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No 18

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Joint Assessment of Commodity Chemicals

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THE ECETOC SCHEME FOR THE

"JOINT ASSESSMENT OF COMMODITY CHEMICALS" (JACC)

This report has been produced as part of a programme for making critical reviews of the toxicology, including ecotoxicology, of selected industrial chemicals.

A number of organisations, world-wide, have produced and are continuing to produce such reviews with the aim of ensuring that, based on an up-to-date knowledge of the toxicological and other relevant information regarding existing chemicals they can continue to be produced and used safely. ECETOC is contributing to this activity with its JACC reviews.

In general, commodity chemicals, ie, those produced in large tonnage by several companies and having widespread and multiple uses, are reviewed jointly by experts from a number of companies concerned. Before it is decided to review a chemical, every effort is made to discover whether an adequate review exists already, in which case no work is necessary.

It should be noted that in a JACC review only the uses of the chemical as such are considered, ie its occurrence as an impurity in other products is not normally taken into account.

In this document a critical assessment of the toxicology and ecotoxicology of vinyl acetate is presented. Whenever good scientific reviews on certain toxicological or ecotoxicological aspects exist, their conclusions are summarised and in these cases only the subsequent literature has been assessed.

CONTENTS

1. SUMMARY AND CONCLUSIONS

Vinyl acetate is produced for the manufacture of polyvinyl acetate and a variety of copolymers. Polymerised vinyl acetate products can contain up to 1% of monomer and therefore may produce significant emissions of vinyl acetate into the environment, mostly to air.

Vinyl acetate is rapidly hydrolysed when in contact with water and readily biodegraded by environmental organisms; bio-accumulation is unlikely to occur. It has been detected in ambient air, drinking water and natural products at ppb or ppt levels.

Vinyl acetate is slightly toxic to fish, invertebrates and micro-organisms, and practically non-toxic to algae.

Kinetic studies in animals show that vinyl acetate is rapidly hydrolysed to acetaldehyde and acetate by esterases. This major route of metabolism can be saturated under high exposure conditions. Glutathione conjugation is a minor metabolic pathway and is unlikely to occur under inhalation exposure conditions commonly encountered in man.

Vinyl acetate possesses a low order of acute toxicity to experimental animals, irrespective of the route of administration. It is irritant, especially to the respiratory system. Subchronic inhalation studies in rats and mice demonstrated No Observed Effect Levels (NOEL) of 200 and 50 ppm (710 and 180 mg/m^3) respectively. Vinyl acetate administered at up to 5,000 ppm in drinking water for 13 weeks produced no evidence of toxicity to rats or mice.

Vinyl acetate and its hydrolysis product acetaldehyde demonstrate a genotoxic potential *in vitro*. Genotoxic effects remote from the site of exposure were observed *in vivo* only when detoxification mechanisms were saturated. Under conditions of normal handling and use, such genotoxic effects of vinyl acetate are unlikely to occur.

Studies on the carcinogenic activity of vinyl acetate showed that rats developed a slightly increased incidence of nasal tumours after prolonged, high level exposure by inhalation of 600 ppm (2,100 mg/m^3). Similar tumours were not seen in mice. Oral exposure of rats induced no increase in tumours in the gastrointestinal tract or elsewhere. The nasal tumours occurred only in those groups in which vinyl acetate produced prolonged irritation of the epithelia of the respiratory tract. No increase in tumour incidence occurred at the level of exposure (50 ppm, 180 mg/m^3) at which irritation was absent. Comparison of the types of tumour produced by vinyl acetate and acetaldehyde suggests that formation of the latter is unlikely to be the cause of tumours arising from exposure to vinyl acetate. Overall the data suggests that prolonged irritation of the respiratory epithelium is a precondition for tumour development with vinyl acetate.

No effects were observed on reproduction or development of rats even at levels of vinyl acetate producing maternal toxicity.

Information is available on the effects of vinyl acetate on man is limited.

Occupational exposure limits have been set on the basis of a need to protect workers from experiencing irritant effects. Exposures at or below these limits should provide adequate protection against the development of respiratory tract irritation and, in consequence, of cancer.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name:	Vinyl acetate
IUPAC name:	Vinyl acetate
Synonyms:	Acetic acid, vinyl ester Acetic acid, ethenyl ester 1-Acetoxyethene 1-Acetoxyethylene Ethanoic acid, ethenyl ester Ethenyl acetate Ethenyl ethanoate Vinyl acetate, monomer Vinyl A monomer Vinyl ethanoate
CA Index name:	Acetic acid, ethenyl ester
CAS Registry No.	108-05-4
EEC No.	607-023-00-0
EINECS No.	2035454
RTECS No.	AK 0875000
Formula:	$C_4H_6O_2$
Molecular weight:	86.09
Structure:	$CH_3 - C(=O) - O - CH = CH_2$

2.2 Physical and Chemical Properties

Vinyl acetate is a highly flammable, colourless liquid with an acrid, ether-like sweetish odour. It is soluble in most organic solvents and moderately soluble in water. The physical and chemical data are summarised in Table 1.

A typical commercial sample of technical vinyl acetate (Wacker, 1981; Rhône-Poulenc, 1986; BP Chemicals, 1988; Hoechst Celanese, 1988; Hoechst Celanese, 1989; Hoechst, 1989; Union Carbide, 1989) has a purity $\geq$ 99.8 % (w/w) and may contain the following impurities:

water	: $\leq$ 0.03	- 0.1 % (w/w)
acidity, as acetic acid	: $\leq$ 0.005	- 0.01 % (w/w)
aldehyde, as acetaldehyde	: $\leq$ 0.005	- 0.02 % (w/w)

Hydroquinone is added at 1.5 - 20 ppm to inhibit polymerisation.

2.3 Conversion Factors

The following conversion factors are used for concentrations in the gas phase at 20°C and 1013 hPa:

1 ppm = 3.57 mg/m^3

1 mg/m^3 = 0.28 ppm

2.4 Analytical Methods

2.4.1 Environmental media

Gas chromatography, coupled with flame ionisation detection (GC/FID) or with mass spectrometric detection (GC/MS), is the most common method for separating, identifying and quantifying vinyl acetate in environmental

samples. For the measurement of low levels of vinyl acetate in ambient air, long-path infrared Fourier transform absorption spectroscopy has proved to be a useful technique.

Determination in Air

Several methods have been developed for measuring vinyl acetate in workplace air. These involve sampling on solid adsorbents and analysis of the desorbed material with GC/FID techniques. Details of adorption-desorption procedures are given in Table 2. The detection limits of these methods range from 8 mg/m^3 (1.5 l sample) (NIOSH, 1978) to 0.35 mg/m^3 (10 l sample) (Sidhu, 1981). At higher concentrations vinyl acetate can be analysed without preceding enrichment (Bianchi *et al*, 1977).

Kimble (1980) and Kimble *et al* (1982) developed special sampling tubes to avoid hydrolysis and polymerisation of vinyl acetate during sampling. The tubes consist of a section with a drying agent (eg, anhydrous calcium sulphate), connected to another containing activated carbon impregnated with a polymerisation inhibitor (eg, hydroquinone). Carbon disulphide containing 2% (v/v) acetone proved to be the best desorption solvent. Concentrations as low as 1 mg/m^3 can be determined in an 18 l sample, at high or low relative air humidity. Andersson and Andersson (1988), in a critical evaluation of the Kimble sampling tubes, showed that recovery falls with decreasing humidity. This is due to adsorption of vinyl acetate on the drying agent when the humidity drops to < 50%. Thus, the Kimble tubes should not be used under these circumstances if recoveries of $\geq$ 80% are required.

A method of enrichment for the determination of trace quantities of vinyl acetate in ambient air was developed by Kuessner (1982). Air samples ($\leq$ 500 l) are scrubbed in liquid carbon disulphide (-78°C), prior to analysis by GC/FID. The detection limit is 3.5 µg/m^3.

Pellizzari (1982) analysed complex mixtures containing vinyl acetate in air such as those found in the vicinity of a chemical waste disposal site. He recommends the collection of large volumes of air ($\leq$ 120 l) followed by

absorption on Tenax and subsequent thermal desorption, and analysis by GC/MS. Levels of vinyl acetate down to 0.5 $\mu g/m^3$ can thus be measured.

Gordon and Meeks (1977) have described the determination of vinyl acetate in ambient air grab samples at concentrations as low as 0.25 mg/m^3 by means of long-path infrared Fourier transform absorption spectroscopy.

Determination in Aqueous Media

Prior to analysis by GC/MS, vinyl acetate can be collected using a purge-and-trap technique. The purged vinyl acetate is trapped on Tenax and subsequently desorbed by heating. The detection limit ranges from 1 - 10 µg/l, dependent upon the type of sample (Spingarn *et al*, 1982; Flotard *et al*, 1986). Montiel and Rauzy (1983) used a head-space technique and analysis by GC/FID to investigate the migration of monomeric vinyl acetate from plastic materials into water. Although the limit of detection was not mentioned it is probably in the µg/l range. Noble *et al* (1980) were able to measure vinyl acetate in the lower ng/l range in Riesling wines using GC/MS analysis with a head-space technique.

Determination in soil

When present at low levels, vinyl acetate is purged from soil samples (1 - 5 g) and trapped on Tenax, followed by thermal desorption and analysis using GC/MS. At higher levels, the purge-and-trap procedure is carried out on an aliquot of a methanol extract of the soil sample (4 g). The estimated detection limits of these two methods are about 10 µg/kg and 1 mg/kg respectively (Flotard *et al*, 1986).

2.4.2 Determination in Biological Tissues

An evaluation of analytical methods for use with biological fluids and tissues has not so far been reported, probably because vinyl acetate is rapidly hydrolysed in such media.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

The most widely used manufacturing process is the oxidative addition of acetic acid to ethylene in the presence of a palladium catalyst at elevated temperature in the gaseous phase, as shown by the equation:

$$CH_3COOH + CH_2{=}CH_2 + \tfrac{1}{2}O_2 \rightarrow CH_3COOCH{=}CH_2 + H_2O$$

Another process of major industrial importance is the addition reaction of acetylene and acetic acid in the presence of a zinc salt catalyst:

$$CH_3COOH + C_2H_2 \rightarrow CH_3COOCH{=}CH_2$$

Other manufacturing processes involve a two-step reaction in which ethylidene diacetate, formed by reaction of acetaldehyde with acetic anhydride or methyl acetate with carbon monoxide and hydrogen, is cracked to vinyl acetate and acetic acid (Roscher *et al*, 1983).

The annual production capacity is 535,000 tonnes in Western Europe and 1,236,000 tonnes in the USA (SRI, 1989a,b).

3.2 Storage and Transport

Vinyl acetate must be protected against spontaneous polymerisation by the addition of an inhibitor, usually 1.5 - 20 ppm hydroquinone, methyl hydroquinone or diphenylamine (the last must be removed by distillation before vinyl acetate is used for polymerisation).

Vinyl acetate must be stored in an atmosphere containing 5 - 21% oxygen for the inhibitor to work properly. An inert gas cover (eg, nitrogen) containing $\leq$ 5% oxygen must not be used (BP Chemicals, 1988). The stabilised material may be stored and transported in mild steel, stainless steel or aluminium containers but contact with copper or copper alloys must

be avoided. Polyethylene, polypropylene or teflon are suitable materials for making joints on storage or transport equipment (BP Chemicals, 1988; Hoechst Chemikalien, 1989; Rhône-Poulenc, 1986).

Peroxide formation occurs when uninhibited vinyl acetate is stored at room temperature in diffuse daylight in contact with air (Barnes, 1945).

3.3 Use

Vinyl acetate is used as a monomer to manufacture homopolymers and a variety of copolymers. Its most important industrial chemical reaction is free-radical polymerisation which can be initiated by organic and inorganic peroxides, azo compounds, redox systems, light and high energy irradiation. Other chemical reactions are those common to esters and compounds containing a double bond and include hydrolysis, trans-esterification and addition reactions (Daniels, 1983; Roscher *et al*, 1983).

