VINYLIDENE CHLORIDE

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

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 75-35-4
Chem. Abstr. Name: 1,1-Dichloroethene
IUPAC Systematic Name: 1,1-Dichloroethylene
Synonym: Asym-dichloroethylene

1.1.2 *Structural and molecular formulae and relative molecular mass*

$C_2H_2Cl_2$ Relative molecular mass: 96.94

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid with sweet, chloroform-like odour (Budavari, 1996)
(*b*) *Boiling-point*: 31.6°C (Lide, 1995)
(*c*) *Melting-point*: –122.5°C (Lide, 1995)
(*d*) *Solubility*: Insoluble in water; soluble in acetone, ethanol and many organic solvents; very soluble in diethyl ether (Lide, 1995; Budavari, 1996; Verschueren, 1996)
(*e*) *Vapour pressure*: 67 kPa at 20°C; relative vapour density (air = 1), 3.25 (Verschueren, 1996)
(*f*) *Flash point*: –19°C, closed cup; –15°C, open cup (American Conference of Governmental Industrial Hygienists, 1992)
(*g*) *Explosive limits*: Upper, 16%; lower, 5.6% by volume in air (American Conference of Governmental Industrial Hygienists, 1993)
(*h*) *Conversion factor*: $mg/m^3 = 3.96 \times ppm$

1.2 Production and use

In 1967, world production of vinylidene chloride was estimated to be 220–330 thousand tonnes; by the early 1980s, it was approximately 306 thousand tonnes. A more recent estimate of worldwide production is 290 thousand tonnes (WHO, 1990).

Vinylidene chloride is used principally in copolymers with vinyl chloride, acrylonitrile and other monomers for packaging materials, adhesives and synthetic fibres (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

The National Occupational Exposure Survey (NOES, 1997) estimated that 2675 workers in the United States were potentially exposed to vinylidene chloride between 1981 and 1983.

National estimates on exposure were not available from other countries.

1.3.2 *Environmental occurrence*

Vinylidene chloride can enter the atmosphere as emissions from its production and use in the manufacture of plastics. It has been detected in wastewater from plastics manufacturing and metal finishing (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 20 mg/m^3 as the threshold limit value for occupational exposures to vinylidene chloride in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

The World Health Organization has established an international drinking-water guideline for vinylidene chloride of 30 µg/L (WHO, 1993).

2. Studies of Cancer in Humans

In one epidemiological study of 138 workers exposed to vinylidene chloride in the United States, no excess of cancer was found, but follow-up was incomplete, and nearly 40% of the workers had less than 15 years' latency since first exposure (IARC, 1986). In a study in the Federal Republic of Germany of 629 workers exposed to vinylidene chloride, seven deaths from cancer (five bronchial carcinomas) were reported; this number was not in excess of the expected value. Two cases of bronchial carcinoma were found in workers, both of whom were 37 years old, whereas 0.07 were expected for persons aged 35–39 years (Thiess *et al*., 1979). The limitations of these two studies preclude assessment of the carcinogenicity of the agent to humans. No specific association was found between exposure to vinylidene chloride and an excess of lung cancer observed in a synthetic chemicals plant in the United States.

3. Studies of Cancer in Experimental Animals

Vinylidene chloride was tested for carcinogenicity in mice and rats by oral administration and by inhalation, in mice by subcutaneous administration and by topical application, and in hamsters by inhalation. Studies in mice and rats by oral administration gave negative results. In inhalation studies, no treatment-related neoplasm was observed in rats or hamsters. In mice, a treatment-related increase in the incidence of kidney adenocarcinomas was observed in male mice, as were increases in the incidence of mammary carcinomas in females and of pulmonary adenomas in male and female mice. In skin-painting studies in female mice, vinylidene chloride showed activity as an initiator, but, in a study of repeated skin application, no skin tumour occurred. No tumour at the injection site was seen in mice given repeated subcutaneous administrations (IARC, 1986).

