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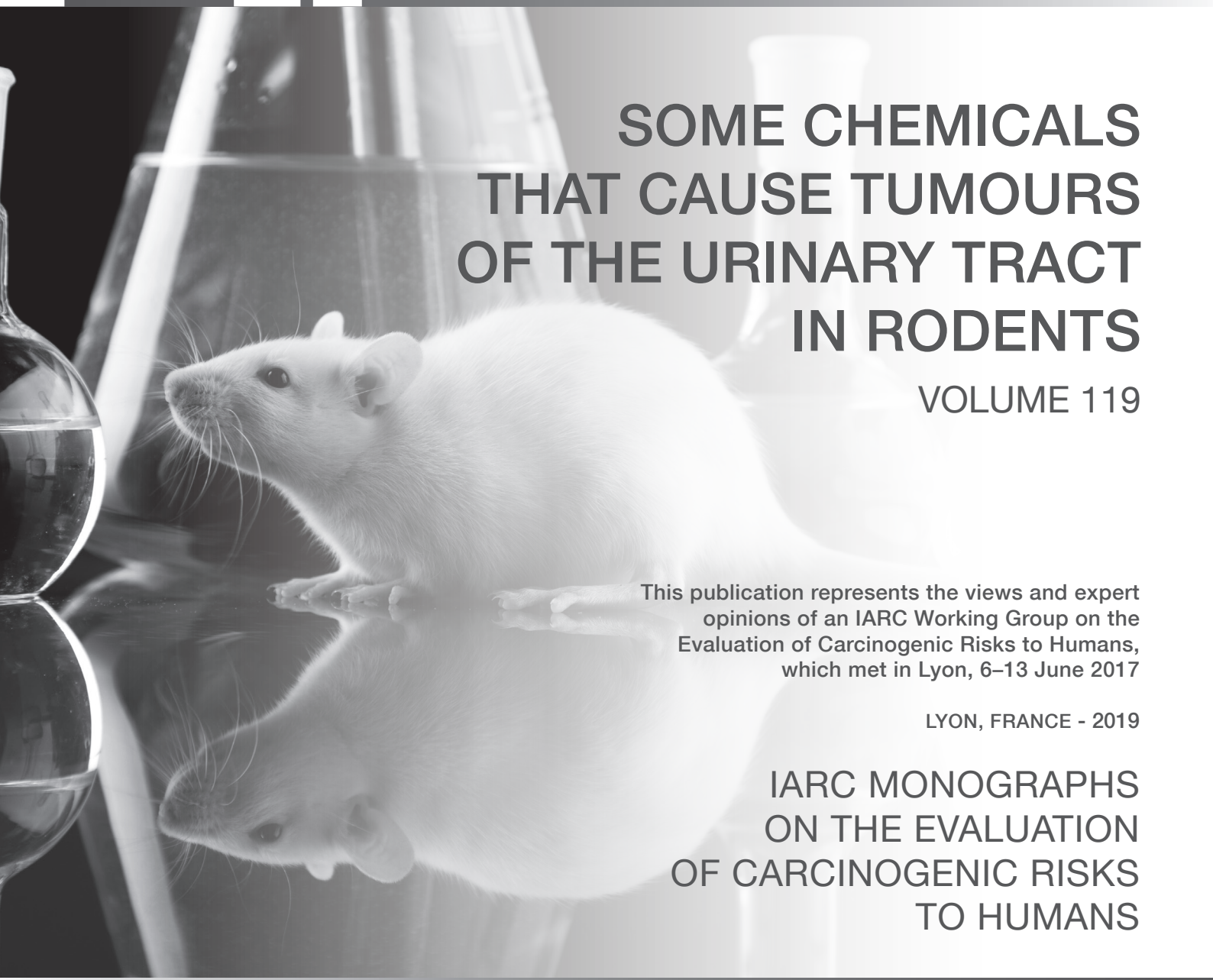

SOME CHEMICALS THAT CAUSE TUMOURS OF THE URINARY TRACT IN RODENTS

VOLUME 119

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 6–13 June 2017

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International Agency for Research on Cancer

World Health Organization

VINYLIDENE CHLORIDE

1. Exposure Data

Data were previously reviewed by the Working Group in 1985 (IARC, 1986) and vinylidene chloride was classified in *Monographs* Supplement 7 as *not classifiable as to its carcinogenicity to humans* (Group 3) (IARC, 1987). This substance was further considered by the Working Group in 1998 (IARC, 1999). New data have become available since that time, and these have been incorporated and taken into consideration in the present evaluation.

