxicity and retarded embryonic growth, and a significant increase in the incidence of minor skeletal alterations (mainly delayed ossification) was seen in fetuses of dams exposed to 1000 ppm, but not at lower doses (Hurtt *et al.*, 1995).

4.4 Genetic and related effects

4.4.1 Humans

People exposed occupationally to vinyl acetate were reported to have an increased frequency of chromosomal aberrations in cultured lymphocytes (Shirinian & Arutyunyan, 1980). [The Working Group noted the inadequate reporting of the study.]

4.4.2 Experimental systems (See also Table 4 and Appendices 1 and 2)

Vinyl acetate did not induce mutations in *Salmonella typhimurium* or SOS repair functions in *Escherichia coli*. It induced DNA–protein cross-links in *Escherichia coli* HB 101 in the presence of rat liver microsomes.

It induced DNA cross-links in isolated human lymphocytes and in isolated rat nasal epithelial cells. It induced sister chromatid exchange in cultured Chinese hamster ovary cells in the presence or absence of exogenous metabolic activation and enhanced the viral transformation of Syrian hamster embryo cells. It also induced sister chromatid exchange, chromosomal aberrations and micronuclei in human whole blood and in isolated lymphocyte cultures *in vitro*.

In mice treated *in vivo* with vinyl acetate, the frequencies of sister chromatid exchange, of micronuclei in bone-marrow cells and of sperm with abnormal morphology were increased, but there was no increase in the frequency of micronucleated meiotic cells. The increased frequency of sister chromatid exchange was not affected by hepatectomy of the mice before treatment (Takeshita *et al.*, 1986).

Vinyl acetate did not produce DNA adducts in the livers of male and female rats exposed either orally or by inhalation (Simon *et al.*, 1985b).

4.4.3 Genotoxicity of metabolites

Acetaldehyde, the primary metabolite of vinyl acetate, is genotoxic in a wide range of assays *in vitro* and *in vivo* (IARC, 1987b).

5. Summary and Evaluation

5.1 Exposure data

Vinyl acetate is used in the production of a wide range of polymers, including polyvinyl acetate, polyvinyl alcohol, polyvinyl acetals, ethylene–vinyl acetate copolymers and polyvinyl chloride–vinyl acetate copolymers, which are widely used in the production of adhesives, paints and food packaging.

Human exposure to vinyl acetate occurs mainly by inhalation or dermal contact during production of the monomer or during production of polymers and water-based paints.

Table 4. Genetic and related effects of vinyl acetate

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
PRB, SOS chromotest (commercial kit), *Escherichia coli* PQ 37	–	–	8600	Brams *et al.* (1987)
***, DNA–protein cross-links, *Escherichia coli* HB 101 pUC13, filter binding assay	–	+	860	Kuykendall & Bogdanffy (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	McCann *et al.* (1975)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Brams *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	260	Florin *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	340[c]	Bartsch *et al.* (1979)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	–	–	340[c]	Bartsch *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA5, *Salmonella typhimurium* TA 1535, reverse mutation	–	–	5000	McCann *et al.* (1975)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	260	Florin *et al.* (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	McCann *et al.* (1975)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	260	Florin *et al.* (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Lijinsky & Andrews (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Linjinsky & Andrews (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	McCann *et al.* (1975)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Brams *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	260	Florin *et al.* (1980)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	500	Brams *et al.* (1987)
DIA, DNA cross-links, rat olfactory epithelial cells *in vitro*	+	0	860	Kuykendall *et al.* (1993a)
DIA, DNA cross-links, rat nasal respiratory epithelial cells *in vitro*	+	0	860	Kuykendall *et al.* (1993a)
SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro*	+	+	11	Norppa *et al.* (1985)
T7S, Cell transformation, SA7/Syrian hamster embryo (SHE) cells *in vitro*	+	0	500	Casto (1981)

