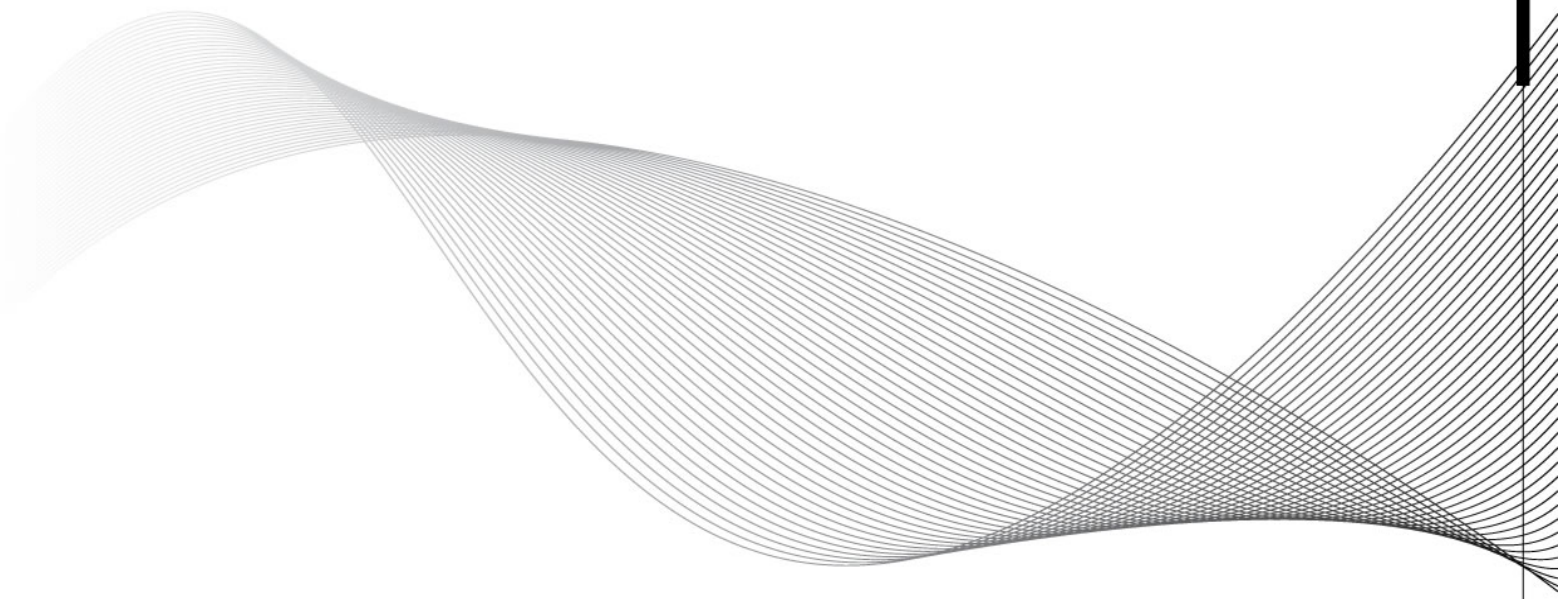
Social Europe



Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,1-Dichloroethene (Vinylidene Chloride)

SCOEL/SUM/132
May 2008

European Commission

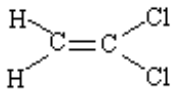
Table of Contents

Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,1-Dichloroethene (Vinylidene Chloride)

8 hour TWA	2 ppm [8 mg/m^3]
STEL (15 min)	5 ppm [20 mg/m^3]
Notation	-

SUBSTANCE IDENTIFICATION

1,1-Dichloroethene

Synonyms	1,1-DCE, 1,1-dichloroethylene, vinylidene chloride, vinylidene dichloride and VDC
EINECS No.	200-864-0
CAS No.	75-35-4
Molecular formula	$C_2H_2Cl_2$
Structural formula	
Molecular weight	96.94 gmol^{-1}
Conversion factor	At 20°C and 101.3 kPa 1 ppm = 4.0 mg/m^3; 1 mg/m3 = 0.25 ppm
EU Classification:	F^+, R12; X_n, R20; Carc.Cat. 3, R40

This document is based on the Concise International Chemical Assessment Document (CICAD, 2004), the references therein, the earlier IPCS monograph (1990), DFG (1997), IARC (1999) and several studies published since the CICAD evaluation.

PHYSICO-CHEMICAL PROPERTIES

At 20°C and 1013 hPa, 1,1-dichloroethene (1,1DCE) is a volatile colourless liquid with a characteristic sweet odour. It has a melting point of -122°C and a boiling point of 32°C. It has a low solubility in water (2,5 g/litre at 25°C). The vapour pressure is 66.5 kPa at 20°C and its measured Henry's law constant is 23.2 Kpa.m^3/mol at 20°C. The vapour is denser than air. The octanol/water partition coefficient as log Pow is 1.32.