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 75-35-4

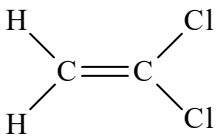
EC/List No.: 200-864-0

Chem. Abstr. Serv. name: 1,1-Dichloroethene

IUPAC systematic name: 1,1-Dichloroethene

Synonyms: Vinylidene chloride; 1,1-dichloroethylene; 1,1-DCE; vinylidene dichloride; ethene, 1,1-dichloro-

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: $C_2H_2Cl_2$

Relative molecular mass: 96.94

1.1.3 Chemical and physical properties

Description: Volatile, colourless, oily liquid with sweet, chloroform-like odour (Budavari, 1996; IPCS, 2014; NIOSH, 2014)

Melting point: –122.5 °C (Lide, 1995)

Boiling point: 31.6 °C (Lide, 1995)

Relative density: 1.2 (water = 1) (IPCS, 2014)

Solubility: Insoluble in water (2.5 g/L) (IPCS, 2014); soluble in acetone, ethanol, and many organic solvents; very soluble in diethyl ether (IARC, 1999; WHO, 2003)

Volatility: Vapour pressure: 67 kPa at 20 °C (WHO, 2003)

Relative vapour density: 3.3 (air = 1) (IPCS, 2014); relative density of the vapour/air mixture at 20 °C (air = 1): 3.25 (Verschueren, 1996)

Octanol/water partition coefficient (P): log K_{ow}, 1.32 (WHO, 2003)

Flash point: –19 °C (closed cup); –15 °C (open cup) (IARC, 1999)

Explosive limits: Lower limit, 5.6%; upper limit, 16% (IPCS, 2014)

Auto-ignition temperature: 530 °C (IPCS, 2014)

Stability: In the absence of an added inhibitor, monomethyl ether of hydroquinone (up to 200 ppm), vinylidene chloride readily polymerizes; in the presence of air or oxygen, shock-sensitive and explosive peroxides are formed (NTP, 2015)

Odour threshold: 190 ppm in air (Amoore & Hautala, 1983)

Henry constant: 23.2 kPa·m^3/mol at 20 °C (WHO, 2003)

Conversion factor: 1 ppm = 3.96 mg/m^3 (IARC, 1999)

1.2 Production and use

1.2.1 Production process

Vinylidene chloride is produced in a closed system using a stainless steel reactor. It is almost exclusively produced from 1,1,2-trichloroethane that is made from 1,2-dichloroethane or vinyl chloride. 1,1,2-Trichloroethane is converted to vinylidene chloride by dehydrochlorination, which is carried out by one of two different routes: liquid-phase or gas-phase reaction. Vinylidene chloride can be obtained from thermal cracking of 1,1,1-trichloroethane. Other production methods use vinyl chloride oxychlorination or tetrachloroethane dehydrochlorination and the high-temperature reaction of methane with chlorinating agents. Patents exist for the catalytic hydrogenation of 1,1,1,2-tetrachloroethane and the reaction of ethane with hexachloroethane to produce a mixture including vinylidene chloride (Dow Chemical, 2002; Dreher et al., 2014).

1.2.2 Production volume

Vinylidene chloride is classified by the Organisation for Economic Co-operation and Development (OECD) as a high production volume substance, that is, it is produced or imported at levels greater than 1000 tonnes per year in at least one OECD member country and/or region (OECD, 2017).

Non-confidential estimates of production capacity for vinylidene chloride are difficult to obtain due to the limited number of global producers and the fact that there is only one producer in the USA. In the early 1980s, estimated annual production of vinylidene chloride was over 91 700 tonnes in the USA (Grayson, 1983) and 306 000 tonnes globally (IPCS, 1990). Current and future demand have been impacted by the phasing-out of hydrochlorofluoro-carbon (HCFC)-141b [1,1-dichloro-1-fluoroethane] (banned in the European Union in 2002 and in the USA in 2003 according to the Montreal Protocol; UNEP, 1989), which used significant quantities of vinylidene chloride as a precursor in one of the commercial routes of manufacture (Dow Chemical, 2002).

In 2012, the global production capacity of vinylidene chloride was estimated at 502 000 tonnes and the global demand was estimated at 354 000 tonnes (Dreher et al., 2014).

