JACC Report

No 5

Vinylindene Chloride
CAS: 75-35-4

August 1985

ISSN-0773-6339-5

ECETOC

14 August 1985

Joint Assessment of Commodity Chemicals

No. 5

VINYLIDENE CHLORIDE

CAS: 75-35-4

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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 the 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 vinylidene chloride 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.

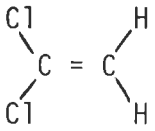
CONTENTS

A. CHEMICAL IDENTITY

Chem. Abstr. Services Reg. No. : 75-35-4.
E.E.C. No. : 602-025-00-8
RTECS No. : KV9275000

Synonyms : 1,1-dichloroethene; ethene, 1,1-dichloro; 1,1-dichloroethylene; ethylene, 1,1-dichloro; VDC; 1,1-DCE.

Formula : $C_2H_2Cl_2$



$CCl_2 = CH_2$

A typical sample of technical product may contain the following impurities :

dichloroacetylene	< 10 ppm
monochloroacetylene	< 1 ppm
vinyl chloride	< 20 ppm
other chlorinated hydrocarbons	<500 ppm
peroxide (as H_2O_2)	< 1 ppm
water	<100 ppm

Vinylidene chloride (VDC) is usually stabilized with 50-200 ppm of p-methoxyphenol (monomethyl ether of hydroquinone). Other stabilizers are sometimes used.

B. PRODUCTION, TRANSPORT, USES AND DISPOSAL

Vinylidene chloride is produced commercially by the dehydrochlorination of 1,1,2-trichloro-ethane with sodium hydroxide or lime. The resulting crude VDC is purified by fractional distillation. The stabiliser is normally added at this distillation step to prevent polymerisation during storage and transport.

The production capacity in Western Europe is reported to be 130,000 tonnes per year, of which 25-30,000 tonnes are utilised in polymer and fibre production and the remainder as an un-isolated intermediate for 1,1,1-trichloroethane production. It is produced only in France, the Federal Republic of Germany, the

Netherlands and the United Kingdom (Battelle, 1983). A small amount is reported to be produced in the German Democratic Republic.

Approximate production figures have been reported for the USA and Japan (SRI, 1976) :

USA	77,000	tonnes per year
Japan	9,000 - 13,500	tonnes per year.

Stabilised VDC is stored and transported in drums and bulk-carriers. The product in bulk-carriers is delivered under nitrogen. More than 90% of the VDC not used to produce 1,1,1-trichloroethane goes into the production of copolymers, of high VDC content, with alkyl acrylates, methacrylates, acrylonitrile (ACN) or vinyl chloride (VC). The remaining 10% or less is used in the manufacture of modacrylic fibres, which are largely based on acrylonitrile with small amounts of VDC and other monomers.

Extruded and coextruded films based on VDC are mainly VDC-VC copolymers, and are used in food packaging, alone or laminated with other plastic films. Vinylidene-vinyl chloride copolymers are also used as films and coatings in cosmetic packagings, as coatings for steel pipes and structures, for the interior of ship tanks and railway tank cars, and as binders and coatings for magnetic, audio, video and computer tapes (Anon, 1981, 1982, 1983, 1984). VDC-copolymers with alkyl methacrylates and/or ACN are used in the form of polymer solutions or dispersions as high barrier coatings for paper, board and a variety of films and as binders in other protective lacquers and coatings.

C. PHYSICAL AND CHEMICAL PROPERTIES

Physical form		: volatile liquid
Molecular weight		: 96.95
Boiling point (°C)		: 31.7
Melting point (°C)		: -122.1
Specific gravity (20°C/40°C) (g/cm³)		: 1.213
Vapour density (air_{20} = 1)		: 3.4
Refractive index n_D		: 1.4249
Vapour pressure in mm Hg (kPa) at		
	-20°C	: 77 (10.2)
	0°C	: 215 (27.7)
	+20°C	: 495 (64.5)
Solubility in water at 21°C (g/kg)		: 2.5
Solubility of water in VDC (25°C) (g/kg)		: 0.4
Solubility in organic solvents		: soluble
Flash point open cup (°C)		: -15
closed cup (°C)		: -19
Flammability limits in air (% vol.) (room temp., atm. pressure)		: 5.6 - 19.5
Explosive limits in air (% vol.)		: 7 - 16
Saturation conc. in air at 20°C (g/m³)		: 2655
Ignition temperature °C		: 440
Heat of evaporation (31,6°C) (J/mol)		: 26.5
Heat of polymerisation (J/mol)		: 75.3
Specific heat (liquid) (J/g.K)		: 1.13
Conversion factors (25°C, 1 atm.)	1 ppm	: 4 mg/m³
	1 mg/m³	: 0.25 ppm

VDC readily polymerises at temperatures above 0°C in the presence of oxygen or other catalysts.

D. ANALYTICAL TECHNIQUES

1. Physical-chemical Methods

A complete review of standardised analytical methods for determining VDC in air, aqueous dispersions, and coatings and resins, and for the evaluation of VDC migrating from PVDC coatings or films, has been published by a European Study Group (1975).

1.1. Air

The presence of VDC in air can be detected by colourimetric reaction in detection tubes usually used for vinyl chloride, such as Dräger, Matheson and Gastech tubes. The detection limit is about 0.2-0.3 ppm. Gas chromatography can also be used for detecting VDC in ambient air, by direct sampling of air or with a portable captor filled with active carbon (NIOSH type). The detection limit, measured under industrial conditions, is in the region of 0.1 ppm. Dispersive infrared analysis can also be used for monitoring of the workplace, the detection limit being 0.5-1 ppm.

1.2. Water

VDC levels in water may be determined by gas chromatography with an electron-capture or flame-ionisation detector. The VDC may be enriched in the gas phase by the head-space technique or by a preliminary extraction from the water with hexane or xylene. The detection limit with this head-space technique is 10 ppb (BASF, 1978). Hollifield and MacNeal (1978) also describe a gas-solid chromatographic determination in three food-simulating solvents. The detection limit is 5-10 ppb. A special "purge and trap" chromatographic technique was developed by US-EPA (1977) for drinking water. With this method a sensitivity of 0.01 ppb can be obtained.

1.3. Packaging materials

Analytical methods for detecting vinylidene chloride in PVDC coatings and films have been developed. A European Study Group (1975) has published methods which permit the detection of VDC over the range 0.008 to 1 mg/dm^2 by head-space chromatography. Birkel et al.(1977) studied the sensitivity of the gas chromatographic method with electron-capture detection and mass spectrometry confirmation. The limit of detection of the method was 5 ppm in PVDC films. Hollifield and MacNeal (1978) also developed a

chromatographic method for the determination of VDC in "saran®" films, the sensitivity being 5-10 ppb.

2. Monitoring of Human Exposure

The odour and irritant properties of VDC are inadequate to give warning of excessive exposure. Human exposure can be adequately assessed by currently available personal monitoring techniques. A method for biological monitoring could be valuable as a complement to such personal monitoring, but although the metabolites of VDC are quite well identified in animals, there is no such information for humans. As this is the basis of biological monitoring, studies to this effect are encouraged.

E. ENVIRONMENTAL DISTRIBUTION AND FATE

1. Environmental Distribution

The value of the Henry constant (distribution constant: water/air), i.e. 1.1×10^{-3}, and the solubility in water (2.5 g/l, De Lassus and Schmidt, 1981) indicate that VDC will, if released, disperse in the atmosphere with little tendency to migrate into water (Eisenreich et al.,1981).

2. Degradation

2.1. Breakdown in the atmosphere

Mill et al.(1981) reported a half-life of 219 days for vinylidene chloride on phototransformation with ozone. The same authors also listed the rate and environmental half-lives of monochloro-, trichloro- and tetrachloro-ethene for phototransformations with OH radicals. The half lives were respectively 1, 2.4 and 4.1 (calc.) days. From these results we might expect a half-life of VDC reacting with OH radicals of the order of 2 days. This indicates that when VDC is released to the environment it will rapidly disappear.

2.2. Breakdown in the hydrosphere

Tabak et al.(1981) claim that VDC undergoes significant biodegradation with gradual adaptation in a static-culture flask screening test during a 7 day incubation period. In view of this incubation period it is doubtful whether any significant biodegradation of VDC was measured, and it may be that most was lost from the incubation medium by volatilisation.

It has been shown (BASF, 1978) that more than 90% of VDC is eliminated from waste water in a waste-water treatment plant. Final concentrations are below 10 ppb, the detection limit.

3. Bioaccumulation

The calculated log partition coefficient octanol/water (1.66; Rekker, 1977) suggests that the potential for bioaccumulation in aquatic species will be low (OECD, 1984).

F. EXPOSURE LEVELS AND STANDARDS

1. Hygiene Standards - Air

A TLV-TWA (8h time weighted average) of 5 ppm (20 mg/m^3),and a TLV-STEL (Short-term Exposure Limit) of 20 ppm (80 mg/m^3) for 15 minutes, have been adopted by ACGIH (1984). The German MAK value (DFG, 1984) is 10 ppm (40 mg/m^3) but a reduction is foreseen. Many other countries follow the ACGIH standards.

2. Exposure Levels in Air

Emissions of VDC in the US in 1975 were estimated to be 277 tonnes from monomer synthesis operations, 308 tonnes from polymer synthesis operations, and 13.8 tonnes from polymer fabrication operations (Hushon & Kornreich, 1978). Currently, emissions of VDC from production and polymerisation operations are much lower.

Industry complies well with the existing hygiene standards, personal monitoring normally indicating exposure levels of below 5 ppm (8h TWA). During polymer fabrication or use the levels are nearly always below 1 ppm.

3. Presence in Water

During the production of VDC approximately 3.5 m^3 of wastewater per tonne of VDC are discharged. The wastewater is treated by injecting steam, with the result that the low-boiling VDC is almost completely removed.

In the past, VDC has been detected in aqueous effluents discharged from chemical manufacturing plants in the Nederlands at a concentration of 32 µg/l (Eurocop-Cost, 1976). It has also been identified in well, river and other untreated waters in the US (Shackelford & Keith, 1976). The US-EPA (1977)

reported concentrations of VDC in finished US drinking-water in Miami of 0.05 and 0.06 µg/l.

Concentrations of VDC in the effluent leaving a production plant were less than 5 ppm (5,000 µg/l)(Battelle, 1983). In the final product from a biological water-treatment plant associated with the production unit, concentrations were below 10 ppb (head space technique)(BASF, 1978).