1. Occurrence/use

1,1-DCE is produced by the dehydrochlorination of 1,1,2-trichlorethane in the presence of excess base or by thermal decomposition of 1,1,1-trichloroethane (methyl chloroform). 1,1-DCE is an intermediate used in the formation of two hydrochlorfluorocarbons (HCFC-141b and HCFC-142b), in the production of chloracetyl chloride and in the production of polyvinylidene chloride (PVDC) polymers (latex and resin). PVDC polymers are produced as emulsions, as solvent-soluble powders for coating applications and as resins for extrusion and co-extrusion. PVDC copolymers with 1,1-DCE contents of 79-90% are used in moisture and vapour barrier coatings, and films used in food packaging. PVDC copolymers with 1,1-DCE contents of 10-70% are used in flame retarded products. Other consumer products containing PVDC include PVDC-latex for carpet backing and photographic film coatings.

METHODS OF EXPOSURE MONITORING AND ANALYSIS

The UK Health and Safety Executive (2000) has published a general method for the sampling of volatile organic compounds in workplace air and their analysis by gas chromatography that is suitable for 1,1-DCE (Methods for Determination of Hazardous Substances 96).

The US Occupational Safety and Health Administration (OSHA) has published a fully validated specific method (OSHA, 1980) for the measurement of 1,1-DCE in workplace air. The method involves collection on charcoal tubes and analysis by gas chromatography (GC/FID) and the limit of reliable quantification is 0.2 mg/m^3 (0.05 ppm) based on a 3 L sample.

The US National Institute for Occupational Health and Safety (NIOSH) Analytical Method 1015, issue 2 (NIOSH, 1994) also involves collection on charcoal tubes and analysis by GC/FID. The limit of detection is stated as 7µg and the method has been validated for concentrations of 7-10 mg/m^3 in air.

There are no well validated methods of biological monitoring.

2 Health effects

2.1 Toxicokinetics

The results of studies in animals indicate that 1,1-DCE is rapidly absorbed following exposure by inhalation or ingestion. There is no information about uptake through the skin, but, given the low molecular mass of 1,1-DCE and its hydrophobic nature, it is likely that dermal absorption occurs (CICAD, 2003).

Most absorbed 1,1-DCE is rapidly metabolised through oxidation by CYP2E1, via DCE-epoxide, to the reactive intermediates 2,2-dichloroacetaldehyde and 2-chloroacetyl chloride. These undergo secondary reactions including oxidation, conjugation with glutathione (GSH) and hydrolysis (see *Figure 1*). Cellular damage observed in the kidney, liver and lung in animal experiments is consistent with the high concentrations of CYP2E1 in certain cell types within these tissues. Elevated levels of exposure to 1,1-DCE can cause depletion in cellular stores of glutathione. It should be noted that the expression of the CYP1E1 enzyme displays some inter-individual and inter-ethnic variability in humans (Bolt et al. 2003). Any ingested or inhaled 1,1-DCE that is not metabolised is exhaled and no significant bioaccumulation of 1,1-DCE occurs in tissues.

Quantitative analysis reveals marked differences in the amounts of these metabolites which are produced by rats and mice. Whereas the first metabolic pathway via monochloroacetic acid operates as described above in the rat, in the mouse the GSH conjugation is rapidly saturated and large amounts of monochloroacetic acid, which accumulates, are excreted in the urine (Jones and Hathway 1978). Monochloroacetic acid, as such not mutagenic (Malaveille *et al.* 1975), is more toxic in the rat than in the mouse (Jones and Hathway 1978). Vinylidene chloride is more toxic in the mouse than in the rat (Maltoni 1977) so that its hepatotoxic effects cannot derive from metabolites such as monochloroacetic acid or its breakdown products. In mice the second metabolic pathway predominates, probably as a result of higher glutathione epoxide transferase activity (Hayakawa *et al.* 1974). This accounts for the fact that *N*-acetyl-*S*-(2-carboxymethyl)cysteine could be detected in mouse urine but not in rats and would also explain why higher levels of 1,1-dichloroethylene oxide or chloroacetyl chloride are available for reaction with DNA in mice (Hathway 1977, Walker and Hathway 1977). An increase in the levels of vinylidene chloride or vinylidene chloride metabolites bound to cell components is associated with an increase in the severity of the hepatotoxicity (McKenna *et al.* 1977, Short *et al.* 1977 b). Particularly high levels of vinylidene chloride bound to tissue macro-molecules have been found in the mouse kidney (McKenna *et al.* 1977, Short *et al.* 1977 b).