1.2.3 Use

Globally, vinylidene chloride is used primarily as an intermediate in the manufacture of 1,1,1-trichloroethane, polyvinylidene chloride polymers, copolymers, and terpolymers (latex and resin), which may in turn be used in a variety of end products such as food plastic wrap, carpet latex backing, fire- and ignition-resistant clothing, vapour barriers for insulation, steel pipe coating, outdoor furniture, paper and board coatings, adhesives, and photographic film. Vinylidene chloride may persist as an unintended

manufacturing residue in some of these items. It may also be used in the production of chloroacetyl chloride and of latex and resins, as an aid in ore flotation, as a solvent in paint and varnish remover, and as a vapour degreaser and industrial cleaning agent (EPA, 2000; WHO, 2003; Health Canada, 2013; Dreher et al., 2014). Vinylidene chloride is also used in the production of certain HCFCs (except HCFC-141b; see Section 1.2.2).

1.3 Analytical methods

Because of its volatility, vinylidene chloride is well suited to determination by gas chromatography using a variety of detectors, including flame ionization, electron capture, electrolytic conductivity detection, and mass spectrometry. Methods are available for quantifying vinylidene chloride in environmental samples (air, water, soil, and sediment) and in biological samples (breath, food, and body tissues) (see Table 1.1) (WHO, 2003).

1.4 Occurrence and exposure

Vinylidene chloride does not occur naturally (IARC, 1986; WHO, 2003; Health Canada, 2013; NTP, 2015). It can be found in the environment from release during its manufacture and use, the breakdown of polyvinylidene chloride products, and the biotic or abiotic breakdown of 1,1,1-trichloroethane, tetrachloroethene, 1,1,2-trichloroethene, and 1,1-dichloroethane. It is frequently found at hazardous waste sites (WHO, 2003), and also appears as an impurity in trichloroethylene (classified as *carcinogenic to humans*, Group 1; IARC, 2013).

1.4.1 Environmental occurrence

(a) Water

Environmental levels of vinylidene chloride in water are very low. In raw industrial wastewater in the USA, mean concentrations ranged from 18 to 760 µg/L; a concentration of 32 µg/L was reported from the Netherlands. Vinylidene chloride concentrations of 0.3–80 µg/L have been measured from the River Rhine. The level in untreated drinking-water is generally not detectable. Median concentrations of vinylidene chloride were 0.28–1.2 µg/L in treated potable water taken from groundwater sources; in public drinking-water supplies, concentrations were generally less than 1 µg/L, although levels of up to 20 µg/L have been detected (IPCS, 1990; Kubota & Tsuchiya, 2010).

A national assessment in 2006 by the United States Geological Survey (USGS) reported the detection of vinylidene chloride in 19 (of 1207) domestic well samples (ATSDR, 2009).

An earlier USGS assessment of untreated, ambient groundwater wells between 1985 and 1995 identified vinylidene chloride in 3% of wells in urban areas (n = 406) and in 0.3% of wells in rural areas (n = 2542). Areas of known point-source contamination were excluded from the assessment (Squillace et al., 1999).

In an analysis of 70 private residential wells in 21 counties in South Carolina, USA, from August 2000 to February 2001, vinylidene chloride was detected in 2 wells (Aelion & Conte, 2004).

Vinylidene chloride was not detected in any of 14 Canadian surveys of drinking-water among different cities between 2003 and 2008 (Health Canada, 2013).

(b) Air

Up to approximately 5% of manufactured vinylidene chloride (a maximum of ~23 000 tonnes) is emitted into the atmosphere annually. The high vapour pressure and low water solubility of