4. Residual VDC in Polymers and Packaging Materials

Residual VDC in commercial polymer (PVDC) generally ranges from undetectable up to a few ppm because all producers have now adopted processes to outgas PVDC. Thus levels are now lower than the 26 ppm measured by Birkel et al.(1977). Elschnig (1978) found levels of 1 µg/dm², or less, of VDC in dispersion-coated materials. No data have been found for residual VDC levels in extrusion-coated materials.

5. Presence in Food

In the UK, information on the levels of VDC in food sold in retail outlets was collected by the MAFF (1980). Of the foods analysed, only snack foods and foods contained in VDC/VC copolymer-coated packs were found to contain measurable amounts of VDC. In most other cases of food packed in barrier-coated materials (polymer films and paper), the VDC content was below the detection limit of 0.03 - 0.05 ppm (Elschnig, 1978). From all the information available, the maximum possible intake of VDC per person, when averaged over the entire UK population, would be no more than 1 µg/d, on the conservative assumption that all the residual VDC in food packaging was in fact ingested (MAFF, 1980).

G. TOXICOLOGICAL DATA

1. Acute

1.1. Human

a) Inhalation. Most persons can detect a mild but definite odour at a VDC concentration of 1,000 ppm in air, and some at 500 ppm. Vapours containing decomposition products have a disagreeable odour and can be detected at concentrations of considerably less than 500 ppm (Torkelson and Rowe, 1982). Rylova (1953) mentioned an odour threshold of 50 ppm and an irritation threshold of 25 ppm, these low values

probably being due to the poor quality of the VDC examined: it contained formaldehyde and HCl. Current production material no longer contains such impurities or decomposition products under normal conditions.

Case histories of two patients suffering accidental acute exposure to VDC-generated vapours suggested that exposure for 8-30 h resulted in irreversible lesions of the trigeminal nerve, causing sensory disturbances of the face and some muscular weakness of the mouth and tongue (Broser et al., 1970). Further investigations suggested that this was due to mono- and/or di-chloroacetylene impurities, which could have been produced under the conditions of this incident (Henschler et al., 1970).

According to MAK (1979), the inhalation of VDC has a depressant effect on the central and peripheral nervous systems at concentrations above 1000 ppm. Irritant effects on the upper respiratory tract and mucous membranes were observed by Rylova (1953) at 25 ppm. Exposure to high (unquantified) concentrations of VDC also results in symptoms of drunkenness, which may progress to anaesthesia (Torkelson and Rowe, 1982).

b) Oral. No data available.

c) Eyes. Haley (1975) reported that contact of the eye with liquid VDC causes pain, conjunctivitis, transient corneal injury and iritis, but usually no permanent lesion.

d) Skin. Haley (1975) reported that contact of the skin with liquid VDC may cause irritation. Chivers (1972) reported effects on two workers in a VDC plant in which the inhibitor, hydroquinone monomethyl ether, was handled. Some depigmentation of the skin of the forearms and forehead were observed.

1.2. Experimental

a) Carpenter et al.(1949) screened 96 compounds for the acute toxicity of their vapour. Groups of 6 rats were exposed for 4 h and the relative toxicity (based on a check list of symptoms, e.g. continuous blinking,

lachrymation, etc.) was evaluated. The concentrations were varied in geometric progression, increasing by a factor of 2 until 2, 3 or 4 of 6 rats were killed within a 14 day observation period. For VDC an approximate LC_{50} value of 32,000 ppm was reported.

Severe respiratory signs such as pulmonary irritation and lung oedema, haemorrhage and pneumonia were observed in cats after 2 h exposure to 500 and 1,500 ppm, and in guinea pigs at 1,250 and 2,000 ppm (Rylova, 1953). As mentioned earlier, the VDC may have been contaminated with formaldehyde and HCl (cf. 1.1. a) above).

Many 4h LC_{50}s for rats have been reported ranging from 32,000 ppm for albino rats (Carpenter et al., 1949), to 8,600 ppm for Sprague-Dawley rats (MAK, 1979), 6,350 ppm for normally fed Sprague-Dawley rats (Siegel et al., 1971), and 500 ppm for male Holtzman rats fasted for 18h (Jaeger, 1975). The observation period was not always mentioned and sometimes differed from the usual 14d.

The influence of animal species, sex and dietary status is summarised in Table 1.

TABLE 1

Comparative 4 h LC_{50} as a function of species, sex and dietary status

(Klimisch, 1977)

		Rats	Hamsters	Mice
18-hour fasted	M	2,300	140	40
	F	6,600	450	115
Non-fasted	M	7,100	1,700	115
	F	10,300	2,900	205

It has been shown that 18 h fasting in rats gave rise to elevated hepatic serum alanine-ketoglutarate transaminase (AKT) levels, while glutathione (GSH) levels decreased. It appeared that this decreased GSH level was insufficient to protect the liver, thereby enhancing susceptibility to hepatic injury and lethality (Jaeger et al., 1974). Elevation of serum AKT also occurred after 4h inhalation exposure at 150 ppm in fasted rats, but in fed rats a significant elevation

occurred only at concentrations of 2,000 ppm and higher. Elevated serum AKT preceded hepatic necrosis and death (Jaeger et al., 1974). One 6h exposure to 10 ppm of VDC appeared not to be hepatotoxic for both fasted and fed Sprague-Dawley rats (McKenna et al., 1978-a). Jaeger et al. (1974) reported that 200 ppm (4h) was a minimum lethal concentration for fasted rats whereas the comparable figure for fed rats was 10,000 ppm. During the fourth hour of exposure to 200 ppm, hepatic hemorrhagic centrilobular and midzonal necrosis appeared in fasted rats.

Histopathological examination of the kidneys of fasted rats exposed to 200 ppm of VDC for 6h revealed marked degeneration of proximal tubular epithelia. The toxicity in fasted rats was characterised by haemoglobinuria which persisted for 12 to 24h following exposure. Fed rats exposed to 200 ppm of VDC showed no exposure-related adverse effects in the kidneys. Kidney damage was not observed in any rats at 10 ppm (McKenna et al., 1978-a).

Male CD-1 mice were exposed to 10 and 50 ppm of VDC for 6h. Histopathological examination showed damage to kidney tissue at both exposure levels, but comparable effects were not seen in the liver (Reitz et al.,1980).

Maltoni and Patella (1983) have carried out acute and subchronic studies in animals and the results are summarised in the section on subchronic toxicity.

b) Ingestion. Liver and kidney are the main target organs. Table 2 shows that there is a marked influence of species but no influence of sex on the LD_{50}.

TABLE 2

The influence of species and sex on LD_{50} (mg/kgbw, gavage)

	RATS (fed)	MICE (dietary status not mentioned)
M	1800 (Ponomarkov and Tomatis, 1980)	201-235 (Jones and Hathway, 1978-c)
F	1500 (Ponomarkov and Tomatis, 1980)	171-221 (Jones and Hathway, 1978-c)

Hepatotoxicity, nephrotoxicity and lethal dose may vary according to :

- Vehicle of administration. Oral administration of single doses of VDC in corn oil and mineral oil induced more severe liver and kidney alterations than did VDC in Tween-80 (Chieco et al., 1981).
- Dietary status. Fasted male rats administered 400 mg/kgbw of VDC by gavage suffered kidney damage, whereas fed rats did not (Jenkins and Andersen, 1978).

  In 18h fasted rats of both sexes, hepatotoxicity and mortality occurred in the dose range 100 to 700 mg/kgbw (Andersen and Jenkins, 1977).

- Size (weight/age). When groups of fasted male rats weighing between 80 and 280 g were dosed with 50 mg of VDC/kgbw, both lethality and hepatotoxicity (measured as increased plasma transaminase activity) were greatest for those weighing 130-160 g. Female rats of all sizes were unaffected under these conditions (Andersen and Jenkins, 1977).

Chieco et al.(1981) described severe hepatotoxicity following a single oral dose of 200 mg/kgbw of VDC in fasted rats. In addition, their kidneys exhibited numerous granular "heme" casts in Henle's loop without apparent degenerative changes in either glomeruli or tubular epithelium. No pathological changes were observed in the heart, lungs,

spleen, adrenals or duodenum in fasted male Sprague-Dawley rats at single doses ranging from 50 to 200 mg/kgbw.

At an oral dose of 100 mg/kgbw a selective necrosis of the non-ciliated bronchiolar cells (Clara cells) was observed. Increasing the dose to 200 mg/kgbw resulted in damage to other pulmonary cell types (Forkert and Reynolds, 1982).

c) Skin irritation. Rylova (1953) assessed the irritant potential of VDC in rabbits. Local non-occluded applications on the shaved skin caused transient redness (5 min. skin contact) or redness which disappeared after only 1h (10 min. skin contact).

Other studies on rabbit skin showed that there was slight skin irritation, with brownish colouration, after occluded application of pure VDC for between 1 and 15 min. and 20h . After one week, rabbits showed dryness of the skin and superficial red-brownish necrosis at the application area (BASF, 1978).

d) Eye irritation. VDC is an irritant to the eyes of rats, mice, guinea pigs and cats (Rylova, 1953).

e) Cardiac sensitisation. VDC inhalation at a single dose level of 25,600 ppm caused epinephrine-induced cardiac arrhythmias in rats. Although a dose of 4 µg/kgbw of epinephrine alone failed to induce cardiac arrythmias in air-exposed animals, a dose as low as 0.5 µg/kgbw induced a continuous series of premature ventricular contractions in the rats exposed to VDC. The effects of the lower sensitising doses were dependent on exposure time, and cardiac sensitisation was found to be completely reversible (Siletchnik and Carlson, 1974).

f) Other routes. Harms et al. (1976) observed severe hepatic lesions following i.p. administration of 610 mg/kgbw of VDC to rats.

Examination of the lung tissue following the i.p. administration of 125 mg/kgbw to mice revealed necrosis, but it was restricted to Clara cells. VDC caused a reduction of cytochrome P-450 levels and related mono-oxygenases in lung microsomes (Krijgsheld et al.,1983).