Polyvinyl acetate is used chiefly in adhesives, paints and coatings. Varying quantities are used for the production of polyvinyl alcohol, polyvinyl butyral, polyvinyl formal and other polymers (25 - 40% in Western Europe and USA, about 70% in Japan) (Rinno *et al*, 1980; Roscher *et al*, 1983; Santodonato, 1985). Copolymers are produced mainly with ethylene (EVA), vinyl chloride (PVC-PVac) and acrylates for a variety of technical applications including foils, packaging materials and fibres (Santodonato, 1985).

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Environmental Distribution

Due to its high vapour pressure and conditions of manufacture and use, vinyl acetate is released into the environment mainly as emissions to air and, to a far lesser extent, to water. A slow transfer from water to air can occur.

Emissions into the atmosphere during manufacture are negligible apart from unquantifiable fugitive emissions due to plant leakage (Pervier *et al*, 1974). This is because the processes are carried out in closed systems and all vent gases are flared or piped to an incinerator.

Vinyl acetate is polymerised predominantly in batch operations using emulsion, solution or suspension techniques. Intermittent emissions into waste water may arise from cleaning operations but account for only minor discharges into the environment. The emission into the atmosphere via exhaust air is estimated to range from 15 - 300 g/tonne vinyl acetate used, according to the type of polymer, product and procedure, the last being influenced by continuous or batch operation (worst case assumption below).

Loading, unloading and transport may be a significant source of air emission unless a compensation pipe or local exhaust ventilation system is used for the removal of vented vinyl acetate by condensation, scrubbing or incineration. Emissions can occur at about 300 - 500 g/tonne vinyl acetate transferred (worst case assumption on the basis of gas displacement, specific gravity and saturation concentration in air, see Table 1).

The most significant source of atmospheric emission is from polymerized vinyl acetate products since they can contain residual monomer levels of $\leq$ 1% w/w of polymer (Daniels, 1983). The monomer is released into the air during fabrication or application of finished products such as adhesives, paints, paper coatings and textile finishes. For example, Glushkov (1976) showed that the quantity released during the drying of polyvinyl acetate dispersions decreased exponentially for a few days and after 30 days vinyl

acetate could not be detected in the polymer film dried at room temperature. There were similar findings with copolymer dispersions by Boikova *et al* (1975) and Boikova and Petrova (1976). An accurate estimate of releases from this source is difficult because of the uncertainty over the amount of vinyl acetate hydrolysed during storage of aqueous products prior to their application or use. During the production of polyvinyl alcohol and other polymers, the residual vinyl acetate monomer undergoes hydrolysis and cannot escape into the atmosphere. Since monomer concentrations in finished products are generally $\leq$ 0.3%, workers applying these products should experience relatively little exposure (Santodonato, 1985).

4.2 Biotransformation and Environmental Fate

4.2.1 Atmospheric fate

The rate constant for the gas-phase reaction of vinyl acetate with hydroxyl radicals has not been measured. The lack of the increment of the acetyl group permits only a rough calculation of the rate constant according to Atkinson (1988), resulting in a k_{OH} value of about 26 x 10^{-12} cm^3 $molecule^{-1}$ s^{-1}.

Assuming that the average global atmospheric concentration of photochemically produced hydroxyl radicals is 5 x 10^5 radicals/cm^3 (Warneck, 1988), the atmospheric half-life would be :

$$t_{\frac{1}{2}} = \frac{\ln 2}{k_{OH} \times [\cdot OH]} = 0.6 \text{ d.}$$

4.2.2 Aquatic fate

In water vinyl acetate hydrolyses rapidly, the environmental half-life for hydrolysis being in the range of 1-2 weeks. The reaction products of hydrolysis are acetic acid and acetaldehyde. Vinyl acetate is readily

biodegradable. Biodegradation may involve enzyme-mediated hydrolysis (section 4.2.4). For most aquatic systems this implies that the environmental half-life for degradation is less than 1 week. Considering the value for Henry's law constant (Table 1) the compound is expected to evaporate slowly. On the basis of the octanol/water partition coefficient (Table 1) no significant sorption onto sediment is expected. The contribution of these latter two processes to the disappearance of vinyl acetate from aquatic systems can be neglected compared to that of biodegradation and hydrolysis.

At 25°C, pH 7 and zero ionic strength, conditions typical of the great majority of fresh water systems, the pseudo-first-order rate constant for hydrolysis is:

$$K_h = 1.1 \times 10^{-6} s^{-1}$$

yielding a half-life of 7.3 d. The half-life at 20°C is about 11 d, and at 14°C 17 d (Skrabal and Zahorka, 1927; Mabey and Mill, 1978).

In distilled and de-ionised water the half-life is about 10 - 12 d. In tap water, half-lives of 14 - 16 d have been measured (Grant and Pullinger, 1979). Lijinsky and Reuber (1983) showed that vinyl acetate disappeared at about 8%/d in water at 20°C and 5%/d at 4°C and pH 7 (Lijinsky, 1988). These rates correspond to half-lives of 8.3 and 13.5 d respectively, based on first-order kinetics. Simon *et al* (1985a) found a half-life of 4.5 h in solutions buffered at pH 7.4, a value which was confirmed by Fedtke and Wiegand (1990).

4.2.3 Terrestrial fate

In soil with sufficiently high content of water, vinyl acetate will disappear very rapidly through hydrolysis and biodegradation under aerobic and anaerobic conditions (see 4.2.2 and 4.2.4). The half-lives for these processes are expected to be the same or less than those in water (see 4.2.2). Considering the value for the solubility in water and the low sorption onto soil (octanol/water partition coeffecients, Table 1) the

compound is expected to leach rapidly into the groundwater. In view of the value for Henry's law constant, the compound is expected to evaporate from soil only moderately rapidly.

4.2.4 Biodegradation

The results of studies on the biodegradability of vinyl acetate, based on measurements of the biochemical oxygen demand (BOD), are summarised in Table 3. Using non-adapted microbial seed, bio-oxidation values of $\geq$ 60% (related to the theoretical oxygen demand for complete conversion to carbon dioxide and water) can be reached within 10 d, following an acclimation period of about 5 d. Vinyl acetate is thus readily biodegradable according to the criteria of the OECD test guideline 301 C (OECD, 1981).

The extent of the bio-oxidation of vinyl acetate measured by BOD is confirmed by earlier studies in which the production of carbon dioxide was determined. Pahren and Bloodgood (1961) showed that 49 % of the theoretical amount of carbon dioxide was formed during a 38 d period, when vinyl acetate (10 mg/l) was degraded by domestic sewage micro-organisms. With acclimatised sewage seed, 42% of the carbon present was recovered as carbon dioxide during a period of 10 d (Ludzack and Ettinger, 1960), and 58% in 22 d (Pahren and Bloodgood, 1961). The fact that the total carbon dioxide was not recovered was attributed to the uptake of carbon for the growth of bacterial cell protoplasm and to volatilisation. Vinyl acetate or intermediate oxidation products could not be detected after several weeks of oxidation.

Biodegradation of vinyl acetate can also occur via enzyme-mediated hydrolysis. Oi and Satomura (1967) found that acetylesterase from the fungus *Sclerotinia libertiana* (Ascinomycetes) efficiently catalysed this hydrolysis.

Berglund (1983) showed that vinyl acetate was removed from a dilute waste gas stream by contact with activated sludge suspended in water (10 g/l) under aerobic or anaerobic conditions. At gas feed concentrations of 1,000 - 5,000 ppm (3.6 - 17.9 g/m^3) $\geq$ 99.9% of vinyl acetate was removed.

Under anaerobic conditions, vinyl acetate (initial concentration 500 mg/l) was completely degraded within 4 d by methanogenic bacteria from acetate enriched cultures. This inoculum initially started as domestic sludge (Chou *et al*, 1979).

A utilisation efficiency of 91% was reached at an effective vinyl acetate concentration of 140 mg/l in long-term (52 d) feeding adaptation studies conducted in anaerobic upflow filters (Chou *et al*, 1979).

4.2.5 Bioaccumulation

No experimental data are available which demonstrate occurrence of bioaccumulation.

The n-octanol/water partition coefficient (log P_{OW}) of vinyl acetate is 0.73 (Table 1), indicating a low potential for bioaccumulation. Rapid biotransformation (esterase-mediated hydrolysis) in biological fluids will also prevent retention and accumulation of the compound in tissues.

4.2.6 Conclusion

The short atmospheric half life, the rapid hydrolysis rate in water, the low n-octanol/water partition coefficient and the ability of biological fluids of mammals and other organisms to degrade vinyl acetate will lead to its rapid removal when released into the environment.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental Levels

5.1.1 Air

Gordon and Meeks (1977) found 0.25 - 2 mg/m^3 vinyl acetate in ambient air grab samples collected at locations in the Houston-Gulf Coast (Texas) industrial area in 1974. A level of 0.5 µg/m^3 was found in ambient air surrounding the Kin Buc waste disposal site near Edison, New Jersey, in 1976 (Pellizzari, 1982).

Vinyl acetate was a constituent of a mixture of volatile organic compounds found in indoor domestic dust by GC/MS analysis (Dmitriev *et al*, 1987). In contrast, vinyl acetate was not detectable in ambient atmospheric dust.

5.1.2 Water

Vinyl acetate was detected (concentrations not stated) in ozone treated drinking water in the Netherlands in 1976 (Eurocop-Cost, 1984) and in drinking water derived from river water in the United Kingdom in 1979 (Fielding *et al*, 1981).

5.1.3 Soil

No data are available, although a method exists (section 2.4.3).

5.1.4 Natural Products

Vinyl acetate has been identified by GC/MS analysis as one of the main volatile metabolites of bacteria growing on cereal grain (wheat, corn). The bacteria include *Pseudomonas trifoli, Pseudomonas fluorescens, Lactobacillus plantarum, Propionibacterium sp., Escherichia coli, Sarcina sp., Bacillus subtilis, Bacillus megaterium and Clostridium sp.* (Kaminski *et al*, 1979). Headspace GC/MS analysis revealed vinyl acetate in white Riesling wines in the lower ng/l range (Noble *et al*, 1980), in watercress,

Rorippa nasturtium aquaticum, (Spence and Tucknott, 1983) and in freshly ground coffee (Wang *et al*, 1983).

5.2 Hygiene Standards - Occupational Exposure Levels

5.2.1 Hygiene Standards

Occupational exposure limits have been established for vinyl acetate in industrialised countries where it is produced and handled (Table 4). The limits were based on the need to avoid workers experiencing the irritant effects of vinyl acetate and on the fact that the common routes of occupational exposure are mainly by inhalation and skin contact. The standards are usually expressed as 8 h time-weighted average (TWA) concentrations; in some cases higher degrees of exposure are allowed for shorter periods.

The labelling requirements for the EC are given in Appendix 1.

5.2.2 Occupational Exposure Levels

The actual concentrations measured in the workplace have generally been well below the limit values, with only occasional excursions above the limit values (Table 5).

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Micro-organisms

Studies on the antifungal activity of vinyl acetate showed the minimum fungistatic concentration to be 10 mg/l for *Aspergillus niger* and 20 mg/l for *Tramete skaveolens*. It was fungicidal to *Aspergillus niger* at 60 mg/l, and at 50 mg/l to *Tramete skaveolens* (So, 1977).

Vinyl acetate had no significant effect on nitrifying bacteria in concentrations of $\leq$ 100 mg/l (Arenshtein *et al*, 1962). The compound did not inhibit either growth or dehydrogenase activity of micro-organisms (mixed culture) at 100 mg/l (Lazareva and Kostina, 1983).