Table 4 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
DIH, DNA cross-link formation, alkaline elution, human lymphocytes *in vitro*	+[d]	0	860	Lambert *et al.* (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	4	Norppa *et al.* (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	8.6	He & Lambert (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	43	Sipi *et al.* (1992)
MIH, Micronucleus induction, human lymphocytes *in vitro*	+	0	43	Mäki-Paakkanen & Norppa (1987)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	17	Norppa *et al.* (1985)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	22	Jantunen *et al.* (1986)
SVA, Sister chromatid exchange, mouse cells *in vivo*	+		370 ip × 1	Takeshita *et al.* (1986)
MVM, Micronucleus induction, mouse bone marrow *in vivo*	+		1000 ip × 1	Mäki-Paakkanen & Norppa (1987)
MVM, Meiotic micronucleus induction, mice *in vivo*	–		1000 ip × 5	Lähdetie (1988)
BVD, DNA binding (covalent), rat hepatocytes *in vivo* (^{14}C label)	–		45 po × 1	Simon *et al.* (1985b)
BVD, DNA binding (covalent), rat hepatocytes *in vivo* (^{14}C label)	–		175 inh 4 h[e]	Simon *et al.* (1985b)
SPM, Sperm morphology, F_1 mice *in vivo*	+		500 ip × 5	Lähdetie (1988)

[a] +, considered to be positive; –, considered to be negative

[b] LED, lowest effective dose; HID, highest effective dose. In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; ip, intraperitoneally; inh, inhalation

[c] Exposure to vapour phase also negative

[d] Negative for single-strand breaks at 1700 μg/ml

[e] Assuming 100% absorption based on mean body weight and vinyl acetate concentration from reported range

***, Not included on the profile

5.2 Human carcinogenicity data

The available data were too limited to form the basis for an evaluation of the carcinogenicity of vinyl acetate to humans.

5.3 Animal carcinogenicity data

Vinyl acetate was tested in one experiment in mice and in one experiment in rats by inhalation. No treatment-related increase in tumour incidence was observed in mice; in rats, an increased incidence of nasal cavity tumours was found in animals of each sex. No increase in tumour incidence was found in rats administered vinyl acetate in the drinking-water *in utero* and then for life.

5.4 Other relevant data

Vinyl acetate is rapidly metabolized by esterases in human blood and animal tissues to acetaldehyde and acetic acid.

Vinyl acetate irritates the eye and respiratory system. Respiratory distress is seen after subchronic exposure by inhalation. Other effects included nasal irritation, nasal mucosal metaplasia, tracheal metaplasia and bronchitis or bronchiolitis. After chronic exposure by inhalation, changes were observed in the lung. Non-neoplastic effects, atrophic and regenerative changes, were seen in the nasal cavity. After chronic exposure via the drinking-water, the only effects observed were decrements in body weight at high doses.

There are no data on the effects of vinyl acetate on human reproduction. A two-generation study in rats showed evidence of parental toxicity and decreased fertility at the highest dose tested. Oral administration of vinyl acetate to rats during pregnancy did not result in maternal or developmental toxicity, whereas exposure by inhalation induced maternal toxicity, retarded embryonic growth and minor skeletal alterations at the highest dose tested.

Vinyl acetate induced sperm abnormalities and sister chromatid exchange in rodents exposed *in vivo*; micronuclei were induced in bone marrow but not in meiotic cells. No DNA binding was seen in rat hepatocytes. In human lymphocytes *in vitro*, vinyl acetate produced chromosomal aberrations, micronuclei, sister chromatid exchange and DNA cross-links. It enhanced viral transformation and sister chromatid exchange in mammalian cells *in vitro*, and it induced DNA–protein cross-links in rat nasal epithelial cells *in vitro*. Vinyl acetate did not induce mutation in bacteria but induced DNA–protein cross-links in plasmid DNA. The primary metabolite of vinyl acetate, acetaldehyde, is genotoxic in a wide range of assays.

5.5 Evaluation[1]

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

There is *limited evidence* in experimental animals for the carcinogenicity of vinyl acetate.

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[1] For definition of the italicized terms, see Preamble, pp. 22–26.