2. Subchronic

2.1. Human. No data on adverse health effects attributable to subchronic VDC exposure are available.

2.2. Experimental. Subchronic studies by inhalation and oral administration indicated that the liver was the main target organ in most species, but the kidney was particularly sensitive in mice.

a) Inhalation. When rabbits (3), monkeys (3), rats (15), beagle dogs (2) and guinea pigs (15) were exposed 8 h/d, 5 d/wk for 6 wks to 100 ppm of VDC, there were no deaths, visible signs of toxicity or histopathological changes. Groups of rats, guinea pigs, dogs and monkeys (the numbers per dose group were as above) were also exposed continuously, 24h/d for 90 days, to 5, 15, 25 and 48 ppm of VDC. A dose-related mortality was observed with guinea pigs and monkeys. Histopathological changes were seen in the liver in all species, and in the kidney in rats, at the highest dose level. At the lower dose levels, histopathological changes were not considered to be exposure-related (Prendergast et al., 1967). It is noted that this type of continuous exposure regime is not directly relevant to occupational exposure (approx. 8h/d, 5d/wk).

Gage (1970) reported nose irritation, retarded weight-gain and liver-cell degeneration in 4M and 4F rats exposed to 500 ppm of VDC, 6 h/d for 20 days. 4M and 4F rats exposed to 200 ppm under the same conditions had slight nose irritation, but the organs were normal on autopsy. These results are in conflict with those from other studies which showed considerably greater toxicity at these dose levels.

Rats (12M and 12F/group) were exposed to 0, 25 or 75 ppm of VDC, 6h/d, 60 times during 90 days. Microscopic evaluation of tissues revealed a minimal degree of hepatocellular cytoplasmic vacuolation in several rats exposed to both dose levels. These minimal hepatocellular changes are interpreted to be reversible (see G.4, Long term toxicity). There were no exposure-related changes in clinical chemistry, gross pathology, organ weight and histopathology in other organs (Quast et al., 1977; Norris, 1977).

Four strains of laboratory mouse, i.e. male and female Ha(ICR) mice, B6C3F1 mice, CD-1 mice, and CF-W mice (10M and 10F/group) were exposed to 0, 55, 100 or 200 ppm of VDC vapour, 6 h/d, 5 d/wk for a total of 10 exposures (Henck et al., 1979). The appearance and demeanour, body weights, haematology, clinical chemistry, organ weights, gross pathology and histopathology were monitored. There were no deaths at 55 or 100 ppm, but considerable mortality at 200 ppm, males being more susceptible than females except in the B6C3F1 strain. Mean body-weights were reduced, liver and kidney weights increased, and the serum glutamic-pyruvic transaminase activity also increased, in a statistically-significant and exposure-related manner. Histopathological examination of surviving mice showed that male CD-1 mice were the most severely affected at all levels of exposure, and had suffered moderate to severe "degenerative nephrosis" at all exposure levels (55, 100 and 200 ppm). Renal failure accounted for mortality in the 200 ppm group. Renal toxicity was insignificant in all female mice when compared to the renal effects in male mice of the same strain. However, hepatotoxicity was more widespread in female than in male mice of the same strain and at the same exposure level. The data suggest that, at the same exposure level, male mice exposed to VDC vapour were affected to a greater degree than were females of the same strain.

Maltoni and Patella (1983) investigated the comparative acute and subchronic toxic effects of VDC by inhalation at 0, 10, 25, 50, 100, 150, and 200 ppm, in Sprague-Dawley rats (30, 60 or 100 per dose/sex for M and F); in the following species of mice: Swiss (30, 60, 150 or 100 per dose/sex for M and F), Balb/c (5 or 30M/5 or 30F), C3H (5 or 30M/5 or 30F) and C57BL mice (5 or 30M/5 or 30F); and in Chinese hamsters (18 or 30M/15 or 30F) for 2d (4h/d), 7d (4h/d) or 28d (4h/d, 4-5d/wk). Mortality, weight, clinical signs and histopathological changes ("mainly in the liver and kidney") were monitored. The results revealed differences, related to species, strain and sex, in the sensitivity of the animals tested. Mice were more susceptible than rats and hamsters. The susceptibility of the male mice, according to the strain, decreased in the following order: Swiss and Balb/c, C3H, C57BL. Female C3H mice appeared to be more susceptible than were the females of the other tested strains. Males were, in general, more

susceptible than females but no such difference was observed in C3H mice. A good correlation was observed among all the different toxicological parameters considered, with the exception of female C3H mice in which VDC produced severe toxic effects, including marked histopathological changes in the liver. Renal changes were very mild. The authors concluded that these results show a clear-cut parallelism between the occurrence of acute toxicity and carcinogenicity, and suggested that the same metabolite or metabolites may be responsible for both.

b) Oral. Norris (1977) and Quast et al.(1983) reported that no adverse effects or gross or histopathological changes were found in groups of 4M and 4F dogs following the daily administration, in capsules, of 6.25, 12.25 or 25 mg/kgbw/d of VDC in peanut oil, for 90 days.

In another 90-day study, groups of 10M and 10F rats were given VDC in their drinking water at concentrations equivalent to dose levels of 0, 6, 10 or 19 mg/kgbw/d for males and 0, 8, 13 or 26 mg/kgbw/d for females. Microscopic evaluation of tissues revealed a minimal degree of hepatocellular cytoplasmic vacuolation in several rats at the highest concentration. These changes were considered to be reversible. No other toxic effects were seen (Quast et al., 1977).

Maltoni and Patella (1983) reported that there were no toxic effects in male (182 in control, and 50 per dose group) and female (177 in control, and 50 per dose group) Sprague-Dawley rats following ingestion by stomach tube at dose levels of 0, 0.5, 5, 10, 20 mg/kgbw/d, 4-5d/wk, for 28d.

3. Mutagenicity and Clastogenicity

3.1. Humans.

No data available.

3.2. Experimental.

The evidence on experimental mutagenicity has been well-reviewed up to 1978 by the MAK Commission (1979). The salient features brought out in this review, together with studies published since that date and some unpublished work, are considered in the following sections.

3.2.1. Prokaryotic systems. Bartsch et al.(1975) found activation-dependent positive responses in two strains of S. typhimurium. They investigated the effect of activating systems derived from the liver, kidney and lung, and showed that activity was in the order: liver > kidney > lung and mouse > rat. Bartsch (1976) considered the predictive value of mutagenicity tests and reported that human liver microsomes were less active (by 10-40%) than were mouse liver microsomes in eliciting a positive response from VDC in S. typhimurium, but he warned of the difficulties in correlating relative mutagenic activity with relative carcinogenic activity.

Jones and Hathway (1978-a) investigated the effect of different metabolic activating systems on the mutagenicity of VDC in S. typhimurium. Systems derived from normal mouse kidney and liver showed marginal responses and the corresponding rat systems were negative. The response increased in systems derived from Arochlor-induced animals, particularly with systems derived from mouse liver and kidney. These results are consistent with the greater susceptibility of mice to the toxic and carcinogenic effects of VDC, but do not correlate with the occurrence of kidney (but not liver) tumours. Exploratory work by the same authors with systems derived from human and marmoset liver suggested that they had a level of activation more similar to the rat than to the mouse.

Oesch et al.(1983) demonstrated that metabolically-activated VDC had mutagenic activity in five strains of S. typhimurium and in E. coli. There was no activity in the absence of activating systems. The relative potency of activating systems derived from mouse, rat, hamster and human liver, and from mouse, rat and hamster kidney, was determined and it was found that all the liver-derived systems were more potent than any kidney- derived system. The observed sequence of potency was: mouse and hamster liver > rat liver > human liver> hamster kidney > male mouse kidney > female mouse and rat kidney. The last two had only an occasional, weak activating effect. These findings are inconsistent with the evidence of carcinogenicity where the male mouse kidney is the only unambiguously- positive target organ, while findings in mouse liver, and rat and hamster liver and kidney are negative (cf. section 4.2.2). The authors suggested that the formation of mutagenic metabolites is probably necessary, but not sufficient, for carcinogenesis to occur in a

particular tissue, and that non-genotoxic effects may be decisive in tumour formation.

A number of other authors have reported positive responses in S. typhimurium (McCarrol et al.1983; Russell et al. 1980; Barbin et al. 1978) and E. coli (Greim et al.,1975; Henschler, 1977), while Laumbach et al.(1976) reported negative responses in E. coli and B. subtilis.

3.2.2. Eukaryotic systems. Drevon and Kuroki (1979) showed that there was no mutagenic response in V79 Chinese hamster cells in the presence of an induced rat-liver activation system.

Bronzetti et al.(1981) reported in vitro mutagenic activity in S. cerevisiae (diploid strain D7) with, but not without, a mouse-liver activation system. He also observed positive responses in a mouse host-mediated assay in yeasts recovered from liver and kidneys, but not from lungs. In a later paper, Bronzetti et al.(1983) reported that VDC had no activity in S. cerevisiae in the presence or absence of a rat-liver activation system.

3.2.3. DNA-related studies. Reitz et al.(1980) investigated DNA alkylation, DNA repair, DNA synthesis and tissue damage in the livers and kidneys of mice and rats exposed to 10 and 50 ppm of VDC for 6 h. The results were compared with those from dimethylnitrosamine (DMN) treated animals. DNA alkylation was minimal in both organs and species, while DNA repair increased very slightly in mouse kidney (<< than in DMN-treated animals). However, tissue damage and increased DNA synthesis (25-fold) were found in the kidneys of VDC-treated mice. There were no comparable effects in mouse liver, or rat liver or kidney. These weak genetic effects elicited by carcinogenic doses are contrasted with the marked increase in DNA synthesis in the mouse kidney, which the investigators correlated with tissue damage also observed in Maltoni's studies (Maltoni, 1977), and Reitz et al.(1980) suggested that epigenetic mechanisms play a role in VDC carcinogenesis.

3.2.4. Chromosomal effects. Sasaki et al.(1980), using a Chinese hamster cell line in vitro, showed that VDC did not induce chromosome breakages. Cerna and Kypenova (1977) carried out cytogenetic analysis of mouse bone-marrow

cells following single (1/2 of the LD_{50}) and repeated (5 x 1/6 of the LD_{50}) i.p. injections. They found no significant increases in chromosomal aberrations.

No chromosomal aberrations were detected in rats exposed to 75 ppm of VDC, 6 h/d, 5 d/wk for 26 wks (Rampy et al., 1977, 1978). Cytogenic studies on rats and mice exposed to 55 ppm of VDC for 1, 3, 6, 9 and 12 months revealed no changes in chromosome frequency or distribution, number of tetraploids, or frequency of chromatid breaks, gaps or translocations (MRI, 1977).