3.1 Inhalation exposure

Rat: Groups of 54 and 60 female Sprague-Dawley breeder rats, 13 weeks of age, were exposed by whole-body inhalation to 0 or 100 ppm [0 or 400 mg/m^3] vinylidene chloride (purity, > 99.9%) for 4 h per day on five days per week for seven weeks and then for 7 h per day for 97 weeks. Also groups of 62 male and 61 female offspring were exposed transplacentally beginning at day 12 of gestation and postnatally to the same concentrations for a total of 104 weeks, with 158 male and 149 female rats serving as unexposed controls. In breeders, vinylidene chloride-exposed females exhibited a 7.4% incidence of malignant mammary tumours compared with 3.3% in controls [no statistical analysis provided]. The incidence of phaeochromocytomas was 7.4% compared with 18.3% in controls and the incidence of leukaemias was also lower in exposed rats. In offspring exposed to vinylidene chloride, malignant mammary tumours were observed in 4.9% of females [no statistical analysis provided] compared with 1.9% in controls. An increased incidence of leukaemia was found in offspring exposed for 104 weeks (16.1% and 6.5% in treated male and female rats, compared with 7.6% and 0.7% in male and female controls, respectively. These percentages roughly correspond to 10/62, 4/61, 12/158 and 1/149 rats with leukaemia/no. of rats at the start) (Cotti *et al*., 1988). [The Working Group noted that details on survival and the absolute tumour data were not reported. Also, the time of appearance of tumours was not reported and no appropriate statistical analysis, taking into account the survival, was performed.]

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

4.1 Absorption, distribution, metabolism and excretion

Large reviews (ECETOC, 1985; WHO, 1990) have analysed and summarized the data including studies assessed by the previous IARC Working Group (IARC, 1986).

However, all of the additional studies reviewed are from the same period (1977–82) and were conducted by the same groups as the studies evaluated by the IARC Working Group and they do not affect the previous evaluation. WHO (1990) reviewed a number of additional studies which have also been assessed here.

4.1.1 *Humans*

Vinylidene chloride has been shown to be activated by human liver S9 supernatant in the Ames assay, suggesting the presence of a cytochrome P450 enzyme. Also, the formation of dichloroacetaldehyde was demonstrated in two human liver microsomal preparations; the rate of formation was approximately the same as in rat liver microsomes (WHO, 1990).

4.1.2 *Experimental systems*

In rats, metabolism, which probably proceeds via a cytochrome P450-generated epoxide intermediate and subsequent either direct or indirect glutathione conjugation, is saturated between doses of 1–50 mg/kg bw orally or 10–200 ppm [40–800 mg/m^3] by inhalation, resulting in a dose-dependent increased elimination via the lungs as unchanged vinylidene chloride. Mice metabolize vinylidene chloride to a greater extent than rats. Also the alkylation of proteins by vinylidene chloride metabolites is greater in mice than in rats. Metabolic activation via epoxidation was suggested (IARC, 1986).

In rats and mice, vinylidene chloride is very quickly absorbed after oral administration; in mice, elimination is tri-exponential (Putcha *et al*., 1986).

Glutathione levels and glutathione *S*-transferase activity are important determinants of metabolic inactivation of primary vinylidene chloride metabolites (Okine *et al*., 1985; Cossec *et al.*, 1996). Covalent binding of vinylidene chloride metabolites is highest in kidney, liver and lung in mice and can be modified by glutathione depletion (Okine *et al*., 1985; Okine & Gram, 1986).

CYP2E1 is the principal catalyst of vinylidene chloride metabolism and metabolic activation. This conclusion is based on the following findings. Inducers (ethanol, acetone) and inhibitors (diethyldithiocarbamate) increase and decrease, respectively, metabolic activation of vinylidene chloride in mouse liver microsomes and in isolated mouse hepatocytes (Kainz *et al*., 1993; Lee & Forkert, 1994; Dowsley *et al*., 1995). Vitamin A treatment increases CYP2E1 activity in rat liver microsomes and also potentiates vinylidene chloride toxicity in liver slices from treated animals (Wijeweera *et al*., 1996). In mouse liver microsomes *in vitro*, vinylidene chloride decreases CYP2E1 levels (Lee & Forkert, 1994).