Overall evaluation

Vinyl acetate *is possibly carcinogenic to humans (Group 2B).*

In making the overall evaluation, the Working Group took into account the following evidence:

(i) Vinyl acetate is rapidly transformed into acetaldehyde in human blood and animal tissues.

(ii) There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde (IARC, 1987b). Both vinyl acetate and acetaldehyde induce nasal cancer in rats after administration by inhalation.

(iii) Vinyl acetate and acetaldehyde are genotoxic in human cells *in vitro* and in animals *in vivo*.

6. References

American Conference of Governmental Industrial Hygienists (1994) *1994–1995 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, p. 35

Anon. (1992) Chemical profile: vinyl acetate. *Chem. Marketing Rep.*, **241**, 42

Anon. (1993a) Facts & figures for the chemical industry. *Chem. Eng. News*, **71**, 38–83

Anon. (1993b) Top 50 list of chemical products. *Chem. Eng. News*, **71**, 10–20

Anon. (1993c) Production of plastics materials in Japan. *Plast. Ind. News*, **39**

Arbeidsinspectie [Labour Inspection] (1994) *De Nationale MAC-Lijst 1994* [National MAC list 1994], The Hague, p. 41

Arbetarskyddsstyrelsens [National Swedish Board of Occupational Safety and Health] (1993) *Hygieniska Gränsvärden* [Occupational exposure limits 1993] (AFS 1993:9), Stockholm, p. 58 (in Swedish)

Bartsch, H., Malaveille, C., Barbin, A. & Planche, G. (1979) Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues. Evidence for oxirane formation by P450-linked microsomal mono-oxygenases. *Arch. Toxicol.*, **41**, 249–277

Battista, S.P. (1976) Cilia toxic components of cigarette smoke. In: Wynder, E.L., Hofmann, D. & Gori, G.B., eds, *Proceedings of the 3rd World Conference on Smoking and Health* (DHEW(NIH) Publication No. 76-1221), Bethesda, MD, US Department of Health, Education, and Welfare, National Institutes of Health, pp. 517–534

Belanger, P.L. & Coy, M.Y. (1981) *Sinclair Paint Company, Los Angeles, CA* (Health Hazard Evaluation Report No. HHE-80-68-871) (US NTIS PB82-214396), Cincinnati, OH, United States National Institute for Occupational Safety and Health

Bogdanffy, M.S. & Taylor, M.L. (1993) Kinetics of nasal carboxylesterase-mediated metabolism of vinyl acetate. *Drug Metab. Disposition*, **21**, 1107–1111

Bogdanffy, M.S., Dreef-van der Meulen, H.C., Beems, R.B., Feron, V.J., Cascieri, T.C., Tyler, T.R., Vinegar, M.B. & Rickard, R.W. (1994a) Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. *Fundam. appl. Toxicol.*, **23**, 215–229

Bogdanffy, M.S., Tyler, T.R., Vinegar, M.B., Rickard, R.W., Carpanini, F.M.B. & Cascieri, T.C. (1994b) Chronic toxicity and oncogenicity study with vinyl acetate in the rat: in utero exposure in drinking-water. *Fundam. appl. Toxicol.*, **23**, 206–214

Boyland, E. & Chasseaud, L.F. (1967) Enzyme-catalysed conjugations of glutathione with unsaturated compounds. *Biochem J.*, **104**, 95–102

Boyland, E. & Chasseaud, L.F. (1970) The effect of some carbonyl compounds on rat liver glutathione levels (Short communication). *Biochem. Pharmacol.*, **19**, 1526–1528

Boxer, P.A. & Reed, L.D. (1983) *National Starch & Chemical, Meredosia, IL* (Health Hazard Evaluation Report No. HETA-82-051-1269) (US NTIS PB84-209923), Cincinnati, OH, United States National Institute for Occupational Safety and Health

Brams, A., Buchet, J.P., Crutzen-Fayt, M.C., de Meester, C., Lauwerys, R. & Léonard, A. (1987) A comparative study, with 40 chemicals, of the efficiency of the *Salmonella* assay and the SOS chromotest (kit procedure). *Toxicol. Lett.*, **38**, 123–133