Chromosomal analyses were carried out on Chinese hamsters following single oral doses (178 µl/kgbw) and 29 repeated inhalation exposures (30 and 100 ppm, 6 h/d, 5 d/wk) (BASF, 1975, 1976). The acute oral exposure led to an increase in gaps and breaks and produced a dicentric chromosome. The subacute inhalation exposure produced a clear increase in gaps and breaks at both dose levels, and fragments and fragmentation of metaphases were also seen. These studies indicate that VDC is weakly, but unequivocally, clastogenic in hamster bone-marrow following repeated inhalation exposure. The effects seen after a single oral dose are statistically marginal but the appearance of a dicentric chromosome is biologically significant.

3.2.5. Dominant lethal assays. VDC was not mutagenic in the dominant lethal test in male CD-1 mice exposed by inhalation to 10, 30 and 50 ppm, 6 h/d for 5 days (Anderson et al.,1977).

Short et al.(1977-a) found no mutagenic effect in male CD rats exposed to 55 ppm for 6 h/d, 5 d/wk for 11 weeks.

4. Long Term

4.1. Human

In a morbidity study by Schmitz et al.(1979), 133 VDC-exposed workers were given an extensive clinical and laboratory examination. No malignant diseases were found. Levels of liver enzymes were not significantly influenced by VDC-exposure, and no abnormalities were found which could be related to VDC exposure.

A mortality and morbidity study on 138 employees exposed for between 12 and 120 months to average levels of VDC ranging from <5 to 70 ppm (TWA) was reported by Ott et al.(1976). No effects on mortality or health parameters were found in this rather small population.

In a preliminary mortality study on 629 workers in a W. German VDC production and polymerisation plant (the population was also exposed to vinyl chloride and acrylonitrile) Thiess et al.(1977) found 39 deaths compared to 57 expected. No specific information was given on the distribution of exposure duration, it being mentioned only that VDC production started in 1955. Seven deaths were from malignant tumours, which was not greater than the expected number. Differences were found in the age-specific rate. Bronchial carcinomas were observed in 2 persons (0.08 expected) both aged 37 years, after exposure periods of 15 and 25 months, respectively. There was, however, no information on smoking habits.

Klimisch et al.(1982) carried out a follow-up investigation 3 years later (it was concluded on 01.01.80) on 535 employees exposed to VDC (average concentration : 10 ppm since 1975) for more than 6 months. The number of total deaths observed (48) was higher than that expected (varying from 43.2 to 46.5, depending on the W. German state) but this was due to an unexpectedly high proportion of cardiovascular diseases (20 observed, 15 expected). The number of malignant neoplasms was only slightly higher than expected (12 observed, 9.8 expected). A markedly higher incidence of bronchial carcinomas was observed in the VDC-exposed group (6 observed, 2.68-2.96 expected). It should, however, be noted that in the comparison group of employees chosen as a matched control group with no VDC exposure, five cases of bronchial carcinomas were found compared with 2.9-3.2 expected. A thorough inspection of occupational and smoking histories showed that 2 cases in the VDC group were most probably unconnected with exposure to VDC because of the short duration (2 years) of exposure. The fact that, in comparison with internal and external control groups, cardiovascular diseases occurred more often than expected was unexplained. In the opinion of Klimisch et al.(1982) the study gave no indication of an increased risk of cancer in the VDC cohort under their working conditions.

4.2. Experimental (for more experimental details see K, Appendix).

4.2.1. Chronic toxicity

Chronic toxicity studies have been performed on several strains of rats and mice by the inhalation, oral and dermal routes, and on Chinese hamsters by inhalation.

a) Inhalation

i) Rat. Sprague-Dawley rats were exposed to 10, 25, 50, 100, 150 and 200 ppm of VDC, 4h/d, 4-5 d/wk, for 52 wks (Maltoni et al., 1984). In the 150 ppm group there was an increased incidence (compared with controls) of "regressive changes" in the liver "such as vacuolisation of hepatocytes, cloudy swelling, fatty degeneration, necrobiosis and necrosis" (56.6% in exposed versus 20.5% in control animals). The effects appeared in the 200 ppm group after only 3 exposures. The highest dose tolerated without VDC-induced histopathological alterations was 100 ppm.

Sprague-Dawley rats (Spartan substrain) were exposed 6 h/d, 5 d/wk to 10 or 40 ppm of VDC for 5 wks, and then to 25 or 75 ppm for 18 m (Rampy et al.,1977; McKenna et al.,1982). No observable increase in mortality, or clinical signs of toxicity, occurred. Clinical chemistry, haematology, urinalysis, body weights and organ weights, determined at intervals throughout the study, revealed no exposure-related changes. Histopathological examination revealed that the liver was the target organ in both exposure groups. The effect was characterised by midzonal hepatocellular fatty change as early as at the 6-month interim sacrifice. The midzonal fatty change was also observed at the 12-month sacrifice but no indication of progression in severity or incidence was apparent. After the last 6 months of the study (post-exposure period) this effect was no longer discernible, and the authors stated that "therefore this alteration was minimal in severity and readily reversible". Histopathological examination revealed that the kidneys were not affected. No no-effect level was obtained from this study.

Lee et al. (1977) exposed 36M and 36F CD rats to 55 ppm of VDC (6 h/d, 5 d/wk for 52 wks) and observed "a mild to markedly-severe

focal, disseminated vacuolisation, probably fatty change" in the livers of most of the rats treated.

Hong et al.(1979, 1981), in a repeat of the investigation by Lee et al.(1977) on groups of 4, 8, 8 and 16 CD rats exposed to 55 ppm of VDC (6 h/d, 5 d/wk for 1, 3, 6 or 10 m respectively, followed by a 1 year post-exposure period), detected no VDC-related histopathological changes.

ii) Mouse. Maltoni et al.(1984) exposed Swiss mice to 50 ppm (4 exposures only) and to 10 or 25 ppm (4 h/d, 4-5 d/wk for 52 m). There was high mortality in the 50 ppm group, and the livers of some animals showed areas of fibrosis with and without calcium deposits, interpreted "as a reparative scar, following severe cell necrosis". At 25 ppm "a higher incidence of more pronounced regressive or phlogistic changes has been found in residual parenchyma of kidneys with renal adenocarcinomas". 10 ppm was apparently tolerated without damage.

In CD-1 mice at an exposure level of 55 ppm (6 h/d, 5 d/wk for 52 wks) Lee et al. (1977) observed inflammatory and degenerative changes in the liver (enlarged and basophilic hepatocytes with enlarged nuclei, many of which had large eosinophilic inclusions; mitotic figures or polyploidy; microfoci of mononuclear cells; focal degeneration and necrosis).

Hong et al.(1979, 1981) in a repeat study in CD-1 mice exposed to 55 ppm of VDC (6 h/d, 5 d/wk for 1, 3 and 6 m, and a post-exposure period of 1 year) found no VDC-induced alterations on histopathological examination.

iii) Chinese Hamster. No signs of chronic toxicity were diagnosed after exposure by inhalation to 25 ppm of VDC (4 h/d, 4-5 d/wk for 52 wks) and observation until spontaneous death (Maltoni, 1977; Maltoni et al.,1977,1984).

is not clear since the liver damage was not seen in the high-dose group of females.

c) Other routes

No data are available.

4.2.2. Carcinogenicity

The results of a total of 18 studies on various strains of rats and mice, and on Chinese hamsters, have been published or communicated since 1977 (K, Appendix, gives more details of the studies).

a) Inhalation. Adenocarcinomas of the kidney were detected in male Swiss mice in an inhalation study reported by Maltoni (1977) and Maltoni et al.(1977,1984). The VDC concentrations were 0, 10, 25 (4 h/d, 4-5 d/wk, 52 wks) and 50 ppm (4 h/d, 4 d). The post-exposure period lasted until spontaneous death. After only 4d exposure at 50 ppm, severe hepatotoxic and nephrotoxic effects and a high mortality were observed. Kidney adenocarcinomas appeared in 2 of 18 surviving males, the first tumour being observed after 55 weeks (Maltoni et al.,1984). Nephrotoxicity and a carcinogenic effect occurred at 25 ppm, but no detectable toxic or carcinogenic effects occurred at 10 ppm. Thus the formation of tumours in the kidney was accompanied by chronic toxic effects in the same organ. All but one of these tumours developed in the male animals.

Maltoni et al.(1977, 1984) found no tumours related to VDC in inhalation experiments (4 h/d, 4-5 d/wk for 52 wks) with Chinese hamsters (0, 25 ppm) and with Sprague-Dawley rats (0, 10, 25, 50, 100 and 150 ppm). The post-exposure period lasted until spontaneous death. The exposed rats and mice in this study had an increased incidence of mammary tumours, but this was not dose dependent. The investigators attributed this to the stress of the inhalation exposure, i.e. "olfactory stimulation with consequent stimulation of the pituitary gland". The contribution of the impurities (20 mg of mono- and dichloro-acetylene per kg VDC) to the induction of tumours by the VDC used in this study is as yet unclear.

In another inhalation study, CD rats and CD-1 mice were exposed to 55 ppm for 6 h/d, 5 d/wk, 52 wks without a post-observation period. Vinyl

b) Oral

i) Rat. Sprague-Dawley rats (Spartan substrain) were given 50, 100 and 200 ppm of VDC in drinking water for 24 months (Rampy et al., 1977; Quast et al.,1983). This corresponds to average daily doses of: 7 and 9 (for the 50 ppm group), 10 and 14 (100 ppm group) and 20 or 30 (200 ppm group) mg/kgbw for males and females respectively. No differences in appearance, demeanour, mortality, body weight, food consumption, haematology, urinalysis, clinical chemistry determinations, organ weights and organ to body-weight ratios were detected between the exposed and control groups. The only treatment-related observation, evident on microscopic examination, was in the liver and was characterised by a minimal amount of hepatocellular swelling with midzonal fatty change, occurring in the females at all dose levels and in the males only at the 200 ppm level. No no-effect level was obtained for female rats. The no-effect level for male rats was 100 ppm, corresponding to a daily dose of 10 mg/kgbw.