Table 1.1 Analytical methods for the analysis of vinylidene chloride

Media	Method	Remarks	Reference
Ambient air	EPA Reference Method 23	Analysis by GC-FID: column temperature, 100 °C; flow rate, 20 mL/min; working range, 0.4–800 mg/m^3 The method has not been validated by the EPA for vinylidene chloride, but a similar analytical procedure has been used to measure occupational exposures	EPA (1985b)
Workplace air	NIOSH Analytical Method 1015	Analysis by GC: for vinylidene chloride, a 100 (front) + 50 (back) mg charcoal tube should be used; desorption solvent, CS_2 General method for volatile organic compounds	Health and Safety Executive (2000)
Workplace air	OSHA Organic Method 19	Analysis by GC-FID: detection limit and limit of reliable quantification, 0.2 mg/m^3 (0.05 ppm) based on a 3-L sample at 0.2 L/min; target concentration, 1 ppm (4.0 mg/m^3); analytical solvent, CS_2 Fully validated specific method; collection on charcoal tubes	OSHA (1980)
Workplace air	NIOSH Analytical Method 1015, issue 2	Analysis by GC/FID: limit of detection, 7 µg; working range, 0.5–5 ppm (2–20 mg/m^3) for a 5-L air sample using a charcoal tube with a flow rate of 0.01–0.2 L/min Validated for concentrations of 7–10 mg/m^3 in air; the capacity of charcoal for vinylidene chloride decreases rapidly with increasing relative humidity, and was also found to be a function of concentration; a capillary column such as 105 m Rtx® 502.2 is required	NIOSH (1994)
Water	EPA Method 524.2	Analysis by GC-MS: detection limit, 0.05 µg/L General-purpose method for purgeable volatile organic compounds in surface water, groundwater, and drinking-water in any stage of treatment; cryogenic trapping, narrow-bore capillary column	EPA (1995)
Water	–	Detection by purge and gas trap chromatography followed by FID or MS; minimum practical quantitation limit, 5 µg/L Based on similarity to seven other volatile organics	Otson et al. (1982), Health Canada (2015)
Soil/sediment	–	Extraction with an organic solvent or purging with an inert gas, trapping, and GC-MS; sample size, 1–3 g; detection limit, 10 µg/g (DeLeon et al., 1980) or 0.40 µg/g (Amaral et al., 1994)	DeLeon et al. (1980), Amaral et al. (1994), WHO (2003)
Films, food, body tissues	–	Detection limit in the 5–10 µg/kg range using a headspace technique, purge and trap, and GC-ECD or GC-MS; vacuum distillation and GC-MS using fused-silica capillary column for fish tissue Quantification limit: 1 µg/m^2 in PVC-containing films, 20 µg/m^3 in foodstuffs, at least 0.14 µg/g of tissue (wet weight)	Gilbert et al. (1980), Easley et al. (1981), Lin et al. (1982), Hiatt, 1983, WHO (2003)

CS_2, carbon disulfide; ECD, electrolytic conductivity detection; EPA, United States Environmental Protection Agency; FID, flame ionization detection; GC, gas chromatography; MS, mass spectrometry; NIOSH, National Institute for Occupational Safety and Health; ppm, parts per million; PVC, polyvinyl chloride

vinylidene chloride favour its relatively higher concentration in the atmosphere compared with that in other environmental compartments. Vinylidene chloride in the atmosphere is expected to have a half-life of approximately 2 days. The measured half-life of 80 mg/m³ vinylidene chloride in sealed quartz flasks exposed outdoors was 56 days (IPCS, 1990). [The relevance of this result to the environmental persistence of vinylidene chloride is difficult to interpret.]

Singh et al. (1981) and Brodzinski & Singh (1983) reported data on vinylidene chloride in ambient air in 30 locations in the USA, and Guicherit & Schulting (1985) measured vinylidene chloride in ambient air at three sites in the Netherlands. According to the World Health Organization (WHO), the three datasets are consistent, indicating typical mean concentrations of 20–120 µg/m³ and maximum concentrations of 40–560 µg/m³ (WHO, 2003). Measurements taken in industrial areas near sources of vinylidene chloride yielded a much higher mean value of 120 × 10³ µg/m³ and a maximum of 270 × 10³ µg/m³. The median concentration of vinylidene chloride in different areas in the USA were reported as: approximately 0.02 µg/m³ in urban and/or suburban ambient air; about 8.7 µg/m³ in industrial areas; and about 90–100 µg/m³ and 25–50 µg/m³ in the atmosphere around vinylidene chloride monomer and polymer manufacturing plants, respectively (EPA, 1985a). Ambient air quality data were compiled from 1982 to 2001 for vinylidene chloride at 87 individual locations throughout the USA; the range in the arithmetic mean values for these locations was 0.004–4 µg/m³ (WHO, 2003).

Health Canada (2013) provided detailed summaries of concentrations of vinylidene chloride in ambient and indoor air from studies carried out during 1986–2008, mainly from Canada and the USA. It was suggested that the highest median concentration in Canada, measured at 0.076 µg/m³ in both outdoor and indoor air, be used to derive estimates of environmental intake. Mean indoor concentrations in three out of four studies in the USA in which vinylidene chloride was quantifiable were reported as 12.06 µg/m³, 1.81 µg/m³, and 5.02 µg/m³.