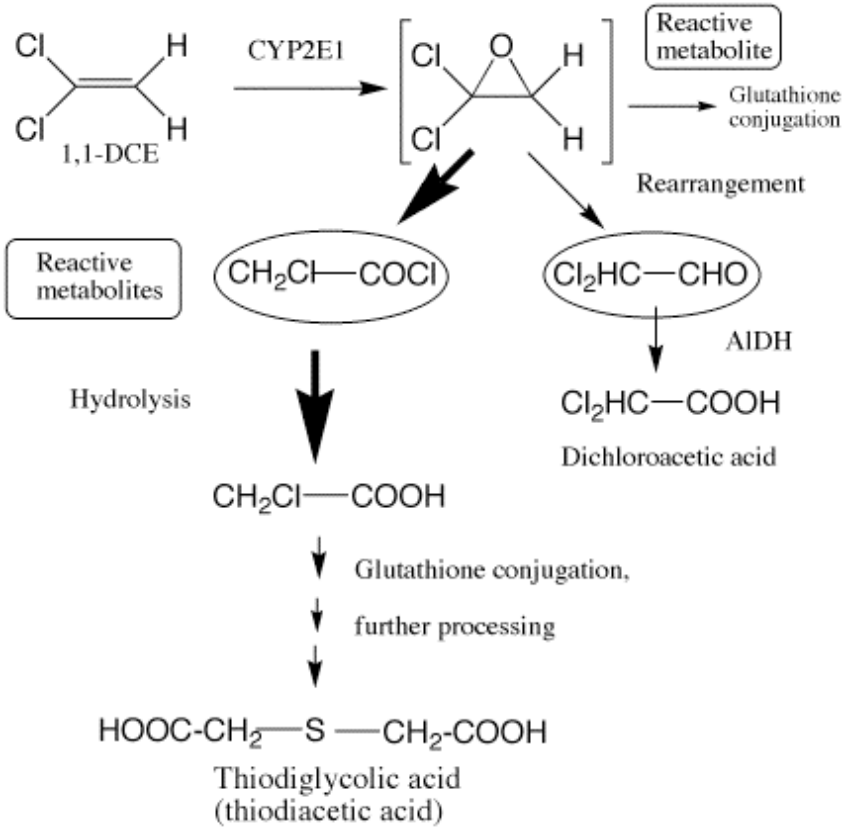


Figure 1: Metabolic pathways for 1,1-dichloroethene (1,1-DCE)

2.2. Acute toxicity

2.2.1. Human data

The IPCS (1990) monograph cites a report linking exposure to a high concentration of 1,1-DCE, e.g., 16,000 mg/m3 (4,000 ppm), to rapid intoxication that can lead to unconsciousness. The anaesthetic effects from short-term exposure were stated to be short-lived.

The IPCS (1990) suggests that some adverse effects that have been reported to be associated with 1,1-DCE (i.e. respiratory irritation, cranial nerve disorders and leukoderma) may be due to contaminants or to the stabilizer (*p*- methoxyphenol) rather than 1,1-DCE itself.

2.2.2. Animal data

Limited data from single dose experiments in rats and mice undertaken during the 1970s cited by the CICAD (2003) indicates that exposures to concentrations between 390 and 25,000 mg/m3 for between 1.4 and 23 hours give rise to mortality rates of 50%. The CICAD (2003) reports LD_{50} values of 194-274 mg/kg body weight in mice and 1,500 – 1,800 mg/ kg body weight in rats. A more recent study (Muralidhara *et al*, 2001) reports an LD_{50} of 8,200 mg/kg body weight in rats.

Acute exposure by either inhalation or ingestion leads to damage of the liver, kidney and Clara cells of the lung. Liver effects include increased liver enzyme levels in serum, severe histopathological damage including disruption of bile canaliculi, cytoplasmic vacuolization and haemorrhagic necrosis, increased covalent bonding of 1,1-DCE and decreased GSH-dependent metabolism of 1,1-DCE. These liver effects arise in conjunction with severe depletion of GSH (60%) arising from DCE-metabolism. Kidney effects include increased kidney weight, increased blood urea nitrogen and creatinine and histopathological changes including vacuolization, tubular dilation and necrosis of the proximal tubules. Effects on Clara cells of the lung include extensive histopathological changes, repair of damage through cell proliferation and depletion of GSH.

2.3. Irritation

The IPCS (1990) monograph reports that exposure to 1,1-DCE has been reported to cause irritation of eye and upper respiratory tract (at levels as low as 100 mg/m3). Irritation has also been reported following skin contact. These effects may have been at least partially due to the stabilizer *p*-methoxyphenol.