In an NTP (1982) study, F344/N rats were administered 1 or 5 mg of VDC/kgbw in corn oil (control : corn oil only) by gavage for 104 wks. No compound-related effects on survival, or clinical signs, were seen. Histopathological examination indicated chronic renal inflammation in the highest dose group of the rats of both sexes. 1 mg/kgbw was the no-effect level. In this NTP (1982) study the target organ was the kidney, whereas in the studies by Rampy et al.(1977) and Quast et al.(1983) it was the liver. However, the strain of the rats, the mode of administration, the doses and the solvents for the VDC were different in the NTP and Rampy/Quast studies.

ii) Mouse. B6C3F1/N mice were administered 2 and 10 mg of VDC/kgbw in corn oil (control: corn oil only) by gavage, for 104 wks, in a parallel study to that in rats (NTP, 1982). No compound-related effects on survival, or clinical signs, were reported. Histopathological examination indicated an increased incidence of necrosis of the liver in high-dose (10 mg/kgbw) male and low-dose (2 mg/kgbw) female mice. The significance of these findings

chloride (VC) was tested in parallel (Lee et al., 1977; 1978). Liver haemangiosarcomas characteristic of VC appeared in 2 out of 35 male and 1 out of 35 female mice. Haemangiosarcoma (mesenteric lymph node or subcutaneous) also occurred in 2 out of 36 male rats. There were no haemangiosarcomas in the controls. The possibility of undesired exposure to VC by cross-contamination was mentioned (Maltoni et al.,1984).

Bronchoalveolar adenomas in the form of very small nodules were also observed in 6 out of 35 male mice exposed to 55 ppm of VDC and in 1 out of 26 male control mice. The opinion of the investigators was that these tumours were very probably not related to VDC; it is known that they occur spontaneously in mice of advanced age (Lee et al.,1978). Likewise, the investigators interpret the hepatomas which occurred in 2 male and 1 female exposed mice as having arisen spontaneously, although none were found in control mice. Small numbers of tumours of this type occur spontaneously in mice of advanced age (Lee et al.,1978).

The result of the first study by Lee et al.(1977, 1978) was not confirmed in a repeat study by Hong et al.(1979, 1981) on CD rats and CD-1 mice, again exposed to 55 ppm of VDC with a post-exposure period of 1 year. VC was again tested in parallel. One poorly-differentiated haemangiosarcoma of the liver was found at the end of the post-observation period in 1 out of 4 male rats exposed for 1 month. None occurred in larger groups of rats exposed for 3, 6 and 10 months (6h/d, 5d/wk), or in mice exposed for 1, 3 and 6 months (6h/d, 5d/wk), both with a one year post-exposure period. In this study, VC caused the typical haemangiosarcomas of the liver with an incidence dependent on both exposure time and concentration in a manner similar to that of the earlier inhalation study (Lee et al.,1977, 1978). Although the maximum tolerated dose was reached or exceeded, the value of the repeat study (Hong et al.,1979, 1981) is limited because of the relatively short exposure-period. In addition, the post-exposure period was limited to 52 wks irrespective of the exposure time (1-10 months).

The insensitivity of the CD-1 mice in these two inhalation studies (Lee et al., 1977, 1978; Hong et al., 1979, 1981) is remarkable. The inhalation of 55 ppm of VDC (6 h/d, 5 d/wk) over a period of 52 weeks was tolerated without significantly-increased mortality compared with the untreated control (Lee et al., 1977). In the repeat study (Hong et al., 1979, 1981) increased mortality occurred only during the post-exposure period following an exposure to 55 ppm of VDC (6 h/d, 5 d/wk) for 3 or 6 months, but not 1 month. This must be considered in relation to the results of Maltoni (1977) and Maltoni et al.(1977, 1984) who had to discontinue the exposure of Swiss mice after only 4 exposures (4h/d) to 50 ppm of VDC because of significant toxicity and high mortality. Further, in a DNA-binding study by Reitz et al.(1980), histopathologically-detected damage in the kidney and an increased DNA replication (25x) were found in male CD-1 mice after a single 6h inhalation of 10 or 50 ppm of VDC.

In an inhalation study reported by Rampy et al.(1977,1978) and McKenna et al.(1982), in which Sprague-Dawley rats were exposed 6 h/d, 5 d/wk to 10 and 40 ppm for 5 wks, and then to 25 and 75 ppm for 18 m, the maximum tolerated dose was again reached, and the observed changes in tumour incidence were judged by the authors not to be VDC-related.

Inhalation studies by Viola and Caputo (1977) on Wistar rats at 0 and 200 ppm (4 h/d, 5 d/wk for 5 m) and 100 ppm (4 h/d, 5 d/wk for 7 m), and on Sprague-Dawley rats at 0, 75, and 100 ppm (4 h/d, 5 d/wk for 12 m) likewise produced no evidence of VDC-induced tumours on gross pathological investigation. As histopathological results were not reported, the study cannot be further assessed.

b) Oral. In a 2-yr study in which Sprague-Dawley rats were administered 0, 50, 100 and 200 ppm of VDC in drinking water (Rampy et al., 1977,1978; Quast et al.,1983) no neoplasms attributable to VDC were found, although the maximum tolerated dose was reached and the duration of administration can be regarded as adequate.

In a gavage study by Maltoni et al.(1977, 1984) in which an adequate number of Sprague-Dawley rats were given 0, 0.5, 5, 10 and 20 mg/kgbw

of VDC in olive oil, 4-5 d/wk for 52 wks, and observed until spontaneous death, no VDC-related tumours were diagnosed.

No VDC-related tumours were reported in an NTP (1982) gavage study in which VDC was administered in corn oil to rats (0, 1 and 5 mg/kgbw/d) and to mice (0, 2 and 10 mg/kgbw/d) for 2 years. A significant increase in lymphomas in female mice of the low dose group occurred, but was not regarded as being VDC-related since it did not occur in the high dose group or in male mice. Despite comments by the authors that the dose levels were insufficiently high, kidney and liver effects were diagnosed on histopathological examination, which in the TF's opinion can be attributed to VDC administration. This suggests that the study was indeed adequate for evaluating carcinogenic potential.

Ponomarkov and Tomatis (1980) administered a single dose of 150 mg/kgbw of VDC in olive oil, by gavage, to pregnant female BD IV rats on gestation day 17. An adequate number of freshly-weaned offspring received 50 mg/kgbw of VDC/wk by oral gavage for life. Judging from the reported liver damage, the maximum tolerated dose was reached or exceeded. Small numbers of liver tumours (1/89 male, 3/90 female) were found in the treated animals, but none in the controls. The number of meningeal tumours in male rats treated with VDC was higher than that in the controls (6/81 vs. 1/49), but was not statistically significant ($p=0.37$). It cannot be ruled out that this was VDC dependent, but it is not very probable. In addition, it should be noted when assessing these results that there were considerable adverse effects on the progeny <u>in utero</u> on the 17th day of gestation (a very sensitive embryonal stage) due to the treatment of the pregnant animals. In the absence of statistically-significant findings, this study must be regarded as inconclusive.

c) <u>Other routes</u>. Van Duuren et al.(1979) performed 3 studies with 30 female Swiss Ha:ICR mice in each. In a 2-phase cancer-induction investigation for an initiating effect, 121 mg of VDC was applied to the dorsal skin by micropipette, once to each animal. Dermal treatment with phorbol myristate acetate (PMA) (5 µg/animal, 3 times/wk) started 14 days later. There was a significant increase in papillomas in 8 out

of 30 animals, and a skin carcinoma occurred in 1 out of 30 mice. The opinion of the authors was that VDC acts as an initiator on the skin. The higher number of papillomas was statistically significant ($P<0.005$) but it is not obvious whether the comparison was performed with the solvent control or the PMA-controls. It should also be noted that, without exception, all the other 14 substances tested in this experiment, including the two PMA-controls, induced a number of papillomas of the skin and sporadic squamous cell carcinomas. In the PMA control groups there were 9 out of 120, and 6 out of 90 papillomas and 1 out of 120, and 2 out of 90, squamous cell carcinomas. In an earlier experiment, Van Duuren et al.(1973) demonstrated that the promotor, PMA, itself induced papillomas in the skin of the same species of female mice at doses of 5 and 25 µg, 3 times/wk, the papillomas being found in 2/20 and 9/20 animals, respectively. In the later study (Van Duuren et al.,1979), 40 and 121 mg of VDC/mouse in 0.2 ml acetone was applied to the skin 3 times weekly for life. No tumours related to VDC were found. When 2 mg of VDC in 0.05 ml of tri-octanoin was administered subcutaneously to the mice, once per week, no carcinogenic effect was found. The numbers of animals in these studies did not comply with present-day requirements.

d) Further studies by Maltoni are known to be under way, but as no results were available they could not be assessed.

5. Reproductive Effects

5.1. Human

No data available.

5.2. Experimental

a) Dominant lethal. In a dominant lethal assay, male CD rats were exposed 6 h/d for 5 d/wk to 0, 50, 250 or 1,000 ppm of vinyl chloride or 55 ppm of VDC. These males were then mated with untreated females, starting on week 11 of exposure (Short et al.,1977-a). There was no evidence of either pre- or post-implantation loss in the pregnant females. Similarly, male mice (20 animals/group) were exposed to 10 and 30 ppm of VDC for 6 h/d for 5 days and the male mice were then mated with untreated females (Anderson et al.,1977). There were no

excess pre- or post-implantation losses. These studies provide no indication of an adverse effect on male reproduction.

ii) Teratogenicity. In an inhalation study by Short et al.(1977-b), rats and mice were exposed to VDC concentrations ranging from 15 to 300 ppm, for up to 23 h/d and during variable periods of organogenesis so as to study the effects on maternal welfare and reproduction. Such studies are valuable both for determining the sensitivity of the embryo to the compound at various stages of development and deducing the toxic effects of the compound. There was a high incidence of early resorptions and an increased number of dams with complete resorptions in mice exposed to 30 ppm and above and in rats exposed to 57 ppm and above. Surviving rat foetuses from dams exposed to 15 ppm and above had an increased incidence of soft-tissue abnormalities, suggesting foetotoxicity. In further teratology studies in mice, with exposure levels of 56, 81 and 112 ppm of VDC, attempts were made to dissociate the direct effects of VDC exposure from the effects of the concurrent inadequate food intake of the dams. In these studies, soft-tissue and skeletal anomalies occurred at a similar, although not statistically-significant, rate in a feed-restricted group. Therefore there is insufficient evidence to ascribe these abnormalities to the VDC exposure. Similarly, a diverse pattern of skeletal abnormalities occurred in both the VDC-exposed group and the feed-restricted group.