Variations in the tissue expression of CYP2E1 appear to underlie the tissue selectivity of vinylidene chloride toxicity. A sex difference in CYP2E1-mediated metabolism of vinylidene chloride correlates with the incidence of renal tumours (Speerschneider & Dekant, 1995). Metabolism in kidney microsomes from male mice was at least six times that in females, while tumours were seen only in males (see Section 3). CYP2E1 could not be detected in rat kidney and no renal tumours were seen in this species. In addition,

there is indirect evidence for a comparable basis for the lung toxicity of vinylidene chloride in mice. The rank order of CYP2E1-supported metabolic activation of vinylidene chloride in mouse lung microsomes (Lee & Forkert, 1995) correlates with the severity of its toxicity to the bronchiolar Clara cells, in the rank order adult female > weanling male = weanling female > adult male (Forkert *et al*., 1996a).

Metabolism of vinylidene chloride, and presumably metabolic activation, is about six times higher in liver microsomes from mice than in those from rats (Dowsley *et al*., 1995).

4.1.3 *Comparison of human and rodent data*

CYP2E1, an enzyme catalysing vinylidene chloride activation, is expressed in various human tissues, including liver, although functional evidence is lacking for many tissues. The level expressed in human liver is similar to that in rodents. CYP2E1 seems to be differentially expressed in kidney microsomes from humans (no expression), rats (no expression) and mice (high expression in males).

4.2 Toxic effects

4.2.1 *Humans*

Vinylidene chloride is a central nervous system depressant. Repeated exposure to low concentrations of vinylidene chloride may cause liver and renal dysfunction (Torkelson & Rowe, 1981). Skin contact with vinylidene chloride causes irritation, which may be due partly to the presence of an inhibitor, hydroquinone monomethyl ether (Chivers, 1972). In one study, spirometry, blood clinical chemistry for liver and renal toxicity, haematological parameters and blood pressure measurements did not differ between vinylidene chloride-exposed workers and controls. Measured past time-weighted average vinylidene chloride concentrations ranged from < 5 to 70 ppm [< 20–280 mg/m^3] (Ott *et al*., 1976).

4.2.2 *Experimental systems*

In a two-year study of male and female Sprague-Dawley rats receiving 60–230 mg/L vinylidene chloride in the drinking-water, no toxicological effect was noted except for a non-dose-related decrease in survival of male rats at 18 and 24 months (Norris, 1977).

Male C57BL/6 mice treated orally with an acute dose of 200 mg/kg bw vinylidene chloride exhibited necrosis and exfoliation of Clara cells in the lung within 24 h (Forkert *et al*., 1985). The severity of the response was increased at two days but was no longer evident seven days after exposure. Intraperitoneal administration of 125 mg/kg vinylidene chloride to male CD-1 mice also resulted in necrosis and covalent binding of vinylidene chloride-derived radioactivity in lung Clara cells (Forkert *et al*., 1986a, 1990). Increased Clara cell toxicity was noted following pretreatment with piperonyl butoxide, while SKF 525-A administration protected against vinylidene chloride-induced pulmonary damage (Forkert *et al*., 1986b).

Male CD-1 mice treated with 75, 125, 175 and 225 mg/kg bw vinylidene chloride by intraperitoneal injection exhibited glutathione (GSH) depletion in lung Clara cells at 75 and 125 mg/kg, with complete loss of GSH at the two highest doses (Moussa &

Forkert, 1992). Administration of 125 mg/kg bw vinylidene chloride to male CD-1 mice by intraperitoneal injection caused a decrease in GSH levels in lung within 6 h after exposure (Forkert & Moussa, 1993). However, GSH concentrations returned to normal levels by 24 h.