There are no recent reports of an association between exposure to 1,1-DCE and respiratory or dermal irritation in humans or animals.

2.4. Sensitisation

There is no evidence that 1,1-DCE causes sensitisation in humans or in animals.

2.5. Repeated dose toxicity

2.5.1. Human data

Although 1,1-DCE has been in use since the 1940s, there are relatively few reports of adverse effects and only one published epidemiological study.

Ott *et al* (1976) studied 138 workers exposed to concentrations of <5 to 75 ppm [20 to 280 mg/m^3] 1,1-DCE in the absence of vinyl chloride exposure. These workers were involved in experimental or pilot plant polymerization operations, in a monomer production process as tank-car loaders, or in a production plant manufacturing a monofilament fibre. Overall, there were no significant differences in haematology, clinical chemistry, or mortality between the exposed cohort and the controls. Two employees suffered hepatic damage, but this could have been linked to alcohol consumption. Relatively little can be inferred from this study because of small study size and limited number of end-points examined.

In an unpublished mortality study described by IPCS (1990), Thiess *et al* (1979) followed up 447 workers exposed to 1,1-DCE, for 6-10 h/day, 42 h/per week, for more than six months in a 1,1-DCE production and polymerization plant. Individuals were exposed to an estimated average 1,1-DCE concentration of 200 mg/m3 (50 ppm) from 1955 to 1965 and subsequently to an average level of approximately 40 mg/m3 (10 ppm) up to 1975. All workers had also been exposed to vinyl chloride and acrylonitrile since 1975. No excess mortality was observed for cancers, infectious diseases, cardiovascular diseases, other natural causes, or external causes. In an unpublished continuation of the same study, Klimisch *et al* (1982) followed up 535 persons exposed for more than 6 months with an estimated average exposure in the years before 1965 of 200 mg/m^3 (50 ppm) and found a significant increase in cardiovascular mortality. IPCS (1990) viewed the significance of this finding as uncertain because of the small study size and inadequate control for confounding exposures, e.g. vinyl chloride and acrylonitrile.

In a further unpublished study cited by IPCS (1990), Schmitz *et al* (1979) found effects on serum enzymes levels (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and gamma-glutamyl transpeptidase) in 133 human subjects exposed to 1,1-DCE, but these effects were unrelated to the duration of exposure.

2.5.2. Animal data

The CICAD (2003) describes a single 90-day inhalation study in which rats, Guinea-pigs, beagle dogs, rabbits and squirrel monkeys were exposed continuously to 1,1-DCE (Prendergast *et al*, 1967). The no effects level (NOAEL) for liver and kidney damage in all the examined species was 101 mg/m3 with a lowest observed effects level (LOAEL) of 47.3 ppm [189 mg/ m^3]. In a two-year experiment (Quast *et al*, 1986), male and female Sprague-Dawley rats (Spartan substrain) were exposed to vinylidene chloride by inhalation for 18 months to assess chronic toxicity and oncogenic potential of the subject test material. Interim sacrifices were performed at 1, 6, and 12 months. Rats were exposed to vinylidene chloride concentrations of 10 and 40 ppm for 6 hr/day, 5 days/week for the first 5 weeks of the study. Based upon the absence of observable treatment-related effects among rats sacrificed after 1 month of exposure, the exposure concentrations were increased to 25 and 75 ppm vinylidene chloride. Exposures were continued at these concentrations through the 18th month of the study after which the surviving animals were held until 24 months and then sacrificed. Cytogenetic evaluations were performed on a separate group of animals, four rats/sex, exposed to 0, 25, or 75 ppm vinylidene chloride for 6 months. There were no exposure-related changes in the following

parameters: mortality, appearance and demeanor, body weight data, clinical chemistry determinations, hematologic evaluations, urinalysis, or cytogenetic evaluation of bone marrow preparations. A target organ effect, characterized by hepatocellular fatty change in the midzonal region of the hepatic lobule which was minimal in severity, was observed in both male and female rats of both the 25- and 75-ppm exposure groups as early as the 6-month interim sacrifice. The midzonal fatty change was also observed at the 12-month sacrifice but no indication of progression of this lesion in either severity or incidence was apparent. During the last 6 months of the study, after exposures had been discontinued, this effect was no longer discernible; therefore this alteration was considered to be readily reversible. Several tumours and/or tumour types were statistically increased or decreased in vinylidene chloride -exposed rats when compared to their respective control groups; none of these differences were judged to be attributable to VDC exposure.