At approximately 1,150 mg/l, vinyl acetate caused 50% inhibition of gas production by anaerobic bacteria in unacclimatised methanogenic cultures (Stuckey *et al*, 1980). In another study, Chou *et al* (1978) demonstrated that 700 mg/l vinyl acetate caused 50% inhibition of gas production. The toxicity threshold for total gas production was 200 mg/l, and 400 mg/l for methane alone (Stuckey *et al*, 1980). These values are in good agreement with results obtained by Wellens (1980), who reported a toxicity threshold for gas production by micro-organisms of 400 mg/l.

Concentrations at which vinyl acetate has no effect on growth of other bacteria and protozoa are listed in Table 6.

The concentration causing a 50% diminution in the light emission of the aerobic bioluminescent marine bacteria *Photobacterium phosphoreum* exposed for 5 min was 2,080 mg/l vinyl acetate (Atkinson and Switzenbaum, 1987).

6.2 Aquatic Organisms

The toxicity threshold (EC_0 to EC_5) for inhibition of cell multiplication (total biomass) of green algae (*Scenedesmus quadricauda*) exposed to vinyl

acetate for 8 d has been determined as 370 mg/l (Bringmann and Kühn, 1977a; 1978 a,b; 1979; 1980a).

Information on the acute toxicity of vinyl acetate to aquatic invertebrates and fish is summarised in Tables 7 and 8. The lethal concentrations (96h LC_{50}) in several species of fish ranged from 18 - 42.3 mg/l. The 96h median tolerance limit values are not significantly lower than the 24h values for all species tested. Vinyl acetate is about twice as toxic to fish in soft water as in hard water. One- and two-day old fry appear to be more sensitive than adult fathead minnows. The highest non-lethal concentration for golden orfe fish exposed for 48 h was 9 mg/l.

6.3 Terrestrial Organisms

Burditt *et al* (1963) investigated the potential of using vinyl acetate as a fumigant to control eggs and larvae of fruit flies *Ceratitis capitata* and *Dacus dorsalis* (both Diptera: Tephritidae). LC_{95} values, based on 2 h exposure followed by 48 h observation, were in the range 60-90 mg/l air.

7. KINETICS AND METABOLISM

7.1 Human

There are no reports of metabolic studies of vinyl acetate in man, although studies on the enzymatic hydrolysis of vinyl acetate by esterases in human blood indicate that this is quantitatively similar to that in rats (Filov, 1959; Strong *et al*, 1980; Simon *et al*, 1985a). The enzyme activity which transforms vinyl acetate to acetaldehyde and acetic acid is confined to the human plasma (Filov, 1959) and purified pseudocholinesterase (butylcholinesterase, EC 3.1.1.8) from human plasma is highly active in hydrolysing vinyl acetate (Simon *et al*, 1985a). The hydrolytic metabolism of vinyl acetate should therefore be similar in man and experimental animals.

7.2 Experimental

Filov (1959) administered vinyl acetate to rats by gavage. Analysis of blood showed the presence acetaldehyde but vinyl acetate itself was not detected. This was investigated in detail later by Cresswell *et al* (1979) and Strong *et al* (1980). After oral administration of ^{14}C-labelled vinyl acetate (labelled in the vinyl moiety; dosage-1 ml 0.5% aqueous solution per animal) to Sprague-Dawley rats, 7.1% of the radioactivity remained in the carcass and 90.9% had been excreted by 96 h. Excretion occurred in urine (3.4%), faeces (1.1%) and expired air (86.3%). Similar data were obtained with rats exposed by inhalation (nose only) to 1,000 ppm (3,600 mg/m^3) of ^{14}C-vinyl acetate for 6 h. After 96 h, 18.7% remained in the carcass, whilst the rest was excreted in the urine (7.1%), faeces (3.9%) and expired air (70.3%). The different amounts retained in the carcass in the two experiments was probably due to the different total doses administered (Cresswell *et al*, 1979).

The above general excretion pattern was corroborated by a subsequent study using different doses (Strong *et al*, 1980). They showed that the main radioactive exhaled gas was $^{14}CO_2$ and that a major urinary product was

^{14}C-urea. The pattern of metabolites was not influenced by the route of administration of ^{14}C-vinyl acetate. Autoradiography of the whole body (Cresswell *et al*, 1979) revealed no major differences in tissue distribution of radioactivity derived from inhaled or ingested ^{14}C-vinyl acetate and this confirmed the results of a tissue distribution study (Strong *et al*, 1980).

Hydrolysis of vinyl acetate has been demonstrated in the blood of man (section 7.1), rat and mouse and in various tissues and organelles (eg, rat liver and lung microsomes *in vitro*). Rat liver microsomes contain especially high esterase activities (Strong *et al*, 1980; Simon *et al*, 1985a). Porcine pancreatic lipase has been reported to hydrolyse vinyl acetate (Brockerhoff, 1970). More recently, the localisation of carboxyl-esterase has been studied in the nasal passages of F344 rats and B6C3F1 mice using the standard substrate, p-nitrophenyl butyrate (Bogdanffy *et al*, 1987). Carboxyl-esterase activities were present; in particular the olfactory mucosa of rats and mice hydrolysed the carboxyl ester more efficiently than the respiratory mucosa. This suggests that inhaled vinyl acetate is hydrolysed by the epithelia of the upper respiratory tract, although this may be completed in the blood. This concept is in agreement with pharmacokinetic studies performed by Simon *et al* (1985a) who exposed Wistar rats by inhalation in a closed chamber to vinyl acetate and found dose-dependent elimination kinetics. They concluded that with exposure to constant vinyl acetate levels of $\geq$ 750 ppm (2,700 mg/m^3) the metabolic pathway(s) become saturated. At concentrations < 2,700 mg/m^3 the metabolic rates were mainly determined by the rate of pulmonary uptake. Distribution of vinyl acetate within the organism was not determined but with continued exposure a transient rise in exhaled acetaldehyde was noted. This suggests that immediate hydrolysis of inhaled vinyl acetate was taking place.

This finding does not contradict that of Boyland and Chasseaud (1970) who reported a transient decrease of hepatic glutathione (determined as non-protein sulphhydryl groups) to 77% of the normal value 30 min after an ip injection of 0.8 ml vinyl acetate/kgbw to female Chester-Beatty rats; this could result from saturation of the hydrolytic enzymes. Similarly, Holub and Tarkowski (1982) injected mice (300 mg/kgbw; strain not

specified), Wistar rats (300 or 450 mg/kgbw) and guinea pigs (500 mg/kgbw) with vinyl acetate and reported slight, transient decreases of hepatic non-protein sulphhydryls; hepatic cytosolic enzymes in rat-liver superhatant catalyse the conjugation of compounds containing an activated double bond, such as vinyl acetate, with glutathione (Boyland and Chasseaud, 1970).

7.2.1 Evaluation

The kinetic studies indicate that vinyl acetate is rapidly hydrolysed to acetaldehyde and acetic acid. Studies *in vivo* show that vinyl acetate is hydrolysed by esterases but that its metabolism can be saturated under extreme exposure conditions. Glutathione conjugation is only a minor metabolic pathway, especially under commonly encountered inhalation exposure conditions.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 Acute Toxicity

The acute toxicity of vinyl acetate is low, irrespective of the route of administration. The lethal dose and concentration were measured in several experiments (Table 9a and 9b).

Exposure of 4 male and 4 female Alderley Park specific-pathogen free rats to saturated vinyl acetate vapour for 5 min at a room temperature of 20°C resulted in rapid anaesthesia and death of all treated animals (Gage, 1970).

8.2 Skin, Respiratory Tract and Eye Irritation; Sensitisation

8.2.1 Skin irritation

Application of 10 mg vinyl acetate to the skin of rabbits for 24 h produced irritation (Smyth and Carpenter, 1948). No signs of irritation appeared when 0.5 ml of neat vinyl acetate was applied to the uncovered abdominal skin of rabbits; when applied for longer periods under an occlusive dressing, desquamation occurred (Mellon Inst., 1946). Only slight irritancy was noted after intracutaneous injection of a 10% solution in corn oil and 5 dermal applications of the undiluted compound was without such effects (Scholz and Weigand, 1969).

8.2.2 Eye Irritation

Slight erythema and conjunctival oedema occurred after instillation of 0.1 ml of neat vinyl acetate into rabbit eyes (Scholz and Weigand, 1969); 0.5 ml caused severe irritation or mild burns (Mellon Inst., 1946).

8.2.3 Respiratory Tract Irritation

Repeated inhalation of 150 ppm (540 mg/m^3) vinyl acetate in CD-1 mice and 500 ppm (1,800 mg/m^3) in CD rats produced signs of respiratory irritation in 90 day studies (Owen, 1979a, 1979b); for details, see 8.3.1. Similar effects were seen in mice (strain and doses not reported) (Goldstein *et al*, 1968). In longer-term studies in rats and mice, repeated exposure of 200 and 600 ppm (710 and 2,100 mg/m^3) revealed signs of irritation with corresponding pathological findings in the respiratory tract (Owen, 1988); for details, see 8.5.

8.2.4 Sensitisation

No data are available.

8.3 Subchronic Toxicity

8.3.1 Inhalation

Groups of 5 male and 5 female Charles River CD-1 mice or CD rats were exposed to 0, 50, 150, 500 or 1,000 ppm (0, 180, 540, 1,800 and 3,600 mg/m^3) of vinyl acetate (6 h/d, 5 d/wk) for 4 weeks; the dose level of the 50 ppm group was increased to 1,500 ppm (5,360 mg/m^3) on exposure day 8 as marked clinical effects had not been not observed at 1,000 ppm. A dose-related decrease in bodyweight gain was noted, especially in females. No treatment-related lesions were observed at necropsy. Concentrations > 150 ppm in mice and > 500 ppm in rats produced changes characteristic of respiratory tract irritation (Owen, 1979a, 1979b).

Groups of 4 male and 4 female Alderley Park specific-pathogen free rats were exposed to vinyl acetate at 100, 250, 630 or 2,000 ppm (360, 890, 2,200 and 7,100 mg/m^3) (6 h/d, 5 d/wk) for 3 weeks; control rats were exposed to air alone. Signs of eye and nose irritation were observed in animals exposed to 2,000 ppm; they suffered from respiratory difficulty, appeared in poor condition and their body weight gain was reduced.

Microscopic examination showed increased numbers of macrophages in their lungs. Female rats exposed to 630 or 250 ppm showed abnormally low weight gains. The results of urine and blood tests on rats exposed at 250 ppm showed no adverse effects. No signs of adverse effects were seen in rats exposed at 100 ppm and no abnormalities were apparent in the organs of rats exposed at 100, 250 or 630 ppm (Gage, 1970). The No Observed Effect Level (NOEL) was 100 ppm (360 mg/m^3) in female rats and 250 ppm (890 mg/m^3) in male rats.

Groups of 10 male and 10 female Sprague-Dawley derived rats were exposed to vinyl acetate vapour concentrations of 0, 50, 200 or 1,000 ppm (0, 180, 710 or 3,600 mg/m^3) (6 h/d, 5d/wk) for 3 months. Exposure to 1,000 ppm decreased body weight gain, produced respiratory difficulties, increased lung-to-body weight ratio (due to lung congestion) and increased the incidence of histiocytosis in the lungs. The effects in the lungs were consistent with the inhalation of irritant vapour. No adverse effects were seen at other concentrations. Thus a NOEL of 200 ppm (710 mg/m^3) was established (Owen, 1980a).