(c) Food

Vinylidene chloride may migrate into foods when plastic food-contact materials containing this monomer are used (HSDB, 2009). Concentrations of vinylidene chloride in food are usually not detectable; in analyses of various food products in Japan and the United Kingdom, a maximum concentration of 20 µg/kg was observed (Gilbert et al., 1980; IPCS, 1990; Ohno & Kawamura, 2006). Vinylidene chloride was not detected in any of the 4 samples of 34 food composites analysed in Canada in several studies in the early 1990s (Health Canada, 2013).

1.4.2 Exposure in the general population

The general population may be exposed by environmental contamination of air or drinking-water, or eating contaminated food. The main exposure is from indoor air (Health Canada, 2013).

Based on personal air sampling in the general population in urban areas, the estimated mean vinylidene chloride exposure was 6.5 µg/m³ (Wallace, 1991). Levels of vinylidene chloride in the breath of residents in North Carolina and New Jersey, USA, ranged from undetectable to 26 µg/m³ (Wallace et al., 1982, 1984). In the early 1980s, vinylidene chloride was found in 3% of approximately 347 overnight personal air samples and in 6% of approximately 340 daytime personal air samples in Bayonne and Elizabeth, New Jersey, USA (Wallace et al., 1986a), and 12% of approximately 300 breath samples from residents of the same cities contained quantifiable levels (0.2–2.0 µg/m³) of vinylidene chloride (Wallace et al., 1986b).

The National Health and Nutrition Examination Survey 2003–2004 conducted by the National Center for Health Statistics in the USA did not detect vinylidene chloride in any of 1367 samples of human blood from adults aged 20–59 years (detection limit, 0.009 ng/mL) (NCHS, 2009). Vinylidene chloride was qualitatively detected in 1 of 12 breast milk samples acquired from four cities in the USA [detection limit unspecified] (Pellizzari et al., 1982). In a related study, vinylidene chloride was qualitatively detected in one of eight samples of breast milk acquired from four cities in the USA [detection limit unspecified] (EPA, 1980).

It has been estimated that the maximum possible intake of vinylidene chloride from food as a result of the use of packaging materials is no more than 1 µg per person per day in the United Kingdom (MAFF, 1980).

Consumers may be exposed via migration of vinylidene chloride from the films and coatings of packaging materials into foods in contact with the packaging (NTP, 2015). However, food sources are expected to be negligible (WHO, 2003). [No reliable data were available to the Working Group to estimate the exposure from food.]

Environment Canada and Health Canada provided a detailed upper-bounding deterministic estimate of vinylidene chloride intake from ambient air, indoor air, drinking-water, food and beverages, and soil based on various studies measuring the occurrence in these matrices. The total intake from all routes of exposure according to age group was 7.67×10^{-2} µg/kg body weight (bw) per day for formula-fed infants, 1.340 µg/kg bw per day for infants not fed formula, 0.911 µg/kg bw per day for those aged 0.5–4 years, 0.591 µg/kg bw per day for those aged 5–11 years, 0.344 µg/kg bw per day for those aged 12–19 years, 0.260 µg/kg bw per day for those aged 20–59 years, and 0.214 µg/kg bw per day for those aged 60 years and older (Health Canada, 2013).

Based on air measurements in the homes of smokers and non-smokers (8-hour average exposures) in Hong Kong Special Administrative Region, Guo et al. (2004) provided exposure estimates of 38.3 ng/kg bw per day and 4.45 ng/kg bw per day, respectively.

Lee et al. (2002) estimated the exposure to vinylidene chloride for residents exposed to groundwater contaminated by a hazardous waste site. The exposure routes included inhalation during showering and dermal absorption during showering and other activities involving skin contact with water. The chronic intake was estimated as 2.64×10^{-2} mg/kg bw per day for inhalation and 3.74×10^{-4} mg/kg bw per day for dermal absorption.

1.4.3 Occupational exposure

No new data on occupational exposure were available to the Working Group. Industrial use of vinylidene chloride is currently within closed systems, minimizing potential occupational exposure. Significant occupational exposure is usually only by inhalation, although skin or eye contamination can also occur. Small numbers of chemical workers are exposed to vinylidene chloride. From the 1980s workers have been exposed to concentrations of less than 20 mg/m^3, although exposure levels could have been as high as about 8000 mg/m^3 until the 1970s.

Exposure to concentrations of about 80 000 mg/m^3 can occur from spillage, and worker exposure before the 1970s may have exceeded 1200–4000 mg/m^3 (Fishbein, 1981).