Mice exposed to 200 mg/m3 for 6 hours per day, 5 days per week showed signs of extreme toxicity after only a few exposures (Maltoni *et al*, 1985). The CICAD (2003) cites a benchmark concentration for a 10% response (BMC_{10}) of 15 ppm [59.9 mg/m^3] with a lower confidence limit of 9.7 ppm [38.9 mg/m^3].

The CICAD (2003) also describes 90-day gavage studies in mice and rats undertaken by the National Toxicology Program (1982). Centrilobular necrosis of the liver was observed in some animals at doses of 100 mg/kg/day (5 days/week) or greater. The NOAEL was identified as 40 mg/kg/day or 28.6 mg/kg/day after adjusting for 5 days per week exposure. The LOEL was identified as 100 mg/kg/day or 71.4 mg/kg/day after adjusting for 5 days/week exposure. A small 97-day study in dogs (Quast *et al*, 1983) found no effects at 25 mg/kg/day, the highest dose investigated.

In a more recent 90 day gavage study, rats receiving 4,000 mg/kg/day showed pronounced CNS depression and more than half died before the end of the study (Muralidhura *et al*, 2001). Rats receiving 2,000 mg/kg/day also showed CNS depression. At both 2,000 and 4,000 mg/kg/day, animals showed decreases in body weight and transient changes in urine enzyme concentrations. No organ damage or changes in enzyme serum concentration were identified. The NOAEL was identified as 500 mg/kg/day and the LOEL as 1,000 mg/kg/day.

In a two-year study, male rats showed minimal hepatocellular fatty change at 20 mg/kg/day and female rats showed similar changes at 14 mg/kg/day. No evidence was found of any abnormality in liver function. The NOAEL was 10 mg/kg/day in male rats and 9 mg/kg/day in female rats (oral dose). The calculated BMD_{10} was 6.6 mg/kg/day with a lower confidence limit of 4.6 mg/kg/day (CICAD, 2003).

2.6 Mutagenicity

The *in vitro* mutagenicity of 1,1-DCE is reviewed in the CICAD (2003). 1,1-DCE causes gene mutations in micro-organisms in the presence of exogenous activation. Most *in vitro* tests with mammalian cells have shown no evidence of genetic toxicity, but no tests have been undertaken to determine chromosomal damage in the mouse lymphoma system. There is insufficient evidence to confirm that 1,1-DCE is not genotoxic.
In single studies *in vivo*, it did not induce micronuclei or chromosomal aberrations in bone marrow or in foetal erythrocytes of mice, nor dominant lethal mutations in mice or rats (IARC 1999).

2.7. Carcinogenicity

2.7.1. Humans

Many workers exposed to 1,1-DCE have also experienced concurrent exposure to vinyl chloride, a proven carcinogen that is associated with angiosarcoma of the liver, and this has limited opportunities to investigate the potential effects of 1,1-DCE. In a study of 4,806 chemical workers with exposures to up to 19 chemicals including vinyl chloride between 1942 and 1973, no association was found between exposure (level not specified) to 1,1-DCE and angiosarcoma (Waxweiler, 1981) or lung cancer (Waxweiler *et al,* 1981).

In the Ott *et al* (1976) study described above (see point 5.5), there was no exposure to vinyl chloride, and no excess of cancers was detected. The study population was, however, small, follow-up incomplete and the time since first exposure was less than 15 years for more than 60% of the study population. The study therefore lacked the power to reliably detect an excess cancer risk. The Thiess *et al* (1979) and Klimisch *et al* (1982) studies described above found no significant excess of cancers. However, for workers who had an estimated average exposure in the years before 1965 of 200 mg/m^3 (50 ppm), the number of malignant tumours was 12 compared with 9.8 expected and including 6 bronchial carcinomas compared with 2.68-2.96 expected. Given the small size of the cohort and the confounding effects of exposure to vinyl chloride, the IPCS concluded that these findings do not provide convincing evidence to link 1,1-DCE to cancer in humans.

IARC (1999) have concluded that there is *inadequate evidence* in humans for the carcinogenicity of 1,1-DCE and that 1,1-DCE is *not classifiable as to its carcinogenicity to humans (Group 3)*.