Bretherick, L. (1985) *Handbook of Reactive Chemical Hazards*, 3rd Ed., London, Butterworths, pp. 430–431

Budavari, S., ed. (1989) *The Merck Index*, 11th Ed., Rahway, NJ, Merck & Co., p. 1572

Casto, B.C. (1981) Effect of chemical carcinogens and mutagens on the transformation of mammalian cells by DNA viruses. In: *Antiviral Chemotherapy—Design and Inhibition of Viral Functions,* New York, Academic Press, pp. 261–278

Chemical Information Services, Inc. (1994) *Directory of World Chemical Producers 1995/1996 Standard Edition*, Dallas, TX, p. 706

Clary, J.J. (1988) Chronic and reproduction toxicologic studies on vinyl acetate. Status report. *Ann. N.Y. Acad. Sci.*, **534,** 255–260

Czajkowska, T., Sokal, J., Knobloch, K., Górny, R., Kolakowski, J., Lao, I., Stetkiewicz, J. & Binkowski, J. (1986) Experimental study on chronic toxic effect of vinyl acetate. *Med. Prac.*, **37**, 26–35

Daniels, W. (1983) Vinyl acetate monomer. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 23, New York, John Wiley & Sons, pp. 817–847

Deese, D.E. & Joyner, R.E. (1969) Vinyl acetate: a study of chronic human exposure. *Am. ind. Hyg. Assoc. J.*, **30**, 449–457

Deutsche Forschungsgemeinschaft (1993) *MAK- und BAT-Werte Liste* [MAK and BAT values list], (Report No. 29), Weinheim, VCH Verlagsgesellschaft, p. 77

Eller, P.M., ed. (1994) *NIOSH Manual of Analytical Methods*, 4th Ed., Vol. 3, (DHHS (NIOSH) Publ. No. 94-113), Washington DC, United States Government Printing Office, Method 1453

Environmental Chemicals Data and Information Network (1993) *Vinyl Acetate*, Ispra, JRC-CEC, last update: 02.09.1993

Fedtke, N. & Wiegand, H.-J. (1990) Hydrolysis of vinyl acetate in human blood (Letter to the Editor). *Arch. Toxicol.*, **64**, 428–429

Finnish Institute of Occupational Health (1994) *Työhygieenisten mittausten rekisteri* (Finnish occupational exposure database), Helsinki (in Finnish)

Florin, I., Rutberg, L., Curvall, M. & Enzell, C.R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology*, **15**, 219–232

Gage, J.C. (1970) The subacute inhalation toxicity of 109 industrial chemicals. *Br. J. ind. Med.*, **27**, 1–18

Guerin, M.R. (1980) Chemical composition of cigarette smoke. In: Gori, G.B. & Bock, F.G., eds, *Banbury Report: A Safe Cigarette?* Vol. 3, Cold Spring Harbor, NY, CSH Press, pp. 191–204

Guyton, A.C. (1947) Measurement of the respiratory volumes of laboratory animals. *Am. J. Physiol.*, **150**, 70–77

Hansch, C., Leo, A. & Hoekman, D.H. (1995) *Exploring QSAR*, Washington DC, American Chemical Society

He, S.-M. & Lambert, B. (1985) Induction and persistence of SCE-inducing damage in human lymphocytes exposed to vinyl acetate and acetaldehyde *in vitro*. *Mutat. Res.*, **158**, 201–208

Hodgson, A.T., Wooley, J.D. & Daisey, J.M (1993) Emissions of volatile organic compounds from new carpets measured in large-scale environmental chamber. *J. Air Waste Manage. Assoc.*, **43**, 316–324

Hoechst Celanese Corp. (1993) *Material Safety Data Sheet: Vinyl Acetate*, Dallas, TX

Holub, I. & Tarkowski, S. (1982) Hepatic content of free sulfhydryl compounds in animals exposed to vinyl acetate. *Int. Arch. occup. environ. Health*, **51**, 185–189