Pulmonary toxicity of vinylidene chloride was related to levels of CYP2E1 activity in male and female adult and weanling CD-1 mice following exposure to 50, 75 and 100 mg/kg bw vinylidene chloride (Forkert *et al*., 1996a). For a given dose of vinylidene chloride, cytotoxicity was greatest in the lungs of male mice, followed in severity by male and female weanling mice and then female mice. Levels of CYP2E1 also followed this pattern, with adult male mice having the lowest concentrations of CYP2E1 in lung tissue and female adult mice having the greatest amount of the enzyme. Inhibition of CYP2E1 in male CD-1 mice by diallyl sulfone pretreatment resulted in an absence of pulmonary cytotoxicity following intraperitoneal injection of 75 mg/kg bw vinylidene chloride (Forkert *et al*., 1996b).

Male Sprague-Dawley rats exposed for 4 h to 0–400 ppm [0–1600 mg/m^3] vinylidene chloride exhibited increased kidney weight to body weight ratios, serum nitrogen and creatinine levels 24 h after exposure to concentrations of 250 ppm [1000 mg/m^3] and above (Jackson & Conolly, 1985). Phenobarbital or polychlorinated biphenyl pretreatment antagonized vinylidene chloride-induced nephrotoxicity. Intraperitoneal injection of 25 and 50 mg/kg bw vinylidene chloride to female and male C57BL/6 mice caused mild tubular dilation in the S1 and S2 segments of the kidney proximal tubules 24 h after exposure (Brittebo *et al*., 1993). Buthionine sulfoximine (a GSH depleter and inhibitor of γ-glutamylcysteine synthetase) or probenecid (an anionic transport inhibitor) pretreatment markedly increased the covalent binding of vinylidene chloride to renal tissue. Pretreatment with carboxymethoxyl amine, metyrapone or piperonyl butoxide had no effect on vinylidene chloride-induced kidney binding in this study. In contrast, probenecid and acivin (a γ-glutamyltranspeptidase inhibitor) had no effect on kidney toxicity (assessed by histopathology) caused by a single oral dose of 200 mg/kg bw vinylidene chloride administered to male Swiss OF1 mice (Ban *et al*., 1995). Proximal tubular damage caused by 200 mg/kg vinylidene chloride was decreased in this study following pretreatment with the cysteine conjugate *S*-oxidase inhibitor methimazole or aminooxyacetic acid (an inhibitor of β-lyase).

Similar trends were noted in fasted male Sprague-Dawley rats following a 4-h inhalation exposure to 180–200 ppm [720–800 mg/m^3] vinylidene chloride (Cavelier *et al*., 1996). Analysis of urine and serum for biochemical markers of toxicity 24 h after exposure revealed increased toxicity following vinylidene chloride exposure. Levels of marker enzymes were similar to control values following pretreatment with aminooxyacetic acid. No effect was noted on vinylidene chloride toxicity following acivicin treatment and only slight increases in vinylidene chloride toxicity were observed following methimazole pretreatment.

A single oral gavage dose of 2 mmol/kg (194 mg/kg bw) vinylidene chloride to fasted male Sprague-Dawley rats produced liver damage, as indicated by increases in serum

markers of toxicity (Cossec *et al.*, 1996). Urinary activities of renal toxicity markers were also increased 24 h after administration of this dose of vinylidene chloride. No toxicity was noted in this study at a dose of 0.5 mmol/kg (48 mg/kg bw) vinylidene chloride.

Male and female Swiss-Webster mice were exposed to 60 ppm [240 mg/m^3] vinylidene chloride for 4 h (Speerschneider & Dekant, 1995). Urine was collected over a 48-h period and animals were then killed. Male mice were more sensitive to vinylidene chloride-induced nephrotoxicity, as assessed by changes in urinary volume, creatinine, glucose and γ-glutamyltranspeptidase levels. Increased necrosis was observed in exposed male mice and female mice pretreated with testosterone. Female mice had no observable kidney lesions or alteration in urinary parameters, suggesting the role of CYP2E1 in vinylidene chloride-induced nephrotoxicity.