2.7.2. Animals

1,1-DCE has been 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. None of the published inhalation studies were consistent with current guidelines. No significant increase in tumours was found in six studies in rats in which animals were exposed to concentrations of up to 150 ppm [600 mg/m^3] (6 hours/day, 5 days/week) for up to 52 weeks (reviewed by the CICAD, 2003). In one study in mice, a dose-related increase in the incidence of kidney adenocarcinomas were observed in male mice exposed to 0, 10 and 25 ppm [0, 40 and 100 mg/m^3] over a 12 month period. A statistically significant increase in mammary carcinomas in females and pulmonary adenomas in male and female mice was unrelated to dose (Maltoni *et al*, 1985). Other studies in different strains of mice at concentrations of up to 220 mg/m^3 failed to detect an excess of tumours (Maltoni *et al*, 1985; Lee *et al*, 1978; Hong *et al*, 1981). No excess of tumours was found in hamsters exposed to 25 ppm [100 mg/m^3] for 4-5 days/week for 52 weeks (Maltoni *et al*, 1985). The induction of kidney tumours in male mice may be a sex and species-specific response related to the expression of CYP2E1 in the kidney of male mice. The CICAD (2003), however, concluded that there was insufficient evidence to conclude that the observed effects were not relevant to the assessment of human health risks. Studies in mice and rats by oral administration gave negative results (CICAD, 2003).

In skin-painting studies in female mice, 1,1-DCE showed activity as an initiator, but in a study of repeated skin application, no skin tumours occurred. No tumour at the injection site was seen in mice following repeated subcutaneous administration (CICAD, 2003).

IARC (1999) concluded that there is *limited evidence* in experimental animals for the carcinogenicity of 1,1-DCE.

5.8 Reproductive toxicity

Fertility

There are no data relating to the effects of 1,1-DCE on fertility. The CICAD (2003) reviewed the results of a three generation study (Nitschke *et al*, 1983), in which rats were exposed to 1,1-DCE in drinking-water with inferred average exposures to 9, 14 and 30 mg/kg/day. No biologically significant changes in fertility index, average number of pups per litter, average body weight of pups, or pup survival at any exposure (up to 30 mg/kg/day). There was a statistically non-significant decrease in neonatal survival in the F2 and F3a litters of dams ingesting 1,1-DCE from drinking-water. Histopathological examination of tissues of rats exposed to 1,1-DCE in the drinking-water in utero, during lactation, and post-weaning revealed slight hepatocellular fatty change and an accentuated hepatic lobular pattern of a reversible nature in the adult rats. These effects were observed in the mid and high dose groups in the F1 generation and in all groups of the F2 generation.

Developmental toxicity

No human data are available.

CICAD (2003) and DFG (1997) reviewed the available inhalation studies. It was summarized that exposure concentrations, which caused little or no maternal toxicity (inhaled 20 ppm in rats and 80 ppm in rabbits, 200 ppm in the drinking water in rats), had no effect on embryonal or foetal development.

In rats exposed to 1,1-DCE for 7 hours per day on gestation days 6–15, there was no maternal toxicity or effect on embryo or foetal development at 20 ppm [80 mg/m^3]. Maternal toxicity was observed at 80 and 160 ppm [320 and 640 mg/m^3] (significantly reduced weight gain) and also a statistically significant increased incidence of wavy ribs and delayed ossification of the skull, regarded as an embryotoxic effect. No teratogenic effects were seen at any exposure (Murray *et al*, 1979).

In mice exposed to 1,1-DCE for 22–23 hours each day on gestation days 6–16, complete early resorption of the litters was observed at 30 ppm [120 mg/m^3]. At 15 ppm [60 mg/ m^3], there was no evidence of maternal toxicity, no decrease in foetal body weight, and no decrease in the percentage of viable foetuses but there was a statistically significant increase in the number of foetuses with incomplete skeletal ossification. Non-significant increases in the mean number of foetuses per litter with hydrocephalus occluded nasal passages, microphthalmia, cleft palate, small liver, and hydronephrosis were also observed (Short *et al*, 1977).

In rabbits exposed for 7 hours per day on gestation days 6–18, there was no maternal toxicity and no effect on embryo or foetal development at 80 ppm [320 mg/m^3]. Maternal toxicity and a marked increase in the incidence of resorptions per litter were observed at 160 ppm [640 mg/ m^3]. There was also a significant change in the incidence of several minor skeletal variations but no teratogenic effects (Murray *et al*, 1979).

The CICAD (2003) also reviewed several oral studies. No teratogenic effects or maternal toxicity were seen in rats exposed on gestation days 6–15 at 40 mg/kg/day in drinking water (Murray *et al*, 1979). In rats exposed to up to 18 mg/kg/day 1,1-DCE both before

and after mating, there was a statistically significant increase in the percentage of foetuses with cardiac changes. No effects were seen when exposure was limited to before mating (Dawson *et al*, 1993). Cardiac tissue is not generally considered to be a tissue with significant potential for metabolism of xenobiotics and the CICAD concluded that there was insufficient evidence to demonstrate the observed cardiac changes were caused by exposure to 1,1-DCE.

RECOMMENDATION

1,1-DCE is rapidly absorbed following inhalation and oral exposure and is also likely to be absorbed through the skin.