Groups of 10 male and 10 female CD-1 mice were exposed to vinyl acetate vapour at concentrations of 0, 50, 200 or 1,000 ppm (0, 180, 710 or 3,600 mg/m^3) (6 h/d, 5 d/wk) for 3 months. At 1,000 ppm reduced body weight gain, clinical effects (breathing difficulties), increased lung weights and histological injury of the lungs, trachea and nasal epithelium occurred. The histological lesions appeared to be treatment-related. At 1,000 ppm, inflammatory and metaplastic changes were observed in the respiratory epithelium; these were thought to have been solely a consequent damage by vinyl acetate or possibly combined with the effects with secondary infection by microbial pathogens. Exposure to 200 ppm resulted in signs of respiratory irritation but no microscopic lesions. A NOEL of 50 ppm (180 mg/m^3) was established (Owen, 1980b).

Rats exposed to 68 mg/m^3 (19 ppm) vinyl acetate for 120 d showed decreased adrenal weight and ascorbic acid content. Oxygen consumption was said to be increased (Kolesnikov *et al*, 1975).

Exposure of 4 dogs by inhalation to 67 - 91 ppm (240 - 320 mg/m^3) vinyl acetate and subsequently to 186 ppm vinyl acetate (6 h/d, 5 d/wk for 11 wk) produced no circulatory, haematological, biochemical or tissue changes apart from evidence of eye irritation at 186 ppm (660 mg/m^3) (Haskell Lab., 1967).

8.3.2 Oral

Groups of 5 male and 5 female Sprague-Dawley rats or CD-I mice were administered vinyl acetate in drinking water at nominal concentrations of 0 (control), 50, 200, 1,000 or 5,000 ppm v/v for 4 weeks (Gale, 1979). The solutions of vinyl acetate in drinking water were prepared daily throughout the study and over formulated by 7-10% to correct for losses over 24 h. During the final week of treatment the dose level of 50 ppm vinyl acetate was increased to 10,000 ppm vinyl acetate. No animals died and all appeared normal. A marked decrease in water consumption was observed in rats drinking 10,000 ppm and slight reductions were seen in both mice and rats drinking $\geq$ 1,000 ppm. To a lesser extent, food consumption was affected in female rats and mice and weight gain was reduced in both sexes of rats and in male mice at 5,000 ppm. Observations *post mortem* revealed no evidence of gross abnormalities in organs associated with treatment in rats or mice. In male and female rats and in female mice the absolute and relative liver weights were lower in all treated groups compared with controls. The significance of this finding is unclear since no evidence of histopathological change was seen in rat liver. The results provided the basis for selection of appropriate dose levels for 13 week studies.

Groups of 10 male and 10 female Sprague-Dawley rats were administered vinyl acetate in drinking water at initial concentrations of 0, 200, 1,000 and 5,000 ppm v/v (Gale, 1980a). The concentration in water was progressively increased during the course of the 13 week study in order to provide each group with a constant intake of vinyl acetate in relation to body weight. There were no deaths during the study in which all animals appeared normal. The consumption of water and food was lower in the high-dose group than in the controls and was associated with a slight growth retardation in male animals. There were no treatment-related changes in the haematological and

blood chemistry indices examined at 4 and 12 weeks in high-dose animals. No increases in the incidence of micronuclei were found in bone-marrow preparations. No treatment-related effects were reported in the organ weights of the animals. Macroscopic and microscopic examination of tissues revealed no differences between high-dose and control groups. In summary, administration of vinyl acetate at ≤ 5,000 ppm in drinking water for 13 weeks produced a slight retardation in growth but failed to elicit other evidence of toxicity in rats. The maximum mean daily intake of vinyl acetate in this study was calculated to be 0.73 ml/kg in male and 0.87 ml/kg in female rats.

Groups of 10 male and 10 female CD-I mice were administered vinyl acetate in drinking water at nominal concentrations of 0, 200, 1,000 or 5,000 ppm v/v for 13 weeks (Gale, 1980b). No deaths were attributable to treatment in the study in which all animals appeared normal. Water consumption was higher than in controls in both sexes receiving 5,000 ppm and in males receiving 1,000 ppm; animals in these groups showed a water consumption pattern which was consistent with greater wastage. The food consumption and weight-gain figures were similar for all treated and control groups throughout the study. No consistent treatment-related effects were seen in the haematology, blood chemistry or organ weight measurements. At *post mortem* no evidence was obtained of macroscopic changes unequivocally attributable to vinyl acetate exposure and this was confirmed by the histopathological investigations. In summary, administration of vinyl acetate ≤ 5,000 ppm in drinking water for 13 wk produced no evidence of toxicity in mice.

8.4 Mutagenicity and Genotoxicity

8.4.1 Gene-mutation in bacteria: Ames-*Salmonella* test

Liquid vinyl acetate (≤ 1,000 µg/plate) was not mutagenic to *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 or TA1538 with or without activation by rat and hamster liver microsomal preparations (S9) (Lijinsky and Andrews, 1980). Negative results were also obtained in strains TA98,

TA1535 and TA1537 when tested at 10,000 µg/plate in the presence or absence of Aroclor-induced rat S9 mix (McCann *et al*, 1975). At concentrations ≤ 5,000 µg/plate, vinyl acetate was not mutagenic to TA 102 with or without metabolic activation (S9) from rat liver (Jung, 1988). In a plate incorporation assay at dose levels of 100-500 µg/ml, liquid vinyl acetate was not mutagenic to strains TA97, TA98 and TA100 with or without rat S9-mix (Brams *et al*, 1987). Vinyl acetate vapour (≤ 2% v/v for 2 or 16 h) was not mutagenic to strains TA100 and TA1530 in the absence or presence of a metabolic system (S9) prepared from livers of phenobarbital-induced mice (Bartsch *et al*, 1979).

8.4.2 SOS-Chromo Test

Vinyl acetate (0.13 - 0.86 mg/ml diluted in 10 % DMSO) was not genotoxic in a SOS chromotest using *Escherichia coli* PQ37 with and without S9-mix (Brams *et al*, 1987).

8.4.3 Gene mutation in mammalian cells

Mutagenic activity was observed in mouse lymphoma L5178Y cells, without metabolic activation (Kirby, 1983).

8.4.4 Chromosome aberrations *in vitro*

Vinyl acetate induced a dose-dependent increase in chromatid-type aberrations and micronuclei in cultured human leukocytes at 0.125 - 2 mM (0.011 - 0.172 mg/ml) (Jantunen *et al*, 1986; Mäki-Paakkanen and Norppa, 1987). There was also a clear dose-dependent increase in structural chromosome aberrations in human whole-blood lymphocyte cultures at 0.05 - 1 mM (0.043 - 0.086 mg/ml) and in Chinese hamster ovary (CHO) cells at 0.125 - 2 mM (0.011 - 0.172 mg/ml) (Norppa *et al*, 1985).

8.4.5 Micronucleus test

A dose-dependent increase in micronucleated polychromatic erythrocytes was observed in the bone marrow of male C57B1/6 mice 30 h after a single ip

injection of vinyl acetate in olive oil (250, 500, 1,000 or 2,000 mg/kgbw; 9 - 14 animals/group). The effect was statistically significant at 1,000 and 2,000 mg/kgbw. However, the mortality at these doses was 6/14 and 8/14 animals, respectively. The number of micronuclei in normochromatic erythrocytes was not affected (Mäki-Paakkanen and Norppa, 1987).

Groups of hybrid male mice (C57B1/6J x C3H/He) were administered a single ip dose (125, 250, 500, 750 or 1,000 mg/kgbw) of vinyl acetate dissolved in olive oil; the mice were killed after 13 days. The chemical did not alter the frequency of micronuclei in early spermatids at any dose level despite the mortality being almost 100% at 750 and 1,000 mg/kgbw. There was a significant increase in the frequency of sperm abnormalities at 500 mg/kgbw and a dose-dependent decrease in sperm production and a reduction of testicular weight at 500 and 125 mg/kgbw (Lähdetie, 1988).

There was no evidence of an increase in the number of micronuclei in bone marrow cells of CD-1 mice and CD rats (5 animals/sex/group) exposed by inhalation to levels of 50, 200 and 1,000 ppm of vinyl acetate for 3 months (Owen, 1980a, 1980b).

Similarly, there was no increase in the number of micronuclei in a 90 day oral study (drinking water) using CD rats and CD-1 mice (5 animals/sex/group) at dose levels of 200, 1,000 and 5,000 ppm (Gale, 1980a,b). For details of the study design, see 8.3.2.

8.4.6 Sister chromatid exchange (SCE)

Vinyl acetate (0.1 - 2.4 mM) (0.009 - 0.207 mg/ml) induced dose-related increases of sister-chromatid exchange (SCE) in human lymphocyte cultures. Cells exposed to vinyl acetate in the late G_1-phase of the cell cycle showed a SCE frequency twice that of cells exposed in early the G_1-phase. This indicates a considerable removal of SCE-inducing lesions during the G_1-phase (He and Lambert, 1985).

A large increase in SCEs occurred in cultured human lymphocytes after a 48 hours treatment with vinyl acetate (0.05 - 1 mM) (0.043 - 0,086 mg/ml), and

similarly a clear dose-dependent induction of SCEs occurred in Chinese hamster ovary (CHO) cells after a 24 h treatment (0.125 - 1 mM) (0.011 - 0.086 mg/ml). The presence of rat liver S9 mix enhanced the SCE-inducing effect of vinyl acetate in CHO cells (Norppa *et al*, 1985).

8.4.7 Interaction with DNA

Human leukocytes were incubated for 4 h at 37°C in the presence of vinyl acetate (10 - 20 mM) (0.86 - 1.72 mg/ml) and DNA damage was analysed by alkaline elution. There was no significant change in the elution rate of DNA in vinyl acetate-treated cells as compared to untreated cells, suggesting that there was no DNA-strand-breaking effect. In cells exposed to both vinyl acetate and X-rays, the elution rate lay between that of control cells and cells receiving only X-rays, indicating that vinyl acetate may have a DNA cross-linking activity of vinyl acetate under the incubation conditions used (Lambert *et al*, 1985).

8.4.8 Viral transformation

Vinyl acetate enhanced the transformation of Syrian hamster embryo cells by adenovirus SA7 (Casto *et al*, 1977).

8.4.9 DNA-binding assay *in vivo*

Male and female Fischer-344 rats were administered a single, trace dose of ^{14}C-labelled vinyl acetate orally, or were exposed by inhalation in a closed system to ^{14}C-vinyl acetate at an initial concentration of 1,200 - 1,800 ppm (4,300 - 6,400 mg/m^3) which fell below 1 ppm after 90 min. The rats were killed after the initial oral or inhalation exposure and the livers were processed for determination of DNA adducts. Although significant amounts of radio-labelled DNA were found, no specific DNA adducts of the type found after exposure of animals to carcinogenic vinyl halides or vinyl carbamates could be detected in hepatic tissues. Some radioactivity was associated with hepatic nucleoproteins (Simon *et al*, 1985b).

8.4.10 Summary and Evaluation

Studies on vinyl acetate *in vitro* with prokaryotic cell systems (Ames test, SOS-chromotest) failed to show genotoxic effects while most investigations in mammalian cells *in vitro* indicated a genotoxic potential. It was mutagenic in a mouse lymphoma point mutation assay, produced dose-dependant aberrations and sister chromatid exchanges in cultured human leukocytes and CHO-cells, and enhanced cell transformation in the SA7-viral transformation assay. An increase of micronuclei and an indication of DNA cross-links in human lymphocytes was also reported. Vinyl acetate was not active in an alkaline elution assay in human leukocytes.

The results from *in vivo* studies are variable. Vinyl acetate did not bind covalently to liver DNA in Fischer rats after inhalation or oral administration. It induced micronuclei in bone marrow cells of mice after a single, high ip dose but did not affect the number of micronuclei in polychromatic erythrocytes in the bone marrow in 90 day oral or inhalation studies.

The number of micronuclei in spermatids was not affected by exposure to vinyl acetate despite of the finding that the compound had reached the target organ where it caused sperm abnormalities. A doubling of aberrations in peripheral blood cells was reported in polyvinylacetate production workers (section 9.4).