In a study by Murray et al.(1979), no teratogenic effects were observed in rats given drinking-water containing 200 ppm of VDC on days 6-15 of gestation, and rats and rabbits given up to 160 ppm of VDC, 7 h/d by inhalation, on gestation days 6-15 (rats) or 6-18 (rabbits). There was, however, some evidence of embryotoxicity and foetotoxicity in both species after inhalation of doses that produced evidence of maternal toxicity.

c) Multi-generation studies. In a 3-generation reproductive study, Sprague-Dawley rats were given drinking-water containing 0, 50, 100 or 200 ppm of VDC (Nitschke et al.,1983). F_{3b} litters from eight dams in the 200 ppm group and eight dams in the control group were randomly reduced to eight pups per litter and cross-fostered.

The fertility of the F_0 animals in the 0, 100 and 200 ppm groups was unusually low during the production of the F_{1a} litters. During the production of the F_{1b} litters, the fertility of the F_0 animals in the 200 ppm group was lower than that of the other groups but higher than that during the production of F_{1a} litters. Fertility was also lowered in the control and 100 ppm groups when F_2 rats produced F_{3c} litters, but advanced age probably contributed to this. The length of gestation was unaffected by treatment in all generations, although there was a significant increase in the average time from cohabitation to delivery in the second mating of the F_0 rats ingesting 100 ppm of VDC. These fluctuations in reproductive performance were not considered to be VDC-related.

The average number of pups per litter and the percentage of pups alive at birth were unaffected by VDC treatment in all generations. Postnatal survival (to 21 days) was unaffected by treatment in the F_{1a} and F_{1b} litters but decreased significantly in all exposed F_2 litters, possibly because of the large size of the F_2 litters at birth. There was a significant dose-related decrease in post-natal survival in VDC-treated F_{3a} litters. However, post-natal survival rates in the F_{3b} and F_{3c} litters were unaffected by treatment and the rates for the cross-fostered F_{3b} litters (0 and 200 ppm groups) were comparable to each other, and to those of the F_{3b} control litters that were not cross-fostered. The reduced post-natal survival seen in some litters is not considered by Nitschke et al. to be causally related to VDC administration because survival in the later litters was normal.

Females in the F_2 200 ppm group had increased liver weights and SGPT activities. Light microscopy showed an accentuated hepatic lobular pattern and minimal hepatocellular fatty changes in F_1 rats given 100 or 200 ppm of VDC, and F_2 rats at all doses. The authors concluded that ingestion of VDC in the drinking-water at concentrations that caused mild dose-related changes in the liver did not affect the reproductive capacity of the rats.

6. Kinetics and Metabolism

6.1. Humans

No data available.

6.2 Experimental

IARC (1979), MAK (1979) and Torkelson and Rowe (1981) have reviewed the absorption, distribution, excretion and metabolism of VDC, and therefore these topics are not treated exhaustively here.

6.2.1. Absorption. VDC is readily absorbed through the lungs and from the gastro-intestinal tract and may be metabolized to more toxic epoxides (Haley, 1975; Putcha et al.,1982) or reactive alkylating species (McKenna et al., 1977).

In a more recent study, anaesthetised rats inhaled 25, 75, 150 or 300 ppm of VDC for 4 hours (Dallas et al.,1982). The percentage uptake varied inversely with VDC concentration. The half-life in the plasma during the initial rapid redistribution phase was approximately 2 minutes, whilst that of the elimination phase was 17 minutes . In 3-hour studies by Dallas et al. (1983), calculations of the amount of VDC taken up in the body revealed that the cumulative uptake of the inhaled chemical was linear for exposures to 25, 75 and 150 ppm. There was a trend towards the establishment of equilibrium in the rats exposed to 300 ppm, although levels of VDC in the blood and breath still rose progressively during the last hour of the 3h exposure.

According to Radding et al.(1977) VDC should not accumulate significantly in animals. Andersen et al.(1979) found that the concentration of VDC in the body as a function of concentration in the chamber at equilibrium was 0.0163 mg/kgbw per ppm in the chamber, equivalent to a body/gas distribution coefficient of 4.04 and indicating that whole-body equilibrium is rapidly reached.

6.2.2. Excretion. After oral, i.p. or i.v. administration to rats, ^{14}C-VDC was partly eliminated via the lung as CO_2 or as unchanged VDC. Other metabolites were excreted via the kidneys. Pulmonary elimination of VDC and CO_2, and urinary excretion of VDC metabolites, lasted for 3 days after an oral dose, whereas more than 60% of a small i.v. dose was excreted unchanged within 5 min. of injection and 80% within 1 hour (Jones and Hathway,1978-b).

Following a 6 h exposure of rats to 10 and 200 ppm of ^{14}C-VDC, more than 70% of the ^{14}C was excreted in urine, 3 - 10% in the faeces, and 8% as CO_2 plus 1.6 to 8.4% as unchanged VDC via the lungs (McKenna et al., 1977, 1978 a-b).

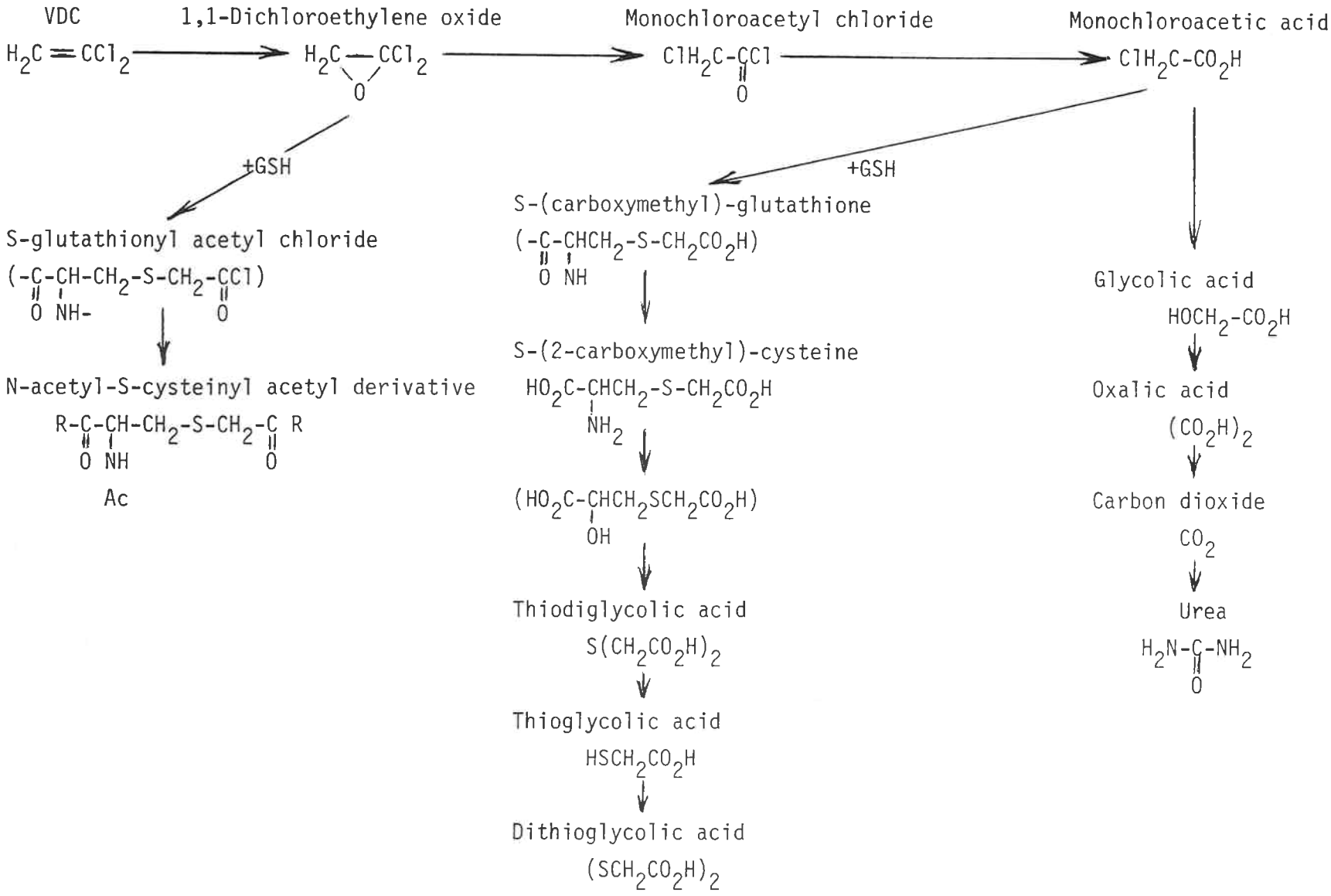
After a single oral dose of 1 mg/kgbw of ^{14}C-VDC in male rats, 78% of the dose was metabolised and excreted in the urine and faeces as non-volatile metabolites, 8 to 11% was exhaled as $^{14}CO_2$ and 1-3% as unchanged VDC. After an oral dose of 50 mg/kgbw, the excretion of VDC via the lungs increased to 19% and 29% in fed and fasted rats, respectively. This indicates that VDC metabolism in rats is a saturable process. As the capacity to detoxify VDC is exceeded, covalent binding to tissue constituents is enhanced (McKenna et al., 1978-b).

Studies on the pharmacokinetics of halogenated ethylenes in rats indicated that the distribution of VDC in the gas phase is determined by physical factors. Metabolic elimination is a saturable, dose-dependant process. When animals were exposed to atmospheric concentrations exceeding the "point of saturation" (150 ppm), elimination was determined by a zero-order law. The maximum rate of elimination of VDC was 100 µmol/h/kgbw (Filser and Bolt, 1979).

6.2.3. Metabolism - Nature of Metabolites. The main metabolic pathways of VDC are represented in Figure 1.

Hathway (1977) found that the relative proportions of urinary products from VDC metabolism in rats after oral gavage were as follows: N-acetyl-S-cysteinyl-acetyl derivative 48%, thiodiglycolic acid 37%, dithioglycolic acid 5%, thioglycolic acid 3%, and monochloroacetic acid 3%. In mice they were, N-acetyl-S-cysteinyl-acetyl derivative 70%, dithioglycolic acid 20%, thioglycolic acid 5% and thiodiglycolic acid 3%. Other investigators have identified two major urinary metabolites in rats, i.e. N-acetyl-S- (2-hydroxyethyl)-cysteine and thiodiglycolic acid, indicating that a major pathway for VDC detoxification is via conjugation with liver glutathione (McKenna et al., 1978-a). The relationship of N-acetyl-S-(2-hydroxyethyl)-cysteine to the other metabolites is not clear, but it may have originated from the identification procedures.