Ott et al. (1976) reported exposure data from a fibre production plant in the USA where vinylidene chloride was used with ethyl acrylate. Between 1955 and 1968, the measured time-weighted average (TWA) exposure levels for production-related jobs ranged from about 40 to 280 mg/m^3, although individual measured exposures ranged from 0 up to about 7500 mg/m^3. Thiess et al. (1979) reported average exposure

measurements of about 40 mg/m³ in a German plant manufacturing vinylidene chloride from 1975 onwards. In the associated polymerization plant, average quarterly concentrations of vinylidene chloride were between 2.6 and 6.7 mg/m³, with 220 peak exposures in excess of 120 mg/m³ during 1976.

The British Health and Safety Executive reported that, during the 1980s, occupational exposure to vinylidene chloride was limited to about 100 people in the country, and that 95% of exposure measurements were less than 20 mg/m³ (HSE, 1996). Fishbein (1981) confirmed that daily average vinylidene chloride exposures were most frequently measured at trace levels at that time.

1.5 Regulations and guidelines

In 1993, WHO established an international drinking-water quality guideline for vinylidene chloride of 30 µg/L (WHO, 2003). WHO did not set a formal guideline value for vinylidene chloride in its latest guidelines for drinking-water quality, however, because it occurs in drinking-water at concentrations well below those at which it is a concern to health (WHO, 2011).

The Committee of Experts on the Transport of Dangerous Goods and Globally Harmonized System of Classification and Labelling of Chemicals of the United Nations Economic Commission for Europe identified vinylidene chloride as: United Nations No. 1303, Hazard Class 3, United Nations Packing Group I (UNECE, 2017).

Commission Regulation (EU) No. 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food includes vinylidene chloride in the list of substances not authorized to be used as an additive or polymer production aid. It is authorized to be used as a monomer, or other starting substance or macromolecule obtained from microbial fermentation (European Commission, 2011).

In 2008 in the European Union, the Scientific Committee on Occupational Exposure Limits proposed an 8-hour TWA of 2 ppm [8 mg/m³] and a short-term exposure limit (15 minutes) of 5 ppm [20 mg/m³] without any notation (SCOEL, 2008).

The European Chemicals Agency hazard classification and labelling, approved by the European Union, warns that vinylidene chloride is an extremely flammable liquid and vapour, is harmful if inhaled, and is suspected of causing cancer. Additionally, vinylidene chloride causes damage to organs through prolonged or repeated exposure, is harmful if swallowed, causes serious eye irritation, and is harmful to aquatic life with long-lasting effects (ECHA, 2017).

The Institute for Occupational Safety and Health of the German Social Accident Insurance association has an information system on hazardous substances (GESTIS) and a database (GESTIS, 2017), with international limit values for different countries for vinylidene chloride as presented in Table 1.2.

In 2014, the French National Institute for Industrial Environment and Risks generated a series of environmental guideline concentration values for vinylidene chloride (INERIS, 2015), namely: fresh water used for the production of drinking-water, 3 µg/L (annual mean concentration); fresh water not used for the production of drinking-water, 8 µg/L (annual mean concentration); maximum concentration acceptable in fresh water, 91 µg/L; based on human health protection via fishing product consumption, 55 µg/kg biota; maximum concentration acceptable in seawater, 9.1 µg/L; and based on the protection of organisms of the aquatic environment, 7.8 µg/L (annual mean concentration).

In 2015, the Canadian Government established a maximum acceptable concentration for vinylidene chloride in drinking-water of 14 µg/L (Health Canada, 2015).

Table 1.2 Eight-hour and short-term limit values for vinylidene chloride in the workplace in different countries and regions

Country or region	8-hour limit value[a]		Short-term limit value[a]	
	ppm	mg/m³	ppm	mg/m³
Australia	5	20	20	79
Austria	2	8	8	32
Belgium	5	20	20	80
Canada (Ontario)	1	4	20	80
Canada (Quebec)	1	4		
Denmark	2	8	4	16
European Union	2	8	5[b]	20[b]
Finland	2	8	5[b]	20[b]
France	5	20		
Germany (AGS)	2	8	4[b]	16[b]
Germany (DFG)	2	8	4	16
Hungary		8		32
Ireland	5	20		
New Zealand	5	20	20	79
Poland		12.5		
Republic of Korea	5	20	20	80
Romania	5	20	20[b]	80[b]
Singapore	5	20	20	79
Spain	5	20		
Sweden	5	20	10[b]	40[b]
Switzerland	2	8	4	16
United Kingdom	10	40		