Hurtt, M.E., Vinegar, M.B., Rickard, R.W., Cascieri, T. & Tyler, T.R. (1995) Developmental toxicity of oral and inhaled vinyl acetate in the rat. *Fundam. appl. Toxicol.*, **24**, 198–205

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon, pp. 341–366

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 39, *Some Chemicals Used in Plastics and Elastomers*, Lyon, pp. 113–131

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Uptating of* IARC Monographs *Volumes 1–42*, Lyon, p. 73

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1–42*, Lyon, p. 64

IARC (1987c) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1–42*, Lyon, pp. 77–78

IARC (1987d) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1–42*, Lyon, p. 70

IARC (1987e) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1–42*, Lyon, p. 70

IARC (1987f) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1–42*, Lyon, pp. 373–376

IARC (1987g) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1–42*, Lyon, p. 70

IARC (1994a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 45–71

IARC (1994b) *Directory of Agents Being Tested for Carcinogenicity*, No. 16, Lyon, p. 72

IARC (1995) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 62, Lyon, pp. 217–362

ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva, pp. 418–419

International Technology Corporation (1992) *Exposure to Volatile Components of Polyvinyl Acetate (PVA) Emulsion Paints During Application and Drying*, Washington DC, National Paint and Coatings Association, Inc., Vinyl Acetate Toxicology Group

Jantunen, K., Mäki-Paakkanen, J. & Norppa, H. (1986) Induction of chromosome aberrations by styrene and vinylacetate in cultured human lymphocytes: dependence on erythrocytes. *Mutat. Res.*, **159**, 109–116

Jedrychowski, W., Prochowska, K., Garlinska, J. & Bruzgielewicz, J. (1979) The occurrence of chronic nonspecific diseases of respiratory tract in workers of vinyl resins establishment. *Przegl. Lék*, **36**, 679–682 (in Polish)

Kelly, T.J., Callahan, P.J., Plell, J. & Evans, G.F. (1993) Method development and field measurements for polar organic compounds in ambient air. *Environ. Sci. Technol.*, **27**, 1146–1153

Kimble, H.J., Ketcham, N.H., Kuryla, W.C., Neff, J.E. & Patel, M.A. (1982) A solid sorbent tube for vinyl acetate monomer that eliminates the effect of moisture in environmental sampling. *Am. ind. Hyg. Assoc. J.*, **43**, 137–144

Kollár, V., Kemka, R., Mišianik, J. & Tölgyessy, J. (1988) Determination of vinyl chloride and vinyl acetate in working atmosphere. *Chem. Pap.*, **42**, 147–160

Kuykendall, J.R. & Bogdanffy, M.S. (1992) Reaction kinetics of DNA–histone crosslinking by vinyl acetate and acetaldehyde. *Carcinogenesis*, **13**, 2095–2100

Kuykendall, J.R., Taylor, M.L. & Bogdanffy, M.S. (1993a) Cytotoxicity and DNA–protein crosslink formation in rat nasal tissues exposed to vinyl acetate are carboxylesterase-mediated. *Toxicol. appl. Pharmacol.*, **123**, 283–292

Kuykendall, J.R., Taylor, M.L. & Bogdanffy, M.S. (1993b) DNA–protein crosslink formation in isolated rat nasal epithelial cells exposed to vinyl acetate and acetaldehyde (Abstract 929). *Proc. Am. Assoc. Cancer Res.*, **34**, 156

Lähdetie, J. (1988) Effects of vinyl acetate and acetaldehyde on sperm morphology and meiotic micronuclei in mice. *Mutat. Res.*, **202**, 171–178

Laib, R.J. & Bolt, H.M. (1986) Vinyl acetate, a structural analog of vinyl carbamate, fails to induce enzyme-altered foci in rat liver. *Carcinogenesis*, **7**, 841–843

Lambert, B., Chen, Y., He, S.-M. & Sten, M. (1985) DNA cross-links in human leucocytes treated with vinyl acetate and acetaldehyde *in vitro*. *Mutat. Res.*, **146**, 301–303

Leonard, E.C. (1970) Vinyl acetate. In: Leonard, E.C., ed., *Vinyl and Diene Monomers*, Part 1, New York, Wiley Interscience, pp. 263–328