Figure 1. METABOLIC PATHWAYS OF VDC (Jones and Hathway, 1978-b)



In rats, the highest concentration of total metabolites was in the kidney (Jaeger et al., 1977). Jones and Hathway (1978-c) concluded that the metabolites, 1,1-dichloroethylene oxide and monochloroacetyl chloride, may be important for DNA covalent binding. They also showed that mice metabolise a greater proportion of an oral dose of 50 mg/kgbw than do rats, implying that the efficiency of VDC metabolism follows the known cytochrome P-450 levels in the organs of these animals. This also implies that mice are exposed to a greater quantity of toxic metabolites.

Monochloroacetyl chloride, a known metabolite of VDC, may be converted into monochloroacetic acid or may react directly with mitochondria (Andersen et al., 1977-78).

6.2.4. Factors influencing metabolism.

a) Fasting. Fasting prior to exposure significantly reduced the metabolism via the detoxifying pathways, and enhanced the covalent binding of metabolites to liver and kidney tissue. Fasted rats exposed to 200 ppm sustained liver and kidney damage, whereas fed rats did not. Fasting had no effect on rats exposed to 10 ppm of vapour (McKenna et al., 1977; 1978-a). After oral administration of 50 mg/kgbw, the elimination of non-volatile metabolites was greater in fed rats, suggesting a reduced capacity of VDC metabolism in fasted rats. Fasting for 18 h prior to a single oral administration of 1 mg/kgbw did not affect the proportions in the different excretion routes. Fasting also increased the VDC concentration in the liver at the higher dose level (McKenna et al., 1978-b).

b) Glutathione availability. Reichert et al. (1978) measured the liver glutathione content after oral administration, to rats, of VDC dissolved in olive oil. After treatment with 100 mg/kgbw of VDC, glutathione decreased to 33% of the control values within 4 h but returned to the control level after 24 h. The depletion of glutathione was dependent on the dosage of VDC. Only at about 80% depletion did the metabolism of VDC change significantly.

Depletion of hepatic glutathione (GSH), which is essential in the detoxification of VDC, may be responsible for an increased sensitivity to VDC (Huffman and Desai-Greenaway, 1976).

c) Animal species. McKenna et al.(1979) compared VDC metabolism in rats and mice. Data for inhaled VDC in mice indicated an enhanced susceptibility to VDC by virtue of a greater uptake and metabolism. Also, the production of alkylating VDC metabolites was greater in mice than in rats. The metabolic differences parallel closely the reported differences in susceptibility and target organ specificity observed in chronic VDC inhalation studies. Pretreatment with alcohol (Sato et al., 1980) enhanced six-fold the ability of liver drug-metabolising enzymes to convert VDC. This may increase its toxicity. Microsomal oxidation was greater in male than in female rats, and greater in mice than in rats.

d) Mono-oxygenase. Oesch et al. (1983) investigated the effect of VDC on the enzyme systems in liver and kidneys involved in metabolism. They exposed mice to 10 and 50 ppm, and rats to 200 ppm, of VDC for 6h/d for 1-8 days. Pretreatment with VDC caused no induction of mono-oxygenase activity; on the contrary there was sometimes a reduction. While the epoxide hydrolase activities were usually unchanged or increased slightly, it was significant that the activity of this enzyme was reduced in the kidney of male mice, the target organ for the chronic-toxic and carcinogenic effects. This was particularly pronounced in respect of glutathione S-transferase activity. The results of the enzyme investigations indicate that there is a decrease in the detoxification of active metabolites in the kidneys of male mice, and this provides a means of interpreting the findings from animal experiments.

e) Dose level. Metabolism is dose dependent in the case of inhalation and oral administration. Following a 6h exposure to 10 ppm of VDC, 98% was metabolised by the rat to non-volatile compounds. At 200 ppm only 92 to 96% was metabolised. Pharmacokinetic data indicated that there are significant quantitative differences in the metabolism of VDC at above the saturation level (McKenna et al.1977; 1978-a). At an oral dose of 50 mg VDC/kgbw,there were signs of saturation (McKenna et al., 1978-b). Dallas et al. (1983) found, in inhalation experiments, that the saturation level was below 300 ppm. Filser and Bolt (1979) also produced evidence of the saturation of metabolic elimination at 150 ppm.

H. ECOTOXICOLOGICAL DATA

Toxicity to Aquatic Organisms

Data, obtained by static procedures, on the toxicity of VDC to aquatic organisms, are summarised in Table 3.

A few results are available from flow-through experiments. The 96-hour flow-through LC_{50} for fathead minnows (Pimephales promelas Rafinesque) was 108 (85 to 117) mg/l. The threshold LC_{50} value in flowing water was 29 (23 to 34) mg/l after 7 days (Dill et al.,1980). The threshold LC_{50} is reached when there is no further decline in the LC_{50} over a period of 3-4 days or more.

The major sublethal toxic effect noted in the static and flow-through fish tests was loss of body equilibrium (swimming disorientation). The toxicity data available indicate that VDC is at most slightly toxic in acute experiments with aquatic organisms. Although no chronic test data are available, both the actual concentrations of VDC measured in the environment and its rapid volatilisation to air suggest that the hazard of VDC to aquatic organisms is minimal, with the possible exception of local discharges or accidental spillages.

TABLE 3

Toxicity of VDC to Aquatic Organisms (Static Procedure)

Species (Reference)	LC_{50} in mg/litre (range) 24 h	48 h	96 h	No Observed Effect Conc. (mg/litre)
Freshwater :				
Water flea (Daphnia magna) (LeBlanc, 1980)	98 (71 - 130)	79 (62 - 110)		< 2.4
Bluegill (Lepomis macrochirus) (Buccafusco et al.,1981)	74*		74* (57 - 91)	
(Dawson, 1975, 1977)			220	
Zebra fish (Brachydanio rerio) (Munk, 1980)	> 500	> 500		> 500
Seawater :				
Tidewater silversides (Menidia beryllina) (Dawson, 1975, 1977)			about 259	
Sheepshead minnow (Cyprinodon variegatus) (Heitmuller et al.,1981)	250 (200 - 340)+	250 (200 - 340)+	250 (200 - 340)+	80

+ Numbers in brackets : 95% confidence interval
* capped jars

I. SUMMARY AND CONCLUSIONS

The exposure of humans to high concentrations of VDC results primarily in CNS depression and associated symptoms of drunkenness which may progress to unconsciousness. Epidemiological studies on occupationally-exposed populations, while possessing the inherent limitations characteristic of most such studies, do not provide evidence that long-term exposure to VDC has an adverse effect on health.

In animals, acute toxicity is very dependent on species, sex and whether the animals have been fasted. Published inhalation LC_{50}s (4h) vary from 40 ppm for fasted male mice to 32,000 ppm for fed rats. The mouse is more sensitive than the Chinese hamster which is more sensitive than the rat. Males are generally more sensitive than females. The liver and kidney are target organs. The no-effect level for nephrotoxicity is reported to be 200 ppm for a 6h exposure for fed rats, while it is 10 ppm for fasted rats. Exposure to 25,600 ppm of VDC by inhalation causes cardiac sensitisation in rats.

Subchronic inhalation studies in rats at various levels between 25 to 100 ppm are reported to produce either no adverse effect or only minimal, but reversible, effects on the liver. Male, but not female, mice of four different strains are reported to show marked nephrotoxicity following 10 exposures at 55 ppm.

Chronic inhalation studies in Swiss mice showed that there were nephrotoxic effects in animals exposed to 25, but not 10, ppm, while comparable studies in rats showed that there were no effects at 100 ppm. Another study indicated that the no-effect level for effects on the liver of rats of the same strain was below 25 ppm; no adequate explanation has been found for this difference. Chronic oral gavage studies have shown that the no-effect level in rats is 1 mg/kgbw.

Dominant lethal assays in mice and rats revealed no adverse effect on male reproduction. Teratology studies conducted according to the usual protocols in rats and rabbits showed no teratogenic effects. Exposure of rats and mice by inhalation for 23h/d during the gestation period at maternally toxic levels led to a reduced feed intake, and produced soft-tissue and skeletal abnormalities. However, when untreated groups of mice were put on a comparable feed intake,

hydrocephalus or diverse skeletal abnormalities occurred at a similar frequency. Therefore VDC is not considered to be teratogenic.

Although in a multigeneration study in rats low fertility was observed in treated groups, this was also seen in the control groups and occurred with an inconsistent pattern. It is concluded that the reproductive capacity of rats is not influenced by VDC.

While there is evidence for genotoxic potential as determined in prokaryotic test systems, this potential does not appear to be generally expressed in higher test systems or whole animals. The overall picture suggests that in mammals the genotoxicity of VDC is highly specific with respect to species, sex and organ. The data on mutagenicity do not correlate well with the observed pattern of animal carcinogenicity and suggest that non-genotoxic mechanisms may have an important and possibly determining role in the expression of carcinogenic activity.

A total of 18 chronic studies has been reported, some of them being inadequate as judged by modern standards. Out of the 18 studies, VDC has shown a carcinogenic effect only in one : the exposure of male Swiss mice to 25 ppm, by inhalation, produced both nephrotoxicity and an increased incidence of renal adenocarcinomas, neither of which occurred on exposure to 10 ppm. Nine other inhalation studies (6 in rats, 2 in mice and 1 in the hamster) at the same or higher concentrations failed to show any carcinogenic effect, as did the remaining 5 ingestion, 2 dermal and 1 subcutaneous studies.

Metabolism in rats and mice is quantitatively different but in both cases glutathione is involved. The identity of the metabolites is largely known. VDC does not accumulate significantly in animals.

Species, sex and strain differences in the sensitivity of animals to VDC have been observed. The differences in lethal effects of VDC on male and female mice correlated with the degree of histopathological changes in the kidneys. Enzyme investigations showed a decrease in the detoxification of active metabolites in the kidney after short exposure. Uptake and metabolism studies indicated that the enhanced sensitivity in going from rats to mice also correlated with increased uptake, and the production of alkylating metabolites.

VDC possesses genotoxic potential as evidenced by prokaryotic test systems, but detoxification pathways appear, in general, to prevent this potential expressing itself as seen from the negative results in mutagenicity tests on eukaryotic test systems in vivo and in vitro. The exception is the male mouse kidney in which one study showed a carcinogenic effect. This is also the most sensitive target for both acute and chronic toxic effects. It seems likely that toxicity and carcinogenicity are associated and that repeated kidney damage either leads directly to the carcinogenic response by a non-genotoxic mechanism, or facilitates the expression of the genotoxic potential of VDC metabolites or impurities in this particular species, sex and organ. The carcinogenic effect in the male mouse kidney does not occur in the other species tested and, overall, is probably not relevant to humans.