AGS, Ausschuff für Gefahrstoffe; DFG, Deutsche Forschungsgemeinschaft; ppm, parts per million

[a] Range of values for an 8-hour period: 1–10 ppm (4–40 mg/m³); range of values for a short period (15 minutes): 4–20 ppm (16–80 mg/m³)

[b] 15-minute average value

Source: GESTIS (2017)

In 1999, the California Environmental Protection Agency (CalEPA) established a non-cancer chronic reference exposure level of 0.07 mg/m³ for vinylidene chloride. The CalEPA reference exposure level is a concentration at or below which adverse health effects are not likely to occur (CalEPA, 2000).

In 1999, the American Conference of Governmental Industrial Hygienists recommended a TWA threshold limit value of 5 ppm for occupational exposures to vinylidene chloride in workplace air (ACGIH, 1999).

The United States Food and Drug Administration categorizes vinylidene chloride as Class 1 in the list of solvents included in the Guidance for Industry table (Q3C). It should not be used in the manufacture of drug substances, excipients, and drug products, because of its unacceptable toxicity. If its use is unavoidable in the production of a drug product with a significant therapeutic property, the concentration limit is 8 ppm (FDA, 2017).

2. Cancer in Humans

Waxweiler et al. (1981) investigated an excess of lung cancer in a cohort of 4806 workers ever employed in a synthetic plastics plant in the USA. Workers were exposed to vinyl chloride, polyvinyl chloride (PVC) dust, vinylidene chloride, and several other chemicals. A statistically significant excess of mortality from lung cancer was observed among all workers at the plant with a standardized mortality ratio (SMR) of 149 ($P < 0.01$). Associations between cancer of the lung and estimates of exposure generated by plant personnel for 19 chemicals, including vinylidene chloride, were analysed using a serially additive expected dose model. A significant association between cancer of the lung and exposure to PVC dust, but not to vinylidene chloride, was observed.

Two other small cohort studies of workers were generally uninformative about the cancer risks from exposure to vinylidene chloride. Ott et al. (1976) studied 138 chemical workers in the USA who were exposed to vinylidene chloride in processes that did not involve vinyl chloride. A total of 5 deaths, of which the only death from cancer was due to cancer of the lung (0.3 deaths expected), were observed during 28 years of follow-up. A statistically significant SMR for cancer of the lung based on 5 deaths was reported in a study of 629 workers exposed to vinylidene chloride in Germany (Thiess et al., 1979). Two of the bronchial carcinoma cases were found in young men (both aged 37 years) who had been employed at the plant for short periods (14 months and 25 months). Workers at this plant were also exposed to vinyl chloride monomer and acrylonitrile. [The Working Group noted that neither of these smaller studies included adjustment for smoking or potential confounders related to occupation.]

3. Cancer in Experimental Animals

Vinylidene chloride was reviewed in *IARC Monographs* Volume 39 (IARC, 1986), Supplement 7 (IARC, 1987), and Volume 71 (IARC, 1999). The *IARC Monographs* Volume 71 Working Group concluded that there was *limited evidence* in experimental animals for the carcinogenicity of vinylidene chloride. This section provides an evaluation of the studies of carcinogenicity in animals reviewed in previous *Monographs* and the Supplement, and a review of any studies published since then.

See Table 3.1.

3.1 Mouse

3.1.1 Inhalation

Groups of 36 male and 36 female CD-1 mice (age, 2 months) were exposed to vinylidene chloride (purity, 99%) at a concentration of 55 ppm in air for 6 hours per day, 5 days per week for up to 12 months, at which point the experiment was terminated. Four mice were killed at 1, 2, 3, 6, and 9 months from the start of the experiment. An increase [not significant] in the incidence of bronchioloalveolar adenoma (1/26 controls vs 6/35 exposed) and an increase [not significant] in the incidence of haemangiosarcoma of the liver (0/26 control vs 2/35 exposed) was observed in males. Three hepatomas [hepatocellular carcinomas] (two in males and one in females) and two skin keratoacanthomas [a benign tumour of the follicular epithelium] were also reported to occur in treated mice [sex unspecified] (Lee et al., 1977, 1978). [The Working Group concluded that this was an inadequate study for the evaluation because of the unsatisfactory study design, the use of only one dose, the limited reporting, and the short duration of exposure.]