Lewis, R.J. (1993) *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold Co., p. 1215

Lide, D.R. (1993) *CRC Handbook of Chemistry and Physics*, 74th Ed., Boca Raton, FL, CRC Press, p. 3–517

Lijinsky, W. (1988) Chronic studies in rodents of vinyl acetate and compounds related to acrolein. *Ann. N.Y. Acad. Sci.*, **534**, 246–254

Lijinsky, W. & Andrews, A.W. (1980) Mutagenicity of vinyl compounds in *Salmonella typhimurium*. *Teratog. Carcinog. Mutag.*, **1**, 259–267

Lijinsky, W. & Reuber, M.D. (1983) Chronic toxicity studies of vinyl acetate in Fischer rats. *Toxicol. appl. Pharmacol.*, **68**, 43–53

Mäki-Paakkanen, J. & Norppa, H. (1987) Induction of micronuclei by vinyl acetate in mouse bone marrow cells and cultured human lymphocytes. *Mutat. Res.*, **190**, 41–45

Mannsville Chemical Products Corp. (1982) *Vinyl Acetate (Chemical Products Synopsis)*, Cortland, NY

McCann, J., Choi, E., Yamasaki, E. & Ames, B.N. (1975) Detection of carcinogens as mutagens in the *Salmonella*/microsome test: assay of 300 chemicals. *Proc. natl Acad. Sci. USA*, **72**, 5135–5139

McNeal, T.P. & Hollifield, H.C. (1993) Determination of volatile chemicals released from microwave-heat-susceptor food packaging. *J. Assoc. off. anal. Chem. Int.*, **76**, 1268–1275

Mebus, C.A., Carpanini, F.M.B., Rickard, R.W., Cascieri, T.C., Tyler, T.R. & Vinegar, M.B. (1995) A two-generation reproduction study in rats receiving drinking water containing vinyl acetate. *Fundam. appl. Toxicol.*, **24**, 206–216

Miller, C.A., Srivastava, R.K. & Ryan, J.V. (1994) Emmissions of organic hazardous air pollutants from the combustion of pulverized coal in a small-scale combustor. *Environ. Sci. Technol.*, **28**, 1150–1158

Norppa, H., Tursi, F., Pfäffli, P., Mäki-Paakkanen, J. & Järventaus, H. (1985) Chromosome damage induced by vinyl acetate through in vitro formation of acetaldehyde in human lymphocytes and Chinese hamster ovary cells. *Cancer Res.*, **45**, 4816–4821

Ott, M.G., Teta, M.J. & Greenberg, H.L. (1989) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. *Am. J. ind. Med.*, **16**, 631–643

Owen, P.E. (1983) Vinyl acetate—three month inhalation toxicity study in the rat and mouse (Abstract). *Hum. Toxicol.*, **2**, 416

Pellizzari, E.D. (1982) Analysis for organic vapor emissions near industrial and chemical waste disposal sites. *Environ. Sci. Technol.*, **16**, 781–785

Rosato, D.V. (1993) *Rosato's Plastics Encyclopedia and Dictionary*, New York, Hanser, pp. 235–236, 573

Roscher, G., Hofmann, E., Armstrong Adey, K., Jeblick, W., Klimisch, H.-J. & Kieczka, H. (1983) Vinyl acetate. In: Gerhartz, W., Mayer, C., Moegling, D., Monkhouse, P. & Pfefferkorn, R., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 4th Ed., Vol. 23, New York, VCH Publishers, pp. 597–618

Sadtler Research Laboratories (1980) *1980 Cumulative Index*, Philadelphia, PA

Sax, N.I. & Lewis, R.J. (1987) *Hawley's Condensed Chemical Dictionary*, 11th Ed., New York, Van Nostrand Reinhold, pp. 491, 945–946, 1222

Schweizerische Unfallversicherungsanstalt [Swiss Accident Insurance Company] (1994) *Grenzwerte am Arbeitsplaz* [Limit values in the work place], Lucerne, p. 104