The genotoxic effects of vinyl acetate *in vitro* appear to be due to the acetaldehyde formed from the rapid esterase mediated hydrolysis of vinyl acetate (see 7.2.1) and the genotoxicity of acetaldehyde must therefore be considered.

Like vinyl acetate, acetaldehyde is not mutagenic in the Ames test (Rosenkranz, 1977; Sasaki and Endo, 1978), but shows activity in a DNA-repair test in *Escherichia coli* (Rosenkranz, 1977); it is mutagenic in the mouse lymphoma-test (Wangenheim and Bolcsfoldi, 1988) and induces aberrations and sister chromatid exchanges in mammalian cells (Bird *et al*, 1982; He and Lambert, 1985; Obe and Ristow, 1977). The possibility that

acetaldehyde is the active genotoxic agent is supported by the studies of He and Lambert (1985), who showed a striking similarity in the time- and concentration-dependent effects of the SCE-frequency with the substances. The authors assumed that ester hydrolysis of vinyl acetate occurs within the cell since the addition of purified carboxyl esterases had no effect on the SCE-frequency caused by vinyl acetate *in vitro*.

Studies by Norppa *et al* (1985), Laib and Bolt (1986), Simon *et al* (1986) and Fedtke and Wiegand (1990) support the idea that vinyl acetate is rapidly split by esterases and is therefore not readily available for epoxidation. Theoretically, oxidation of vinyl acetate by mono-oxygenases could lead to aceto-oxirane, the epoxide of vinyl acetate, a substance which is mutagenic in the Ames test without metabolic activation (Simon *et al*, 1986). However, vinyl acetate is not genotoxic in the Ames test. Rapid hydrolysis would compete with expoxide formation or other mode of metabolic activation and, moreover, the initial half-life of the epoxide in phosphate buffer (pH 7.8, at 37°C) is only 2.8 min whilst its mutagenicity is abolished completely by S9 mix (Simon *et al*, 1986).

When administered *in vivo* by the oral and inhalation routes, vinyl acetate did not produce genotoxic changes in tissues and organs remote from the site of administration. Only high dose levels, close to the LD_{50}, given by ip injection increased the number of micronuclei in bone marrow cells; spermatids were not similarly effected. The variability in the results of the micronucleus assays may be explained by differences in dose levels and routes of exposure. Administration of vinyl acetate by inhalation or in the drinking water would produce a relatively constant intake of material into the body at a slow rate over a long period. This would allow rapid and complete metabolism of the vinyl acetate and of the acetaldehyde formed without exposure of cells remote from the site of administration. On the other hand, ip injection leads to rapidly rising tissue levels and a greater likelihood of saturation of the detoxification mechanisms and of exposure of target tissues to significant concentrations of vinyl acetate and acetaldehyde. The transient, if slight, decrease in glutathione reported after ip injection supports this view.

In summary, vinyl acetate, like its hydrolysis product acetaldehyde, possesses genotoxic potential *in vitro*. Genotoxic effects remote from the site of exposure were observed only in animals under experimental conditions in which the detoxification mechanisms were saturated. In man, the conditions of normal handling and use (section 5.2.2) are such that systemic genotoxic effects, ie, in cells away from the site of exposure, of vinyl acetate are unlikely to occur.

8.5 Chronic toxicity and carcinogenicity

8.5.1 Inhalation

Wistar rats were exposed to 0, 2.8, 28 or 140 ppm (0, 10, 100 or 500 mg/m^3) vinyl acetate (5 h/d, 5 d/wk) for 10 months. Bronchial epithelial metaplasia was detected at all treatment levels. Exposure to 100 and 500 mg/m^3, but not to 10 mg/m^3, caused fatty degeneration of the liver with proliferation of the endoplasmic reticulum and changes in the biliary canaliculi (Czajkowska *et al*, 1986).

Sprague-Dawley rats (total 96, sex not specified) were exposed to vinyl acetate vapour at 2,500 ppm (8,900 mg/m^3, 4 h/d, 5 d/wk) for 52 weeks and, after cessation of exposure, observed for up to 83 weeks for tumorigenic effects. No tumours were found in the vinyl acetate-exposed rats; although they occurred in 6 of 68 control animals. No toxic effects from exposure to vinyl acetate were reported, but only 49 of 96 exposed animals (51%) survived at 26 wk; 58 of 68 control animals (85%) were alive at that time. Histopathological examination of the nasal cavity was not undertaken (Maltoni and Lefemine, 1975).

Groups of 90 male and 90 female Sprague-Dawley derived CD rats and CD-1 mice (60 for the main study and 30 for laboratory investigations and pathological examinations after shorter exposure periods) were exposed to 0, 50, 200 or 600 ppm (180, 710 or 2,100 mg/m^3) vinyl acetate (6 h/d, 5 d/wk) for $\leq$ 104 weeks in whole-body inhalation chambers. There were no adverse effects on survival, haematology, clinical chemistry or urinalysis

in either species at any concentration. In high-dose rats and mice, body weight gain was significantly lower than in controls. Lung weights were increased at the 600 ppm concentration, probably associated with chronic irritation of the respiratory tract. In both species pathological changes of the respiratory tract were noted (Owen, 1988). In the rats, atrophy of the olfactory epithelium, epithelial changes in the lung airways and histiocyte accumulation in the alveoli were found at 600 ppm. Also at this concentration, 11 nasal tumours and 1 squamous cell carcinoma of the larynx were present. Histologically, 8 of the nasal tumours were diagnosed as papillomas and 3 as squamous cell carcinomas at the laboratory conducting the study, and as 5 as papillomas and 6 as squamous cell carcinomas at the TNO-CIVO Institute. Rats exposed to 200 ppm showed olfactory epithelial atrophy and one rat had a nasal papilloma. Exposure to 50 ppm did not cause any treatment-related changes.

High-dose (600 ppm, 2,100 mg/m^3) CD-1 mice also showed atrophy of the olfactory epithelium and changes in the repiratory tract. Rhinitis, hyperplasia of the nasal and tracheal respiratory epithelium, one squamous cell carcinoma (a rare tumour type in this strain of animal) and one preneoplastic squamous nodule in the lungs were found at this concentration. Mice exposed to 200 ppm showed some degenerative changes in the airways but no tumours were found. No treatment-related changes were seen at 50 ppm. There was no evidence of an increased tumour incidence in tissues other than the respiratory tract following inhalation of vinyl acetate at any treatment level in either rats or mice. Thus, in this study in rats and mice, a NOEL of 50 ppm (180 mg/m^3) vinyl acetate was established (Owen, 1988).

Respiratory tract tumour data of the long-term inhalation studies with rats and mice are summarised in Tables 10 and 11. Since vinyl acetate is rapidly hydrolysed to acetaldehyde, the tumour incidences in a similar long-term inhalation study on acetaldehyde have been given in Table 12 (Woutersen *et al*, 1986).

8.5.2 Oral

Groups of 20 male and 20 female F344 rats were given 0, 1,000 or 2,500 mg/l vinyl acetate in drinking water for 100 weeks (Lijinsky and Reuber, 1983). The animals, caged in groups of four, were given only 20 ml water/rat/d for 5 d/wk. On the remaining 2 d tap water was given *ad libitum*. The authors considered that each would have received at least half the nominal dose because of loss of vinyl acetate by "decomposition". The actual dose received was not known. All rats died naturally or were killed when moribund. Gross lesions and major organs were sampled at autopsy and subjected to microscopic examination. The survival of the rats was unaffected by treatment and the incidence of most types of neoplasm was similar in treated and untreated groups. There was a dose-related increase in the incidence of adenocarcinoma of the uterus and of C-cell adenoma of the thyroid in female rats, and an elevated incidence of neoplastic nodules in the liver in treated rats of both sexes. The authors acknowledged the limitations of the study design.

In a more recent study (Shaw, 1988) groups of 60 male and 60 female Sprague-Dawley rats were given drinking water containing nominal concentrations of 0, 200, 1,000 or 5,000 ppm (v/v) vinyl acetate for 2 years. An additional 30 animals of each sex and group were assigned for interim clinical pathology and *post mortem* investigations after 52 or 78 weeks of treatment. All animals were obtained from the F_1 litters of animals treated with corresponding levels of vinyl acetate in the drinking water before mating and during lactation. These *in utero* exposed pups were allocated to their appropriate continuing treatment at weaning (21 d *post partum*). The solutions in vinyl acetate in the drinking water were prepared daily throughout the study and over-formulated by 5% to correct for hydrolysis over 24 h. There was a dose-related reduction in water consumption during the first year of the study with only the mid- and high-dose groups clearly affected in the second year. In these high dose rats, there was also reduced body-weight gain (10 - 17% in males, 6 - 11% in females) and food consumption. There was no evidence of consistent treatment-related effects on the appearance or behaviour of the animals, their survival, or haematological or clinical chemistry indices. The

relative kidney weights of high-dose male rats were greater than those of the controls; although statistically significant ($P < 0.05$), the increase was small and there was no evidence of treatment-related histopathological changes in this organ, nor of any significant findings in the urine studies. The effect is therefore of doubtful toxicological significance. No other organ weight changes were reported which could be attributed to exposure to vinyl acetate. The gross and microscopic pathology observations showed that the type and incidence of tumours encountered in the study were generally consistent with those expected in animals of this strain and age and showed no treatment-related trend.

The study shows that rats dosed for 2 years with vinyl acetate in drinking water at 200, 1,000 or 5,000 ppm (v/v) exhibited a dose-related reduction in water consumption associated and, in the 5,000 ppm group, reduced food intake and body weight gain. No convincing evidence of organ damage was obtained nor was there any treatment-related carcinogenic response. These findings differ from those of Lijinsky and Reuber (1983), although the latter study design was significantly flawed.

8.5.3 Summary and Evaluation

The results of studies show that the carcinogenic activity of vinyl acetate is confined to tissues which are in intimate contact with high concentrations over a protracted period. While inhalation exposure led to an increased incidence of tumours of the nose and larynx in rats, there was no increase in the incidence of cancers remote from these sites. Oral administration of high doses failed to provide conclusive evidence of carcinogenicity in the gastro-intestinal tract or elsewhere in the body even though the material was widespread throughout body tissues.

Although a clear but weak carcinogenic response occurred after prolonged inhalation exposure in rats, no increase in tumours occurred in mice. Both species developed chronic inflammatory changes in the respiratory tract when exposed to high concentrations of vinyl acetate. It is significant, however, that at concentrations which produced no respiratory tract

irritation in rats (50 ppm, 180 mg/m^3), no increase in respiratory tract tumours occurred.

Acetaldehyde is the primary metabolite of vinyl acetate and its formation might therefore account for the local irritant and tumorigenic effects of vinyl acetate. Comparison of the results obtained from inhalation studies with acetaldehyde (Table 12) and vinyl acetate (Table 11) reveals qualitative and quantitative differences. At comparable exposure levels (700 ppm acetaldehyde; 600 ppm vinyl acetate) vinyl acetate produced a much lower incidence of papillomas and squamous cell carcinomas. In addition acetaldehyde induced a pronounced increase in adenocarcinomas; this was not seen with vinyl acetate. The findings suggest that the effects of vinyl acetate when administered by inhalation are not mediated through the production locally of high concentrations of acetaldehyde. While many factors such as cellular distribution and pharmacokinetics of activation and deactivation may explain these differences, the intrinsic irritant properties of vinyl acetate itself appeared to be associated with the local tumour production. It is significant that levels of exposure producing marked cellular damage and proliferation in rats induced the development of papillomas and squamous cell carcinomas while no such tumour occurred at non-irritant exposure levels. Overall, significant and prolonged irritation of the epithelia of the respiratory tract appear to be a precondition for the development of tumours.