In the light of the nephrotoxicity and hepatotoxicity in rats and mice at relatively low levels, the established occupational exposure standard of 10 ppm in some countries should be critically reviewed.

When released into the environment VDC will rapidly volatilise to the air compartment where it will be phototransformed, with an expected half-life of about 2 days, by OH radicals.

VDC is at most slightly toxic to aquatic organisms. Because of its high volatility, the concentrations to which aquatic organisms are exposed will be low, and so will its hazard. The low octanol/water partition coefficient indicates that VDC is unlikely to bioaccumulate significantly in aquatic species.

J. PRACTICAL ADVICE

1. First Aid and Medical Treatment

1.1. Inhalation

The patient should be removed to fresh air and kept warm and at rest. Medical attention should be obtained, and if the patient is in a state of stupor or coma, oxygen should be administered. If breathing ceases, or becomes weak and irregular, artificial respiration should be applied and oxygen inhalation continued. The use of adrenaline and similar

sympathomimetic drugs should be avoided as there may be a danger of producing cardiac arrhythmia.

The patient should be kept under medical review because of the possibility of liver, kidney and lung injury.

1.2. Eye contact

The eye should be irrigated thoroughly with eyewash solution or clean water for at least 10 minutes. Medical attention should always be obtained.

1.3. Skin contact

Contaminated shoes and clothing should be removed. The affected area of skin should be washed thoroughly with soap and water. Where necessary medical attention should be obtained.

1.4. Ingestion

Immediate medical attention should be obtained. The mouth should be rinsed out with water. The patient should be kept under medical review for possible liver and kidney effects.

2. Safe Handling

2.1. Personal protection

Atmospheric levels should be kept as low as reasonably practicable below the recommended occupational exposure limit. Skin and eye protection should be worn and suitable respiratory protection should be readily available.

2.2. Plant/explosion hazards

VDC is a flammable volatile liquid with a flash point of -15°C. The explosive limits in air are 7-16% v/v at 25°C. Adequate ventilation should be provided and smoking prohibited. Any electrical equipment used should be of a type that satisfies local legal requirements.

2.3. Storage

VDC should be stabilised for storage, which should be in closed containers under nitrogen or carbon dioxide to prevent the ingress of moisture and oxidation by air to organic peroxides. Exposure to light should be avoided. Material stored in bulk should be frequently tested for the presence of acidity, peroxides and polymers. The storage period should be minimised.

3. Management of Spillages and Waste

3.1. Leaks of vinylidene chloride

For small leaks, the product should be allowed to evaporate provided there is adequate ventilation. Material from larger leaks should be covered with sand and removed to a place where the VDC can safely evaporate. If there is a very large spillage, a medium-expansion synthetic foam should be used to control evaporation. The vapour can then be dispersed by means of water spray curtains. The technique of elimination by water jet should not be used. Leaks in the equipment must be plugged at once in all cases.

3.2. Fire

Carbon dioxide, dry chemical or foam fire extinguishers are recommended. VDC is normally inhibited to prevent polymerisation which may occur at elevated temperatures with possible violent rupture of the container.

K. APPENDIX

Results of Long-Term / Carcinogenicity Studies

Species/strain (reference)	Route (vehicle)	Number of animals in each group		Doses (ppm or mg/kgbw)	Duration of administration*	Post-exposure period	Incidence of tumours related to VDC**	
		male	female				male	female
Rat, Sprague-Dawley (Maltoni, 1977; Maltoni et al.,1977, 1984)	inhalation	100	100	0 ppm	4 h/d, 4-5 d/wk, 52 wks	to spontaneous death		
		30	30	10 ppm			-	-
		30	30	25 ppm			-	-
		30	30	50 ppm			-	-
		30	30	100 ppm			-	-
		60	60	(200[1]) 150 ppm			-	-
Rat, CD (Lee et al., 1977, 1978)	inhalation	36	36	0 ppm	6 h/d, 5 d/wk, 52 wks	none		
		36	36	55 ppm		none	-	-
Rat, CD (Hong et al., 1979)	inhalation	4	4	0 ppm	6 h/d, 5 d/wk	1 m	52 wks	
		8	8	0 ppm		3 m		
		8	8	0 ppm		6 m		
		16	16	0 pmm		10 m		
		4	4	55 ppm		1 m	-	-
		8	8	55 ppm		3 m	-	-
		8	8	55 ppm		6 m	-	-
		16	16	55 ppm		10 m	-	-

1) only 2 treatments because of the high toxicity

* m = month
wk = week
d = day
h = hour

** - = no VDC-related tumours observed

Appendix (continued 1)

Species/strain (reference)	Route (vehicle)	Number of animals in each group		Doses (ppm or mg/kgbw)	Duration of administration	Post-exposure period	Incidence of tumours related to VDC	
		male	female				male	female
Rat, Sprague-Dawley (Rampy et al., 1977, 1978; McKenna et al.,1982)	inhalation	86	86	0 ppm				
		86	86	10 ppm first 5 wks, 25 ppm subsequently	6 h/d, 5 d/wk, 18 m total	6 m	-	-
		86	86	40 ppm first 5 wks, 75 ppm subsequently			-	-
Rat, Wistar (Viola and Caputo, 1977)	inhalation	30	30	0 ppm		to spontaneous death or moribund state		
		51	23	200 ppm first 5 m, 100 ppm subsequently;	4 h/d, 5 d/wk, 12 m total		-	-
Rat, Sprague-Dawley (Viola and Caputo, 1977)	inhalation	30	30	0 ppm	4 h/d, 5 d/wk 12 m	to spontaneous death or moribund state (22-24m)	only gross pathology performed	
		16	16	75 ppm				
		30	30	100 ppm				
Mouse, Swiss (Maltoni, 1977; Maltoni et al.,1977, 1984)	inhalation	190	190	0 ppm	4 h/d, 5 d/wk, 52 wks	up to 121 wks	0/190	0/190
		30	30	10 ppm			0/30	0/30
		150	150	25 ppm			28/150	1/150
		30	30	50 ppm	4 h/d, 4 d*	to spontaneous death	kidney adenocarcinomas 2/18	0/14

* only 4 treatments because of the high toxicity and mortality

Appendix (continued 2)

Species/strain (reference)	Route (vehicle)	Number of animals in each group		Doses (ppm or mg/kgbw)	Duration of administration	Post-exposure period	Incidence of tumours related to VDC	
		male	female				male	female
Mouse, CD-1 (Lee et al., 1977, 1978)	inhalation	36	36	0 ppm	6 h/d, 5 d/wk, 52 wks	none		
		36	36	55 ppm		none	-	-
Mouse, CD-1 (Hong et al., 1979, 1981)	inhalation	16	16	0 ppm	6 h/d, 5 d/wk: 1 m			
		16	16	0 ppm	3 m			
		28	28	0 ppm	6 m	52 wks		
		8	8	55 ppm	1 m		-	-
		8	8	55 ppm	3 m		-	-
		12	12	55 ppm	6 m		-	-
Chinese Hamster (Maltoni, 1977; Maltoni et al., 1977, 1984)	inhalation	18	17	0 ppm	4 h/d, 4-5 d/wk, 52 wks	to spontaneous death		
		30	30	25 ppm			-	-
Rat, Sprague-Dawley (Rampy et al., 1977, 1978; Quast et al.,1983)	oral (drinking water)	80	80	0 ppm		none		
		48	48	50 ppm (M = 7 mg/kgbw) (F = 9 mg/kgbw)	daily for 24 m	none	-	-
		48	48	100 ppm (M = 10 mg/kgbw) (F = 14 mg/kgbw)		none	-	-
		48	48	200 ppm (M = 20 mg/kgbw) (F = 30 mg/kgbw)		none	-	-

Appendix (continued 3)

Species/strain (reference)	Route (vehicle)	Number of animals in each group		Doses (ppm or mg/kgbw)	Duration of administration	Post-exposure period	Incidence of tumours related to VDC	
		male	female				male	female
Rat, Sprague-Dawley	gavage	100	100	olive oil (0 mg/kgbw)				
(Maltoni, 1977;	(olive oil)	82	77	olive oil (0 mg/kgbw)	daily	to spontaneous		
Maltoni et al.,1977,		50	50	0.5 mg/kgbw		death	-	-
1984)		50	50	5 mg/kgbw	4-5 d/wk, 52 wks		-	-
		50	50	10 mg/kgbw			-	-
		50	50	20 mg/kgbw			-	-
Rat, F344/N	gavage	50	50	0 (corn oil)	daily	none		
(NTP, 1982)	(corn oil)	50	50	1 mg/kgbw	104 wks	none	-	-
		50	50	5 mg/kgbw		none	-	-
Rat, BD IV	gavage	53	53	0 (olive oil)	1x/wk	none		
(Ponomarkov and	(olive oil)	89	90	50 mg/kgbw	for life	none	-	-
Tomatis, 1980)								
Mouse, B6C3F1/N	gavage	50	50	0 (corn oil)	daily	none		
(NTP, 1982)	(corn oil)	50	50	2 mg/kgbw	104 wks	none	-	-
		50	50	10 mg/kgbw		none	-	-
Mouse, Swiss Ha: ICR	dermal	100 (sex?)		0		none		
(Van Duuren et al.,	(in 0.2 ml	30		0.1 ml acetone	3x/wk to sponta-	none		-
1979)	acetone)	30		40 mg/mouse	neous death	none		-
		30		121 mg/mouse	or moribund state	none		-
Mouse, Swiss Ha: ICR	s.c.	100 (sex?)		0	1x/wk, 649 d	none		
(Van Duuren et al.,	(in 0.05 ml	30		0.05 ml water	636 d	none		
1979)	trioctanoin)	30		0.05 ml trioctanoin	631 d	none		-
		30		2 mg/mouse	548 d	none		-

Appendix (continued 4)

Species/strain (reference)	Route (vehicle)	Number of animals in each group		Doses (ppm or mg/kgbw)	Duration of administration	Post-exposure period	Incidence of tumours related to VDC	
		male	female				male	female
Mouse, Swiss Ha: ICR (Van Duuren et al., 1979)	dermal (initiation test on the skin)		30	121 mg/mouse, then 5g PMA* per animal	once, to spontaneous death or moribund state; PMA 3x/wk	none		8/30 papillomas, 1/30 skin carcinoma

* PMA = phorbol myristate acetate

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