Male Wistar rats exposed by inhalation to 2000 ppm [8000 mg/m^3] vinylidene chloride for 6 h exhibited only slight and insignificant elevation of serum hepatotoxic enzyme activities 24 h after exposure (Siegers *et al.*, 1985a). Exposure to equal concentrations of vinylidene chloride under low oxygen conditions resulted in no vinylidene chloride-induced effects. Inhalation exposure of male Wistar rats to 1000 ppm [4000 mg/m^3] vinylidene chloride for 3 h caused only small increases in serum markers of liver toxicity 24 h after exposure. Toxicity was enhanced following pretreatment with phorone, a GSH-depleting agent (Siegers *et al.*, 1985b). Oral administration of 1.5 mL/kg (1820 mg/kg bw) vinylidene chloride to male Sprague-Dawley rats caused increased activity of liver toxicity markers 8 and 24 h after gavage (Long *et al.*, 1989). Decreases in calcium pump activity in liver endoplasmic reticulum were also noted 0.5–8 h after exposure.

Administration of 0–225 mg/kg vinylidene chloride to male CD-1 mice resulted in GSH depletion in both lung and liver, increased covalent binding to liver tissue and necrosis 1 h after exposure (Forkert & Moussa, 1993). In male Sprague-Dawley rats, GSH depletion was also noted following intraperitoneal injection of 50 mg/kg vinylidene chloride and was more pronounced in fasted rats than in fed animals (Kanz *et al.*, 1988). Exposure of BALB/c mouse hepatocytes to vinylidene chloride *in vitro* indicated that GSH conjugation is a critical detoxification step (Kainz *et al.*, 1993) and CYP2E1 is involved in vinylidene chloride metabolic activation. Similar results were noted *in vivo* when male Sprague-Dawley rats pretreated with high levels of vitamin A (an inducer of CYP2E1) exhibited a dose-dependent increase in the liver toxicity marker alanine aminotransferase 24 h after intraperitoneal treatment with 0–200 mg/kg bw vinylidene chloride (Wijeweera *et al.*, 1996). In the same study, inactivation of Kupffer cells with gadolinium chloride decreased the toxicity of vinylidene chloride in the liver of vitamin A-pretreated animals. Vinylidene chloride-induced liver toxicity (assessed by histopathology) in male Wistar rats was noted to be greater following total inhalation exposure over a four-week period to 33 533 ppm.h at a nominal concentration of 50 ppm [200 mg/m^3] vinylidene chloride in a constant profile group compared with a fluctuating exposure scenario (Plummer *et al.*, 1990).

Hyperthyroidism was noted to increase the hepatotoxicity, covalent binding and biliary clearance of vinylidene chloride in male Sprague-Dawley rats following oral administration of 50 mg/kg (Kanz *et al*., 1988, 1994). Increased serum levels of markers of liver toxicity and decreases in hepatic glutathione *S*-transferase and alcohol dehydrogenase levels were noted in hypothyroid rats (Kanz *et al*., 1991). Vinylidene chloride administered orally at doses of 50 or 200 mg/kg bw caused alterations in biliary excretion of inulin and other marker solutes (indocyanine green and phenolphthalein glucuronide) (Moslen *et al*., 1985; Moslen & Kanz, 1993). These vinylidene chloride doses were also reported to cause damage to the bile canaliculi, with fasted rats exhibiting greater damage than fed rats (Moslen *et al*., 1985, 1989; Moslen & Kanz, 1993).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In a dominant lethal assay, male CD rats were exposed to 55 ppm [220 mg/m^3] vinylidene chloride for 6 h per day on five days per week (Short *et al*., 1977). On week 11 of exposure, males were mated with untreated females. There was no evidence of pre- or post-implantation loss in the pregnant females. Male CD-1 mice exposed to 10, 30 or 50 ppm [40, 120 or 200 mg/m^3] vinylidene chloride for 6 h per day for five days and subsequently mated with untreated females exhibited no pre- or post-implantation loss (Anderson *et al*., 1977), indicating an absence of adverse effects on male reproduction.