Occupational health limits have been set at levels which avoid the development of irritant effects in man. Control of exposure at or below these limits should provide adequate protection against the development of prolonged respiratory tract irritancy and, in consequence, of carcinogenic activity in man.

8.6 Reproduction, Embryotoxicity, Teratogenicity

Groups of 24 mated female Sprague-Dawley derived rats were exposed to vinyl acetate vapour at 0, 50, 200 and 1,000 ppm (0, 180, 710 and 3,600 mg/m^3) (6 h/d) on days 6 - 15 of gestation. At 1,000 ppm, maternal toxicity (growth

retardation, congestion of the lungs) and foetotoxicity (growth retardation) occurred. The foetotoxic effect was considered to be secondary to maternal toxicity. No treatment-related teratogenic effects were found (Irvine, 1980).

Groups of 23 mated female Sprague-Dawley rats were administered vinyl acetate in their drinking water from day 6 to day 15 of gestation at nominal concentrations of 0 (control), 200, 1,000 or 5,000 ppm v/v (Irvine, 1980). The test solutions were prepared daily and over-formulated by between 7 and 10% to correct for vinyl acetate loss over 24 hours. On day 20 of gestation, terminal examination of the dams and their uterine contents was conducted. There were no statistically significant differences between treated and control groups of animals in appearance, behaviour or pregnancy index. Initially, there was a slightly reduced intake of food and water associated with a slight retardation of body weight gain in the high-dose dams; only the reduced water intake assumed statistical significance. No changes attributed to treatment were observed in the *post mortem* examination of the dams or in the examination of foetal parameters including the total incidence of abnormalities. A slightly higher number of pre-implantation losses in vinyl acetate treated animals compared to controls was not statistically significant and the difference was thought to be the result of an unusually low incidence in the untreated dams. It was concluded that administration of vinyl acetate in the drinking water at up to 5,000 ppm v/v, a dose which results in slight maternal toxicity, was not embryotoxic or teratogenic in the rat.

Groups of 18 male and 36 female Sprague Dawley rats were administered vinyl acetate in drinking water at nominal concentrations of 0 (control), 200, 1,000 or 5,000 ppm v/v (Shaw, 1987). The test solutions were freshly prepared daily and over-formulated by 5% to correct for vinyl acetate losses over 24 hours. The initial parental generation (F_1) received vinyl acetate for 10 weeks prior to mating and the treatment continued throughout gestation and lactation. From the first litters, groups of 25 male and 25 female pups (F_1) were selected; they continued to receive vinyl acetate for 10 weeks after weaning and then allowed to mate within their groups to produce the second generation (F_2). The study was terminated following the

weaning of the F_2 litters. The reproductive performance of the F_0 and F_1 animals was evaluated from indices which included litter number, viability and size. Weights of the pups were recorded from birth to weaning as were developmental and functional parameters. Post-mortem examinations were carried out on the F_0 and F_1 parental animals and on a representative selection of weaned F_2 pups. There was a significant decrease in water consumption in mid- and high-dose F_0 and F_1 groups and this was assocatiated with slightly reduced body-weight gain in high-dose F_0 parents and F_1 pups. Throughout the study there were no deaths or clinical or behavioral abnormalities attributable to treatment with vinyl acetate. No effects were observed in the reproductive performance of the F_0 animals, but the mating of the F_1 animals resulted in a lower number of pregnancies in the high-dose group (19/24) compared with controls (24/25). While the difference was slight and not statistically significant, cross-mating of some of the animals of the two groups pointed to a marginally reduced male fertility. All other observations, including those made at necropsy and subsequent histopathological examinations showed no adverse effects due to vinyl acetate.

Thus no effects were seen on reproductive performance, or on the resulting litters of male and female rats exposed to 200 or 1,000 ppm vinyl acetate in the drinking water. At 5,000 ppm a lower number of females became pregnant although cross-mating studies suggested that the effect, which was marginal and not statistically significant, was associated with male reproductive performance. Effects on the litters of animals exposed to 5,000 ppm vinyl acetate were confined to a significant reduction in pup weight gain.

9. EFFECTS ON MAN

9.1 Acute Toxicity

No reliable data are available.

A worker exposed to a large leak of vinyl acetate suffered severe, irreversible lung damage (Anonymous, 1987).

The mean odour threshold of vinyl acetate varies from 0.43 - 1 mg/m^3 (Gofmekler, 1960; Verschueren, 1983). This odour threshold represents a possible warning signal, despite subjectivity and individual variations in perception.

9.2 Subchronic Toxicity

No data are available.

9.3 Irritation and Sensitisation

9.3.1 Skin irritation

Continuous contact with the skin, as afforded by clothing wet with vinyl acetate, resulted in severe irritation or blister formation (Union carbide, 1958; Deese and Joyner, 1969; INRS, 1985).

No serious skin burns due to vinyl acetate occurred in a group of 21 workers in a US vinyl acetate production plant with a total of 320 man-year service. Skin irritation and rashes were reported in three of this group (Deese and Joyner, 1969).

A quarter of the workers of a Soviet plant manufacturing polyvinyl acetate evidently had some kind of skin disorder (no further details available) (Nargizyan *et al*, 1978). An evaluation is not possible.

9.3.2 Eye irritation

Minor burns resulted from splashes of undiluted material in the eye (Deese and Joyner, 1969).

One case of human cornea burn was reported following direct contact with vinyl acetate liquid. The cornea recovered without sequellae within 48 h (McLaughlin, 1946).

Eye irritation by vinyl acetate vapours was reported to occur at levels of 69 mg/m^3 and 256 mg/m^3 (NIOSH, 1978).

Atmospheres containing 22 ppm (80 mg/m^3) irritated the eye. No irritancy occurred in four of five workers exposed to 10 ppm (36 mg/m^3) , but the fifth subject reported slight eye irritation even at 5.7 ppm (20 mg/m^3) (Deese and Joyner, 1969).

9.3.3 Respiratory Tract Irritation

Vinyl acetate produced signs of upper respiratory tract irritancy (hoarseness and cough) at 20-22 ppm (70 - 80 mg/m^3) , but not at 10 ppm (36 mg/m^3) (Mellon Institute, 1968; Deese and Joyner, 1969). One out of five individuals noted hoarseness at 4.2 ppm (15 mg/m^3) (Deese and Joyner, 1969).

A group of 21 chemical operators exposed to vinyl acetate vapour (76 mg/m^3) in a production plant developed a slight irritation of the pharynx (Deese and Joyner, 1969). No other effects of irritation were observed at this level.

Examination of a group of 250 persons occupationally exposed to vinyl acetate vapour (140 mg/m^3) and to unknown levels of other chemicals, including acetaldehyde, butyraldehyde and methanol, showed no evident correlation between exposure and symptoms of chronic bronchitis (Agoranian and Amatuni, 1980).

9.3.4 Skin Sensitisation

A study of the medical records over a 5-year period of 21 US workers suggested that vinyl acetate was not a significant inducer of allergic contact dermatitis (Deese and Joyner, 1969).

9.3.5 Respiratory sensitisation

No data are available.

9.4 Mutagenicity

An elevated level of chromosomal damage was reported in Soviet workers in a polyvinyl acetate production plant (Shirinian and Arutyunyan, 1980). Details are not available and an evaluation is not possible.

9.5 Chronic Toxicity

A retrospective study was conducted on 21 chemical operators (mean age 45.3 years) exposed to vinyl acetate vapour in a production plant. The mean period of exposure was 15.2 years, whilst the exposure levels ranged from 17.6 mg/m^3 to 35 mg/m^3. The workforce exhibited no overt signs of occupationally-induced injury other than local irritant reactions (section 9.3.3). The group of chemical operators was matched with a group of people who had similar jobs, but were not exposed to vinyl acetate. Surveillance of medical and biochemical parameters, including hematocrit, WBC, alkaline, phosphatase activity, cholesterol, albumin, globulins, creatinin, glucose, BUN, lung function (VC/FEV_1), chest X-ray and blood pressure, did not

reveal differences between the exposed operators and the control group (Deese and Joyner, 1969).

9.6 Carcinogenicity

In a study of a cohort of 4,806 persons in a synthetic chemical plant, 45 cases of lung cancer occurred from 1942 to 1973. The results showed no association between exposure to vinyl acetate and excess lung cancer (exposure to 19 chemicals was involved) (Waxweiler *et al*, 1981).

The possible association of the occurrence of gliomas of the brain and working activities was examined in a study of people working in a petrochemical plant in Texas. They had been exposed to a variety of chemicals, including vinyl acetate. No significant differences between exposed and non-exposed groups were observed following exposure to any of the chemicals (Leffingwell *et al*, 1983).

9.7 Reproductive Toxicity

No data are available.

9.8 Neurotoxicity

No reliable data are available.

Neurological disorders and changes in the liver function were reported in the "majority" of people working in a vinyl acetate production plant (Nargizyan *et al*, 1978). Insufficient data are given to permit an evaluation.

9.9 Other effects

An increased incidence of non-specific effects such as fainting spells, pain around the heart area and amplitude decrease in ECG were observed in 250 people studied by Agoranian and Amatuni (1980) (section 9.3.3).

9.10 Recommendations for medical surveillance

Pre-employment examinations should include medical and work histories with special attention for pre-existing respiratory or skin disorders, and chronic eye irritation such as conjunctivitis or keratosis.

If periodic examinations are undertaken, particular attention should be paid to clinical examination of the eye, skin and respiratory tract.

10. FIRST AID AND SAFE HANDLING ADVICE

10.1 First Aid and Medical Treatment

Eye Contact: Immediately flush eyes with plenty of water. Ensure adequate flushing of the eyes by separating the eyelids with fingers. Obtain medical attention.

Skin Contact: Contaminated clothing should be removed and the affected area of the skin thoroughly washed with soap and water.

Inhalation: Provide fresh air. Monitor breathing and give oxygen if breathing is difficult. If breathing shows signs of failing, apply mouth to mouth ventilation. Obtain medical attention urgently.

Ingestion: Wash out mouth with water. Do not induce vomiting. Monitor breathing and give oxygen if breathing is difficult. If breathing shows signs of failing, apply mouth to mouth ventilation. Obtain medical attention urgently.

10.2 Safe Handling

General Precautions: Vinyl acetate has a low flash point and may form explosive mixtures with air at normal temperatures. It has a high electrical resistivity and can readily accumulate static electricity. All equipment must therefore be explosion proof and properly earthed and bonded. Avoid splashing during during loading operations.

Personal Protection: Atmospheric levels should be kept below the recommended occupational exposure limits by engineering controls such as local exhaust ventilation. Wear respirator with approved organic vapour cartridge in areas where these limits are likely to be exceeded. Skin and eye protection should be worn where exposure to liquid may to occur. Neoprene or synthetic rubber gloves are recommended.

Storage: Uncontrolled polymerisation can cause rapid evolution of heat and increased pressure which can result in violent rupture of storage vessels or containers. In order to prevent polymerisation, containers should be kept tightly closed and stored in a cool and dry place. Contact with polymerisation initiators such as peroxides or radiation (sunlight, ultraviolet, X-ray) must be avoided. The storage area should be well ventilated.

10.3 Management of Spillage and Waste

In the event of severe spillage, evacuate the area.

Decontamination personnel should wear protective equipment, ie, self-contained breathing apparatus, protective gloves, goggles or face shield and boots. If fire potential exists, blanket with foam or use water spray to disperse vapours.

For large scale spillages, the liquids should be prevented from spreading by the use of sand or earth. The liquid should be transferred to a salvage tank if possible. The local authorities should be informed at once if the spilt liquid enters the surface water drains.

Small or medium scale spillages should be absorbed with sand or earth and all material should be removed to a safe place for subsequent incineration.

Waste Disposal: The material should be burned in an incinerator suitable for chemical waste. It should not be buried or dumped in a landfill.