Shirinian, G.S. & Arutyunyan, R.H. (1980) Study of cytogenetic change levels under PVA production. *Biol. Z. Armenii*, **33**, 748–752

Simon, P., Filser, J.G. & Bolt, H.M. (1985a) Metabolism and pharmacokinetics of vinyl acetate. *Arch. Toxicol.*, **57**, 191–195

Simon, P., Ottenwälder, H. & Bolt, H.M. (1985b) Vinyl acetate: DNA–binding assay *in vivo*. *Toxicol. Lett.*, **27**, 115–120

Sipi, P., Järventaus, H. & Norppa, H. (1992) Sister-chromatid exchanges induced by vinyl esters and respective carboxylic acids in cultured human lymphocytes. *Mutat. Res.*, **279**, 75–82

Stepanyan, I.S., Padaryan, G.M., Airapetyan, L.K. & Maslyukova, D.F. (1970) Ionization–chromatographic method for determining some components of waste waters from the plant 'Polivinilatsetat'. *Prom. Arm.*, **9**, 76–78 [*Chem. Abstr.*, **74**, 90928p] (in Russian)

Takeshita, T., Iijima, S. & Higurashi, M. (1986) Vinyl acetate-induced sister chromatid exchanges in murine bone marrow cells. *Proc. Jpn Acad.*, **62**, 239–242

Työministeriö [Ministry of Labour] (1993) *HTP-Arvot 1993* [Occupational exposure limits 1993] Tampere, p. 19 (in Finnish)

Union Carbide Corp. (1981) *Product Information Sheet: Vinyl Acetate Monomer*, Danbury, CT

Union Carbide Corp. (1994) *Product Specification Sheet: Vinyl Acetate*, South Charleston, WV

United Kingdom Health and Safety Executive (1993) *Occupational Exposure Limits 1993* (EH 40/93), London, Her Majesty's Stationery Office, p. 27

United States Agency for Toxic Substances and Disease Registry (1992) *Toxicological Profile for Vinyl Acetate* (Clement International Corp., Contract No. 205-88-0608), Washington DC, United States Department of Health and Human Services

United States Environmental Protection Agency (1986) Method 8240. Gas chromatography/mass spectrometry for volatile organics. In: *Test Methods for Evaluating Solid Waste—Physical/-Chemical Methods* (US EPA No. SW-846), 3rd Ed., Vol. 1A, Washington DC, Office of Solid Waste and Emergency Response, pp. 1–43

United States Food and Drug Administration (1984) Food and Drugs. *US Code fed. Regul.*, **Title 21**, Parts 175.105, 175.300, 175.350, 176.170, 176.180, 177.1010, 177.1200, 177.1350, 177.1360, 177.1670, 177.2260, 177.2800, 178.3910, pp. 133, 145, 160, 180, 189, 199, 211, 225, 255, 271, 289, 348

United States National Institute for Occupational Safety and Health (1978) *Criteria for a Recommended Standard for Occupational Exposure to Vinyl Acetate* (DHEW (NIOSH) Pub. No. 78-205), Cincinnati, OH

United States National Institute for Occupational Safety and Health (1994a) *NIOSH Pocket Guide to Chemical Hazards* (DHHS (NIOSH) Publ. No. 94-116), Cincinnati, OH, pp. 328–329

United States National Institute for Occupational Safety and Health (1994b) *National Occupational Exposure Survey (1981–83)*, Cincinnati, OH

United States Occupational Safety and Health Administration (1990) *OSHA Analytical Methods Manual*, 2nd Ed., Part 1, Vol. 2, Salt Lake City, UT, United States Department of Labor, pp. 51-1–51-14

Waxweiler, R.J., Smith, A.H., Falk, H. & Tyroler, H.A. (1981) Excess lung cancer risk in a synthetic chemicals plant. *Environ. Health Perspectives*, **41**, 159–165

Weast, R.C. & Astle, M.J. (1985) *CRC Handbook of Data on Organic Compounds*, Vols I & II, Boca Raton, FL, CRC Press, pp. 22 (I), 451 (II)