Sprague-Dawley rats were exposed by inhalation to 80, 316 or 630 mg/m^3 vinylidene for 7 h per day on days 6–15 of pregnancy. New Zealand rabbits were exposed to 316 or 630 mg/m^3 on days 6–18 of pregnancy (Murray *et al*., 1979). Toxicity was noted in the dams at 316 mg/m^3 in rats and 630 mg/m^3 in rabbits. Resorptions in dams and skeletal variations in pups were increased in rabbits at 630 mg/m^3. Skeletal variations were also noted in rats exposed to 316 mg/m^3 and 630 mg/m^3.

No adverse effects were noted in Sprague-Dawley rats exposed to 200 mg/L vinylidene chloride in the drinking-water on days 6–15 of pregnancy (Murray *et al*., 1979). In a three-generation reproductive toxicity study in which Sprague-Dawley rats were exposed to 50, 100 or 200 mg/L vinylidene chloride in the drinking-water, no adverse effects were noted in the reproductive capacity of either sex (Nitschke *et al*., 1983).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Vinylidene chloride induced mutations in *Salmonella typhimurium* and *Escherichia coli* in the absence of an exogenous metabolic system. In *Saccharomyces cerevisiae*, vinylidene chloride induced reverse mutation and mitotic gene conversion *in vitro* and in a host-mediated assay in mice. In a single study in *Saccharomyces*, it induced aneuploidy in the presence and absence of metabolic activation. *In vitro*, gene mutations were increased in mouse lymphoma cells but not in Chinese hamster lung cells with or without an exogenous metabolic system. In a single study, vinylidene chloride induced sister chromatid exchanges in Chinese hamster lung cells in the presence of an exogenous metabolic system but not in its absence. In single studies *in vivo*, it did not induce micronuclei or chromosomal aberrations in bone marrow or in fetal erythrocytes of mice, nor dominant lethal mutations in mice or rats.

5. Summary of Data Reported and Evaluation[1]

5.1 Exposure data

Exposure to vinylidene chloride may occur during its production and in the production of copolymers. It has been detected in wastewater.

5.2 Human carcinogenicity data

Two cohort studies were performed in workers exposed to vinylidene chloride. Both studies have major limitations and do not allow evaluation of the carcinogenicity of the compound.

No specific association was found between exposure to vinylidene chloride and an excess of lung cancer observed in a synthetic chemical plant in the United States.

5.3 Animal carcinogenicity data

Vinylidene chloride was tested for carcinogenicity in mice and rats by oral administration and inhalation exposure, in mice by subcutaneous administration and topical application and in hamsters by inhalation. Studies in mice and rats by oral administration gave negative results. In inhalation studies, no treatment-related neoplasm was observed in rats or hamsters. In mice, treatment-related increases in the incidence of kidney adenocarcinomas were observed in male mice, as were increases in mammary carcinomas in females and pulmonary adenomas in male and female mice. In skin-painting studies in female mice, vinylidene chloride showed activity as an initiator, but in a study of repeated skin application, no skin tumour occurred. No tumour at the injection site was seen in mice given repeated subcutaneous administration.

[1] Summary (but not the evaluation) prepared by the Secretariat after the meeting.