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TABLE 1

Physical and Chemical Properties of Vinyl Acetate

Property	Value	References
Boiling point, °C at 1013 hPa	72.3 - 72.9	Marsden and Cuthbertson, 1933; Nozaki and Bartlett, 1946; Tong and Kenyon, 1949; Kimble et al, 1982; Rhône-Poulenc, 1986; Weast, 1988; BP Chemicals 1988; Hoechst Celanese, 1988, 1989; Wacker, 1989.
Freezing point, °C	-93.2	Weast, 1988; Hoechst, 1989.
Specific gravity (20°C/4°C)	0.9317	Staudinger and Schwalbach, 1931; Weast, 1988;
	0.9324	Rhône-Poulenc, 1986;
(20°C/20°C)	0.9338	Hoechst Celanese, 1989;
	0.9342	Morrison and Shaw, 1933.
Refractive index, n_D^{20}	1.3952 - 1.3959	Staudinger and Schwalbach, 1931; Morrison and Shaw, 1933; Matheson et al, 1949; Wacker, 1981; Weast, 1988; Hoechst Celanese, 1989; Hoechst 1989;
n_D^{25}	1.3934	Nozaki and Bartlett, 1946.
Viscosity, mPa.s at 20°C	0.42 - 0.43	Staudinger and Schwalbach, 1931; Morrison and Shaw, 1933; Wacker, 1981 Rhône-Poulenc, 1986; BP Chemicals, 1988; Wacker, 1989; Hoechst, 1989; Hoechst Celanese, 1989.
Vapour density (air = 1)	3.0	
Vapour pressure, hPa at 20°C	120 (117.3 - 122.6)	Marsden and Cuthbertson, 1933; Kimble et al, 1982; Rhône-Poulenc, 1986; BP Chemicals, 1988; Hoechst, 1989; Hoechst Celanese, 1989; Wacker, 1989.
hPa at 25°C	156.5	Coniglio and Parts, 1971.
Saturation concentration in air at 20°C, g/m^3	398 (≙ 11% (v/v))	BP Chemicals, 1988; Verschueren, 1983.

TABLE 1 (cont.)

Physical and Chemical Properties of Vinyl Acetate

Property	Value	References
Flash point, °C (closed cup)	-8	Morrison and Shaw, 1933; The Associated Factory Mutual Fire Insurance Companies, 1940; Wacker, 1981.
	-9	Rhône-Poulenc, 1986; Hoechst, 1989; Hoechst Celanese, 1989; Wacker, 1989.
Autoignition temperature, °C	385	Wacker, 1981; BP Chemicals, 1988; Wacker 1989; Hoechst, 1989.
Flammable limits in air at 1013 hPa		Wacker, 1981; Rhône-Poulenc, 1986; BP Chemicals, 1988; Hoechst, 1989; Hoechst Celanese, 1989; Wacker, 1989.
- lower limit, % (v/v)	2.6	
- upper limit, % (v/v)	13.4	
Solubility in water		
at 20°C, % (w/w)	2.19	Lissi et al, 1983;
	2.3	Wacker, 1981; Hoechst Celanese, 1989; Hoechst, 1989;
at 25°C, % (w/w)	2.55	Coniglio and Parts, 1971;
	2.67	Richon and Viallard, 1985.
Soluble in most organic solvents such as diethyl ether, methanol, ethanol, acetone, glacial acetic acid, ethyl acetate, hexane, cyclohexane, benzene, carbon disulphide, trichloromethane, tetrachloromethane		Staudinger and Heuer, 1934; Weast, 1988.
Henry's law constant H, $Pa.m^3.mol^{-1}$ at 20°-25°C	45 - 50	Calculated
n-Octanol/water partition coefficient, log Pow - Flask-shaking method	0.73	Chan and Hansch, 1985.
- (HPLC method	0.21	Fujisawa and Masuhara, 1981).
Air odour threshold, mg/m^3	1.0	Gofmekler, 1960.
absolute perception limit, mg/m^3	0.43	Verschueren, 1983.
50 % recognition, mg/m^3	1.43	Verschueren, 1983.
Water odour threshold, mg/l	0.088	Amoore and Hautala, 1983.
Water taste threshold, mg/l	0.25	Goeva, 1966.
Vinyl acetate does not absorb significantly in UV light at $\lambda > 250$ nm.		
Molar extinction coefficient ϵ at $\lambda > 290$ nm	$\leq 3 \times 10^{-3}$	Bengough and Melville, 1954.

TABLE 2

Preparation of Samples for the Determination of Vinyl Acetate in Air by GC/FID

Adsorbent	Desorption	References
Porous polymers or resins	thermal	NIOSH, 1978; Foerst and Teass, 1980.
Activated carbon	With carbon disulphide	Foerst and Teass, 1980; Dobecki and Krajewski, 1980; Sidhu, 1981.
	With nitromethane	Kollar et al, 1988.
Silica gel	With water	Guénier et al, 1986; Guénier and Muller, 1986.

TABLE 3

Biodegradability of Vinyl Acetate based on BOD measurements

Inoculum	Test duration (d)	Medium	Bio-oxidation (%)	Reference
Non-adapted standard activated sludge	5	Fresh water	51.3	Takemoto et al, 1981.
Non-adapted standard activated sludge	5	Sea water	42	Takemoto et al, 1981.
Municipal activated sludge	5	Fresh water	38.7	Wellens, 1980.
Industrial activated sludge	20	Fresh water	90	Wellens, 1980.
Not mentioned	Not mentioned	Fresh water	59.7	Lazareva and Kostina, 1983.
Microbial seed from settled domestic waste water:				
Non-adapted	5	Fresh water	34	Price et al, 1974.
Non-adapted	10	Fresh water	34	Price et al, 1974.
Non-adapted	15	Fresh water	31	Price et al, 1974.
Non-adapted	20	Fresh water	32	Price et al, 1974.
Adapted	5	Fresh water	62	Price et al, 1974.
Adapted	10	Fresh water	70	Price et al, 1974.
Adapted	15	Fresh water	66	Price et al, 1974.
Adapted	20	Fresh water	72	Price et al, 1974.
Non-adapted	5	Salt water	51	Price et al, 1974.
Non-adapted	10	Salt water	61	Price et al, 1974.
Non-adapted	15	Salt water	69	Price et al, 1974.
Non-adapted	20	Salt water	58	Price et al, 1974.

TABLE 4

National Occupational Exposure Limits for Vinyl Acetate

Country of entering into force	TWA concentration (mg/m3)	Short-term exposure or excursions (mg/m3)	Ceiling values (mg/m3)	Legal status	Reference
UK, 1990	30	60		Regulatory	HSE, 1990.
Netherlands, 1989	30			Advisory	Arbeidsinspectie, 1989.
USA: OSHA, 1989	30	60		Regulatory	OSHA, 1989.
FRG, 1988	35	Category 1		Regulatory	DFG (MAK-Kommission) 1989.
Sweden, 1990	35	50		Advisory	National Swedish Board of Occupational Safety and Health, 1989.
USA: ACGIH, 1989	35	70		Advisory	ACGIH, 1989.
USA: NIOSH, 1988			15 (15 min)	Advisory	Milbert and Chandler, 1978; NIOSH, 1988.
France, 1985	30			Advisory	INRS, 1985.
Belgium, 1978	30			Advisory	ILO, 1978.
Switzerland, 1978	35			Advisory	ILO, 1978.
USSR, 1977			10	Regulatory	ILO, 1978.
Poland, 1976			10	Regulatory	ILO, 1978.
Romania, 1975	50		100	Regulatory	ILO, 1978.
Yugoslavia, 1971			10	Regulatory	ILO, 1978.

TABLE 5
Occupational Levels of Vinyl Acetate in Various Industries
(Modified from IARC, 1989)

Industry	Type of Sample	Concentration (mg/m^3 air)	Reference
Vinyl acetate production	personal	1.4-17	Milbert and Chandler, 1978;
Vinyl acetate production and polymerization	personal	0-17.6	Deese and Joyner, 1969.
Polymer adhesive manufacture	personal	<0.4-18.2	Boxer and Reed, 1983.
Latex paint manufacture	personal	<6.7-126	Belanger and Coy, 1981.
	area	<4.2-36.6	
Vinyl acetate production	area	0.63-4.29	Jedrychowski et al, 1979.
Polyvinyl acetate production	area	1.17-1.40	Jedrychowski et al, 1979.
Vinyl copolymer production	area	9.73-11.48	Jedrychowski et al, 1979.

TABLE 6

Toxicity of Vinyl Acetate to Microorganisms

Species	Duration of experiment	NOEL, growth inhibition (mg/l)	Reference
Bacteria			
Pseudomonas putida	16 h	6	Bringmann and Kühn, 1976; 1977a; 1979; 1980a.
Microcystis aeruginosa	8 d	35	Bringmann and Kühn, 1976; 1978a; 1978b.
Protozoa			
Saprozoic flagellate *(Chilomonas paramaecium)*	48 h	9.5	Bringmann *et al*, 1980; Bringmann and Kühn, 1981.
Bacteriovorous flagellate *(Entosiphon sulcatum)*	72 h	81	Bringmann, 1978; Bringmann and Kühn, 1979; 1980a; 1981.
Bacteriovorous ciliate *(Uronema parduczi)*	20 h	91	Bringmann and Kühn, 1980b; 1981.

TABLE 7

Acute Toxicity of Vinyl Acetate to Aquatic Organisms - Invertebrates

Test species	Parameter	Result (mg/l)	Reference
Freshwater			
	Lethality		
water flea *(Daphnia magna)*	LC_0 (24 h)	16	Bringmann and Kühn, 1977b.
	LC_{50} (24 h)	330	
	LC_{100} (24 h)	1000	
	Immobilisation		
	EC_0 (24 h)	17	Bringmann and Kühn, 1982.
	EC_{50} (24 h)	52 (44-62)*	
	EC_{100} (24 h)	128	
	Marine		
Brine shrimp *(Artemia salina)*	LC_{50} (24 h)	45	Price *et al*, 1974.
Polychaete *(Ophryotrocha diadema)*	LC_{50} (48 h)	35	Parker, 1984.