Short-term human exposure to very high concentrations of 1,1-DCE (4000 ppm [16,000 mg/m^3]) can cause neurotoxic effects leading to unconsciousness. The few studies of the long-term effects of 1,1-DCE exposure in the workplace involve small numbers of workers, have insufficient follow up and/or are complicated by confounding exposures to other chemicals (Ott *et al*, 1976, Thiess *et al*, 1977; Klimisch *et al* 1982; Schmitz *et al*, 1979). These studies are not particularly informative about the risks to human health.

1,1-DCE is metabolised to reactive intermediates that cause depletion of glutathione stores. The organ toxicity of 1,1-DCE is likely connected with this metabolic activation.

The results of animal experiments indicate that the main target organs for 1,1-DCE are the liver, kidney and Clara cells in the lung (Quast *et al*, 1986; Maltoni et *al*, 1985). In a subchronic (90 days) study in rats, guinea pigs, dogs, rabbits and monkeys, a NOAEL of 25 ppm [101 mg/m3] and a LOAEL of 47.3 ppm [189 mg/m3] were reported for liver and kidney effects following continuous exposure to 1,1-DCE. This is compatible with the results of a two-year study in rats (Quast et al. 1986). In this study, the lowest effect observed was a minimal hepatocellular fatty change in the midzonal region of the hepatic lobule, which appeared after 6 months of the study(6 hours/day, 5 days/week), and which was completely reversible upon cessation of exposure. This occurred at 25 ppm [100 mg/ m^3] exposure. In a two year study in which rats were exposed to 1,1-DCE in drinking water, the NOAEL for liver cell changes was 9 mg/kg/day and the LOAEL, 14 mg/kg/day.

There is insufficient evidence to determine whether 1,1-DCE causes cancer in humans. There is limited evidence that it may cause cancer in animals. In a single inhalation study, male, but not female, mice showed a dose-dependent increase in kidney adenocarcinomas. No statistically significant increase in cancer risk has been observed in other species or other strains of mice.

The point of departure for setting an OEL is hepato- and nephrotoxicity, at an experimentally well established LOAEL of 25 ppm [100 mg/m^3] (see above). The metabolic toxification process of 1,1-DCE is mediated by CYP2E1, which shows considerable variability of enzyme expression in humans. Considering such possible interindividual variability in toxicity to humans and the LOAEL as a point of departure, an OEL (8 h TWA) of 2 ppm [8 mg/m^3] is proposed. With an excursion factor of 2.5 a proposed STEL (15 min) is 5 ppm [20 mg/m^3], which remains reasonably close to the NOAEL.

Adverse effects on fertility, embryo and foetal development in animals have only been observed at doses that cause maternal toxicity. With this respect, the proposed OEL provides an adequate margin of safety.

At these levels of exposure, analytical difficulties are not expected.

At body temperature, 1,2-DCE is in the gaseous state. Therefore, a relevant skin absorption under conditions of industrial use appears not likely.

REFERENCES

Bolt HM, Roos PH, Thier R (2003) The cytochrome P-450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. Int Arch Occup Environ Health 76:174-185.

CICAD (2003) see: IPCS (2003).

Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB. (1993). Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. Journal of the American College of Cardiology; 21:1466–1472.

DFG (1997) Vinylidene Chloride. In: Occupational Toxicants, Critical Data Evaluation for MAK Values and Classification of Carcinogens, Volume 8, pp. 109-139. WILEY-VCH, Weinheim

Hayakawa T, Lemahieu RA, Udenfriend S (1974) Studies on glutathione-S-arene oxidase transferase – a sensitive assay and partial purification of the enzyme from sheep liver", Arch. Biochem. 162, 223

Hong CB, Winston JM, Thornburg LP, Lee CC, Woods JS. (1981). Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice; tumor incidence and mortality subsequent to exposure. Journal of Toxicology and Environmental Health;7:909–924.

IARC (1999). Vinylidene Chloride. In: International Agency for Research on Cancer. Re-evaluation of some organic chemicals, hydrazine, and hydrogen peroxide (part 3). Lyon: IARC. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71): 1163–1180.

IPCS (2003). 1,1-Dichloroethene (Vinylidene Chloride). Concise International Chemical Assessment Document 51.

IPCS. (1990) .Vinylidene chloride. Geneva: WHO. (International Programme on Chemical Safety. Environmental Health Criteria 100).

Jones BK, Hathway DE (1978) Differences in metabolism of vinylidene chloride between mice and rats, Br. J. Cancer 37, 411

Klimisch JH., Link R, Stocker WG, Thiess AM. (1982) Investigation of the mortality of workers predominantly exposed to vinylidene chloride. In: Proceedings of the Medichem Congress, Paris, 1982.