Table 1. Genetic and related effects of vinylidene chloride

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAF, *Salmonella typhimurium* BA13/BAL13, forward mutation	–	+	500	Roldán-Arjona *et al*. (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	2% in air	Malaveille *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	5% in air	Jones & Hathway (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	5% in air	Simmon & Tardiff (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	5% in air	Waskell (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	2% in air	Bartsch *et al*. (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	375 ppm in air	Oesch *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	+	125	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	–	500	Strobel & Grummt (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	3% in air	Baden *et al*. (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	+	5% in air	Jones & Hathway (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	375 ppm in air	Oesch *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	(+)	375 ppm in air	Oesch *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	375 ppm in air	Oesch *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	(+)	125	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA92, reverse mutation	–	+	375 ppm in air	Oesch *et al*. (1983)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	+	5	Strobel & Grummt (1987)
ECK, *Escherichia coli* K12, forward or reverse mutation	–	(+)	242	Greim *et al*. (1975)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	+	375 ppm in air	Oesch *et al*. (1983)
SCG, *Saccharomyces cerevisiae* D7, gene conversion	–	+	2910	Bronzetti *et al*. (1983)
SCG, *Saccharomyces cerevisiae* D7, mitotic gene conversion	+[c]	–	7300	Koch *et al*. (1988)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	–	+	2910	Bronzetti *et al*. (1981)
SCR, *Saccharomyces cerevisiae* D7, reverse mutation	+[c]	+	4876	Koch *et al*. (1988)
SCN, *Saccharomyces cerevisiae* D61.M, aneuploidy	+	+	2435	Koch *et al*. (1988)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G9H, Gene mutation, Chinese hamster lung V79 cells, *hrpt* locus *in vitro*	–	–	10% in air	Drevon & Kuroki (1979)
G9O, Gene mutation, Chinese hamster lung V79 cells, ouabain resistance *in vitro*	–	–	10% in air	Drevon & Kuroki (1979)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	?	+	0.16% in air	McGregor *et al*. (1991)
SIC, Sister chromatid exchange, Chinese hamster lung cells *in vitro*	–	+	75	Sawada *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster DON-6 cells *in vitro*	–	NT	2910	Sasaki *et al*. (1980)
CIC, Chromosomal aberrations, Chinese hamster fibroblast CHL cells *in vitro*	–	NT	2000	Ishidate *et al*. (1983)
CIC, Chromosomal aberrations, Chinese hamster lung cells *in vitro*	–	+	250	Sawada *et al*. (1987)
HMM, Host-mediated assay, *Saccharomyces cerevisiae* D7 in CD mouse hosts	+	NT	100 po × 23	Bronzetti *et al*. (1981)
HMM, Host-mediated assay, *Saccharomyces cerevisiae* D7 in CD mouse hosts	+	NT	400 po × 1	Bronzetti *et al*. (1981)
MVM, Micronucleus test, mouse bone marrow *in vivo*	–		200 po × 1	Sawada *et al*. (1987)
MVM, Micronucleus test, mouse fetal erythrocytes *in vivo*	–		100 ip × 1	Sawada *et al*. (1987)
CBA, Chromosomal aberrations, Sprague-Dawley rat bone marrow *in vivo*	–		75 ppm inh 6 h/d 3 d/wk 2 y	Rampy *et al*. (1977)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DLM, Dominant lethal test, male CD-1 mice	–		50 ppm inh 6 h/d 5 d	Anderson *et al.* (1977)
DLR, Dominant lethal test, CD rats	–		55 ppm inh 6 h/d 5 d/wk 11 wk	Short *et al.* (1977)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; po, oral; ip, intraperitoneal; inh, inhalation

[c] Positive in cells growing in logarithmic phase

5.4 Other relevant data

Vinylidene chloride is oxidized principally by CYP2E1, the activity of this cytochrome P450 being higher in those tissues (particularly mouse Clara cells and male mouse kidney) that are targets for toxicity of vinylidene chloride. Glutathione levels and conjugation are important in its inactivation and protect against covalent binding. It causes gene mutations in microorganisms, but its genetic activity has not been extensively studied in mammalian cells.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of vinylidene chloride.

There is *limited evidence* in experimental animals for the carcinogenicity of vinylidene chloride.

Overall evaluation

Vinylidene chloride is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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