*) 95% confidence limits

TABLE 8

Acute Toxicity of Vinyl Acetate to Aquatic Organisms - Vertebrates

Test species	Parameter	Result (mg/m^3)	Water hardness and pH	Reference
Freshwater				
Golden orfe *(Leuciscus idus melanotus)*	LC_0 (48 h)	9	Unknown	Juhnke and Lüdemann, 1978.
	LC_{50} (48 h)	26		
	LC_{100} (48 h)	93		
Bluegill *(Lepomis idus melanotus)*	LC_{50} (24 h)	18.5 (15.7-22.1)*	Soft 7.5	Pickering and Henderson, 1966.
	LC_{50} (48 h)	18.0 (15.0-21.5)		
	LC_{50} (96 h)	18.0 (15.0-21.5)		
Goldfish *(Carassius auratus)*	LC_{50} (24 h)	42.3 (33.5-53.5)	Soft 7.5	Pickering and Henderson, 1966.
	LC_{50} (48 h)	42.3 (33.5-53.5)		
	LC_{50} (96 h)	42.3 (33.5-53.5)		
Guppy *(Lebistes reticulatus)*	LC_{50} (24 h)	31.1 (26.1-36.6)	Soft 7.5	Pickering and Henderson, 1966.
	LC_{50} (48 h)	31.1 (26.1-36.6)		
	LC_{50} (96 h)	31.1 (26.1-36.6)		
Fathead minnow *(Pimephales promelas)*	LC_{50} (24 h)	22.2 (19.2-27.1)	Soft 7.5	Pickering and Henderson, 1966.
	LC_{50} (48 h)	20.3 (17.0-25.6)		
	LC_{50} (96 h)	19.7 (16.3-25.1)		
	LC_{50} (24 h)	24.0 (18.9-30.5)	Soft 7.5	
	LC_{50} (48 h)	24.0 (18.9-30.5)		
	LC_{50} (96 h)	24.0 (18.9-30.5)		
	LC_{50} (24 h)	36.8 (32.6-42.7)	Hard 8.2	
	LC_{50} (48 h)	36.8 (32.6-42.7)		
	LC_{50} (96 h)	35.8 (31.4-41.7)		
	LC_{50} (24 h)	39.2 (34.1-47.6)	Hard 8.2	
	LC_{50} (48 h)	39.2 (34.1-47.6)		
	LC_{50} (96 h)	39.2 (34.1-47.6)		
Fathead minnow *(Pimephales promelas)*				
Young, 1 day	LC_{50} (24 h)	14-18	Medium 7.8	Pickering and Henderson, 1966.
	LC_{50} (48 h)	14-18		
	LC_{50} (96 h)	14-15		
2 days	LC_{50} (24 h)	15-18	Medium 7.8	
	LC_{50} (48 h)	15-17		
	LC_{50} (96 h)	15		
4 days	LC_{50} (24 h)	25-28	Medium 7.8	
	LC_{50} (48 h)	24-27		
	LC_{50} (96 h)	23-26		
Adult	LC_{50} (24 h)	24-44	Medium 7.8	
	LC_{50} (48 h)	22-44		
	LC_{50} (96 h)	20-44		

*) 95% confidence limits

TABLE 9a

Acute Toxicity - Lethal Dose

Species	Strain	Route	LD_{50} (mg/kgbw)	Reference
Rat	-	Oral	2,920 - 3,730	Mellon Inst., 1946; 1969.
Mouse	-	Oral	1,610	Goeva, 1966.
Rabbit	-	Dermal (24-h contact)	2,340	Smyth and Carpenter, 1948.
Rabbit	-	Dermal	>5,000	Mellon Inst., 1946.

TABLE 9b

Acute Toxicity - Lethal Concentration

Species	Strain	Exposure period (h)	LC_{50} (ppm)	LC_{50} (mg/m^3)	Reference
Rat	Sherman	4	4,000	(14,000)	Mellon Inst., 1946; Carpenter *et al*, 1949.
Rat	-	4	3,680	(13,000)	Carnegie-Mellon Univ., 1973.
Mouse	-	4	1,550	(5,400)	Mellon Inst., 1968.
Mouse	-	4	1,460	(5,150)	Carnegie-Mellon Univ., 1973.
Rabbit	-	4	2,500	(8,800)	Mellon Inst., 1968.
Rabbit	-	4	2,760	(9,900)	Carnegie-Mellon Univ., 1973.
Guinea pig	-	4	5,210	(18,600)	Carnegie-Mellon Univ., 1973.
Dog	Beagle	4	>3,280	(11,700)	Carnegie-Mellon Univ., 1973.

TABLE 10

Incidence of Tumours of the Respiratory Tract of Crl:CD(SR)BR Rats Exposed to Vinyl Acetate (Owen, 1988).

Vinyl acetate (ppm):	Male rats				Female rats			
[n]*:	0 [59]	50 [58]	200 [58]	600 [56]	0 [60]	50 [59]	200 [60]	600 [60]
Nasal cavity								
papilloma	0	0	1	7	0	0	0	1
squamous cell carcinoma	0	0	0	0	0	0	0	3
Lung								
adenoma	0	0	0	0	1	0	0	0
Larynx								
squamous carcinoma	0	0	0	0	0	0	0	1

* Number of animals which survived more than 52 weeks

TABLE 11

Incidence of Tumours of the Respiratory Tract in Crl:CD-1(ICR)BR Mice Exposed to Vinyl Acetate (Owen, 1988).

Vinyl acetate (ppm):	Male mice				Female mice			
[n]*:	0 [57]	50 [53]	200 [57]	600 [49]	0 [60]	50 [56]	200 [58]	600 [53]
Nasal cavity								
papilloma/carcinoma	0	0	0	0	0	0	0	0
Lung								
adenoma	17	6	9	10	10	10	12	17
multiple adenoma	4	3	6	2	2	1	0	1
carcinoma	4	0	0	0	3	1	1	0
carcinoma/adenoma	0	0	0	0	1	0	0	0
squamous cell carcinoma	0	0	0	1	0	0	0	0
Larynx								
papilloma	0	0	0	0	0	0	0	1

*) Number of animals which survived more than 52 weeks

TABLE 12

Tumours of the Respiratory Tract in Wistar Rats Exposed to Acetaldehyde (Woutersen et al, 1986).

Acetaldehyde (ppm):	Male rats 0	700	1,500	3,000*	Female rats 0	750	1,500	3,000*
Nasal cavity [n]**:	[49]	[52]	[53]	[49]	[50]	[48]	[53]	[53]
papilloma	0	0	0	0	0	1	0	0
squamous cell carcinoma	1	1	10	15	0	0	5	17
carcinoma *in situ*	0	0	0	1	0	0	3	5
adenocarcinoma	0	15	30	21	0	6	26	21
Lung [n]**	[55]	[54]	[55]	[52]	[53]	[52]	[54]	[54]
poorly differentiated adenocarcinoma	0	0	0	0	0	1	0	0
Larynx [n]**	[50]	[50]	[51]	[47]	[51]	[46]	[47]	[49]
carcinoma *in situ*	0	0	0	0	0	0	1	0

* The concentration was reduced to 1,000 ppm

** Number of animals which survived 28 months

APPENDIX I

Classification and Labelling for the EC
(Dangerous Substances Directive 67/548/EEC and following)
(EC, 1987)

Vinyl acetate	Nº 607-023-00-0	Nota D*
Symbol F	Highly flammable	 F
Risk phrase	R11 - Higly flamable	
Safety phrases	S11 - Keep away from sources of ignition - No smoking S23 - Do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by the manufacturer) S29 - Do not empty into drains S33 - Take precautionary measures against static discharges.	

*) Certain substances which are susceptible to spontaneous polymerisation or decomposition are generally placed on the market in a stabilised form. It is in this form that they are listed in Annex I to this Directive. However, such substances are sometimes placed on the market in a non-stabilised form. In this case, the manufacturer or any other person who places such a substance on the market must state on the label the name of the substance followed by the words "non-stabilised".

APPENDIX 2

Members of the Task Force

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* Indicates Steward responsability.

LIST OF ECETOC PUBLICATIONS

MONOGRAPHS

No.	Title
No.1	Good Laboratory Practice
No.2	Contribution to Strategy for Identification and Control of Occupational Carcinogens
No.2	Definition of a Mutagen, for 6th Amendment
No.3	Risk Assessment of Occupational Chemical Carcinogens
No.4	Hepatocarcinogenesis in Laboratory Rodents : Relevance for Man
No.5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology)
No.6	Acute Toxicity Tests, LD_{50}(LC_{50}) Determinations and Alternatives
No.7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies
No.8	Structure-Activity Relationships in Toxicology and Ecotoxicology: An Assessment
No.9	Assessment of Mutagenicity of Industrial and Plant Protection Chemicals
No.10	Identification of Immunotoxic Effects of Chemicals and Assessment of their Relevance to Man
No.11	Eye Irritation Testing
No.12	Alternative Approaches for the Assessment of Reproductive Toxicity (with emphasis on embryotoxicity/teratogenicity)
No.13	DNA and Protein Adducts: Evaluation of their Use in exposure Monitoring and Risk Assessment
No.14	Skin Sensitisation Testing
No.15	Skin Irritation

TECHNICAL REPORTS

No.	Title
No.1	Assessment of Data on the Effects of Formaldehyde on Humans
No.2	The Mutagenic and Carcinogenic Potential of Formaldehyde
No.3	Assessment of Test Methods for Photodegradation of Chemicals in the Environment
No.4	The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man
No.5	Toxicity of Ethylene Oxide and its Relevance to Man
No.6	Formaldehyde Toxicology : an Up-Dating of the ECETOC Technical reports 1 and 2
No.7	Experimental Assessment of the Phototransformation of Chemicals in the Atmosphere
No.8	Biodegradation Testing: An Assessment of the Present Status
No.9	Assessment of Reverse-Phase Chromatographic Methods for Determining Partition Coefficients
No.10	Considerations Regarding the Extrapolation of Biological Data in Deriving Occupational Exposure Limits
No.11	Ethylene Oxide Toxicology and its Relevance to Man : An Up-Dating of ECETOC Technical Report n°5
No.12	The Phototransformation of Chemicals in Water : Results of a Ring-Test
No.13	The EEC 6th Amendment : A Guide to Risk Evaluation for Effects on the Environment
No.14	The EEC 6th Amendment : A Guide to Risk Evaluation for Effects on Human Health
No.15	The Use of Physical-Chemical Properties in the 6th Amendment and their Required Precision. Accuracy and Limiting Values
No.16	A review of Recent Literature on the Toxicology of Benzene
No.17	The Toxicology of Glycol Ethers and its Relevance to Man : An Up-Dating of ECETOC Technical Report n°4
No.18	Harmonisation of Ready Biodegradability Tests
No.19	An Assessment of Occurrence and Effects of Dialkyl-o-Phthalates in the Environment
No.20	Biodegradation Tests for Poorly-Soluble Compounds
No.21	Guide to the Classification of Carcinogens, Mutagens and Teratogens Under the 6th Amendment
No.22	Classification of Dangerous Substances and Pesticides in the EEC Directives. A Proposed Revision of Criteria for Inhalational Toxicity
No.23	Evaluation of the Toxicity of Substances to be Assessed for Biodegradability
No.24	The EEC 6th Amendment : Prolonged Fish Toxicity Tests

No.25	Evaluation of Fish Tainting
No.26	The Assessment of Carcinogenic Hazard for Human Beings Exposed to Methylene Chloride
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No.37	Tetrachloroethylene : Assessment of Human Carcinogenic Hazard
No.38	A Guide to the Classification of Preparations Containing Carcinogens, Mutagens and Teratogens
No.39	Hazard Assessment of Floating Chemicals After an Accidental Spill at Sea
No.40	Hazard Assessment of Chemical Contaminents in Soil
No.41	Human Exposure to N-Nitrosmaines, Their Effects and a Risk Assessment for n-Nitrosodiethanolamine in Personal Care Products

JACC REPORTS

No.	Title
No.1	Joint Assessment of Commodity Chemicals, Melamine
No.2	Joint Assessment of Commodity Chemicals, 1,4-Dioxane
No.3	Joint Assessment of Commodity Chemicals, Methyl Ethyl Ketone
No.4	Joint Assessment of Commodity Chemicals, Methylene Chloride
No.5	Joint Assessment of Commodity Chemicals, Vinylidene Chloride
No.6	Joint Assessment of Commodity Chemicals, Xylenes
No.7	Joint Assessment of Commodity Chemicals, Ethylbenzene
No.8	Joint Assessment of Commodity Chemicals, Methyl Isobutyl Ketone
No.9	Joint Assessment of Commodity Chemicals, Chlorodifluoromethane
No.10	Joint Assessment of Commodity Chemicals, Isophorone
No.11	Joint Assessment of Commodity Chemicals, (HFA-132b) 1,2-Dichloro-1,1-Difluoroethane
No.12	Joint Assessment of Commodity Chemicals, (HFA-124) 1-Chloro-1,2,2,2-Tetrafluoroethane
No.13	Joint Assessment of Commodity Chemicals, (HFA-123) 1,1-Dichloro-2,2,2-Trifluoroethane
No.14	Joint Assessment of Commodity Chemicals, (HFA-133a) 1-Chloro-2,2,2-Trifluoromethane
No.15	Joint Assessment of Commodity Chemicals, (HFA-141B) 1-Fluoro 1,1-Dichloroethane
No.16	Joint Assessment of Commodity Chemicals, (HCFC-21) Dichlorofluoromethane

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