Lee CC, Bhandari JC, Winston JM, House WB, Dixon RL, Woods JS. (1978). Carcinogenicity of vinyl chloride and vinylidene chloride. Journal of Toxicology and Environmental Health; 24:15–30.

Malaveille C, Bartsch H, Barbin A, Camus AM, Montesano R, Croisy A, Jacquignon P (1975) Mutagenicity of vinyl chloride, chloroethylene-oxide, chloroacetaldehyde and chloroethanol", Biochem. Biophys. Res. Commun. 63, 363

Maltoni C (1977) Recent findings on the carcinogenicity of chlorinated olefins, Environ. Health Perspect. 21, 1

Maltoni C, Lefemine G, Cotti G, Chieco P, Patella V. (1985). Experimental research on vinylidene chloride carcinogenesis. In: Maltoni C, Mehlman MA, eds. Archives of research on industrial carcinogenesis. Volume III. Princeton: Princeton Scientific Publishers.

McKenna M, Watanabe XPG. Gehring PJ (1977) Pharmacokinetics of vinylidine chloride in the rat, Environ. Health Perspect. 21, 99

Muralidhara S, Ramanathan R, Mehta SM, Lash LH, Acosta D, Bruckner JV. (2001). Acute, subacute, and subchronic oral toxicity studies of 1,1-dichloroethane in rats: application to risk evaluation. Toxicological Sciences; 64:135-45.

Murray FJ, Nitschke KD, Rampy LW, Schwetz BA. (1979). Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits. Toxicology and Applied Pharmacology; 49:189–202.

NIOSH [US National Institute for Occupational Health and Safety] (1994). Analytical Method 1015 (issue 2) (www.cdc.gov/niosh).

Nitschke KD, Smith FA, Quast JF, Norris JM, Schwetz BA. (1983). A three-generation rat reproductive toxicity study of vinylidene chloride in the drinking water. Fundamental and Applied Toxicology, 3:75–79.

NTP. (1982). Carcinogenesis bioassay of vinylidene chloride in F344 rats and B6C3F1 mice (gavage study). North Carolina: NTP. (NTP Technical Report Series No. 228).

OSHA [US Occupational Safety and Health Administration] (1980). OSHA organic method 19 (www.osha.gov).

Ott MG, Fishbeck WA, Townsend JC, Schneider EJ. (1976). A health study of employees exposed to vinylidene chloride. Journal of Occupational Medicine; 18:735–738.

Prendergast JA, Jones RA, Jenkins LJ Jr, Siegel J. (1967) Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene.
Toxicol Appl Pharmacol. 10:270-289.

Quast JF, Humiston CG, Wade CE, Ballard J, Beyer JE, Schwetz RW, Norris JM (1983) A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. Fundam Appl Toxicol. 3:55-62.

Quast JF, McKenna MJ, Rampy LW, Norris JM. (1986). Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats. Fundamental and Applied Toxicology, 6:105–144.

Schmitz T, Thiess AM, Penning E. (1979). [Inquiry into morbidity among workers exposed to vinylidene chloride (VDC) and polyvinylidene chloride (PVDC).] In: [Report on the Tenth Annual Meeting of the German Occupational Medicine Society together with the Federation of Industrial Employers Associations, Munster, 2-5 May, 1979,] (in German). Stuttgart: Gentner Verlag

Short RD, Minor JL, Peters P, Winston JM, Ferguson P, Unger T, Sawyer M, Lee CC. (1977a). The developmental toxicity of vinylidene chloride inhaled by rats and mice during

gestation. Report prepared by Midwest Research International, Kansas City, MO, for US Environmental Protection Agency, Washington, DC (EPA 560/6-77-022; PB-281-713).

Short RD, Winston JM, Minor JL, Hong JH, Seifter JB, Lee CC (1977b) Toxicity of vinylidene chloride in mice and rats and its alteration by various treatments. J Toxicol Environ Health 3: 913.

Thiess, AM, Frentzel-Beyme R, Penning E. (1979). Mortality study of vinylidene chloride exposed persons. In: Heim C, Kilian, DJ, ed. Proceedings of the 5th Medichem Congress, San Francisco, September 1977: 270-278.

UK Health and Safety Executive. (2000). Volatile organic compounds in air. Sudbury: HSE Books. (Methods for Determination of Hazardous Substances 96). (www.hse.gov.uk).

Waxweiler RJ.(1981). Epidemiologic problems associated with exposure to several agents. Environ Health Perspectives; 42:51-6.

Waxweiler, RJ, Smith, AH, Falk, H, Tyroler, HA. (1981) Excess lung cancer risk in a synthetic chemicals plant. Environmental Health Perspectives; 41: 159-165.