Groups of 8–12 male and 8–12 female CD-1 mice (age, 2 months) were exposed to vinylidene chloride (purity, 99%) in air at 55 ppm for

Table 3.1 Studies of carcinogenicity with vinylidene chloride in rodents

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, Swiss (M) 16 wk Lifetime (up to 121 wk) Maltoni et al. (1984)	Inhalation (whole-body) Vinylidene chloride, 99.9% Air 0 (non-chamber controls), 10, 25 ppm, 4 h/d, 4–5 d/wk for 52 wk and observed for life 100, 30, 30 NR, NR, NR	*Kidney*, adenocarcinoma: 0/54, 0/24, 3/21 (14.3%)* *Lung*, pulmonary adenoma: 3/80 (3.7%), 11/28 (39.3%)*, 7/28 (25%)*	*[$P < 0.02$, Fisher exact test] *$P < 0.05$, Fisher exact test	Principal limitations: short duration of exposure; small number of animals in some of the exposure groups; lack of a concurrent chamber control Experiment BT402: initial experiment (using control group A)
Full carcinogenicity Mouse, Swiss (F) 16 wk Lifetime (up to 121 wk) Maltoni et al. (1984)	Inhalation (whole-body) Vinylidene chloride, 99.9% Air 0 (non-chamber controls), 10, 25 ppm, 4 h/d, 4–5 d/wk for 52 wk and observed for life 100, 30, 30 NR, NR, NR	*Mammary gland*, tumours (mainly carcinomas): 2/98 (2%), 6/30 (20%)*, 4/30 (13.3%)* *Lung*, pulmonary adenoma: 4/92 (4.3%), 3/30 (10%), 7/29 (24.1%)*	*$P < 0.05$, Fisher exact test *$P < 0.05$, Fisher exact test	Principal limitations: short duration of exposure; lack of a concurrent chamber control Experiment BT402: initial experiment (using control group A)
Full carcinogenicity Mouse, Swiss (M) 9 wk Lifetime (up to 121 wk) Maltoni et al. (1984)	Inhalation (whole-body) Vinylidene chloride, 99.9% Air 0 (non-chamber controls), 25 ppm, 4 h/d, 4–5 d/wk for 52 wk and observed for life 90, 120 NR, NR	*Kidney*, adenocarcinoma: 0/66, 25/98 (25.5%)* *Lung*, pulmonary adenoma: 3/74 (4%), 16/113 (14.2%)*	*[$P < 0.0001$, Fisher exact test] *$P < 0.05$, Fisher exact test	Principal limitations: short duration of exposure; lack of a concurrent chamber control Experiment BT402: additional control group (B) and additional group exposed at 25 ppm
Full carcinogenicity Mouse, Swiss (F) 9 wk Lifetime (up to 121 wk) Maltoni et al. (1984)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0 (non-chamber controls), 25 ppm, 4 h/d, 4–5 d/wk for 52 wk and observed for life 90, 120 NR, NR	*Lung*, pulmonary adenoma: 3/86 (3.5%), 11/118 (9.3%)* *Mammary gland*, tumours (mainly carcinomas): 1/89 (1.1%), 12/118 (10.2%)*	*$P < 0.05$, Fisher exact test *$P < 0.05$, Fisher exact test	Principal limitations: short duration of exposure; lack of a concurrent chamber control Experiment BT402: additional control group (B) and additional group exposed at 25 ppm

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (M) 5–6 wk 105 wk NTP (2015)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0, 6.25, 12.5, 25 ppm, for (6 h + T_{90} (10 min))/d, 5 d/wk for 105 wk 50, 50, 50, 50 29, 40, 32, 19	*Kidney* Renal tubule adenoma: 0/50*, 5/50 (10%)**, 19/50 (38%)***, 10/50 (20%)***	*$P < 0.001$ (trend), poly-3 test; **$P = 0.041$, poly-3 test; ***$P < 0.001$, poly-3 test	Principal strengths: well-conducted GLP study Historical incidence of hepato-cholangiocarcinoma (mean ± standard deviation): inhalation studies, 2/299 (0.7 ± 1.0%), range 0–2%; all routes, 10/949 (1.1 ± 2.2%), range 0–8%
		Renal tubule carcinoma: 0/50*, 7/50 (14%)**, 31/50 (62%)***, 18/50 (36%)***	*$P < 0.001$ (trend), poly-3 test; **$P = 0.012$, poly-3 test; ***$P < 0.001$, poly-3 test	
		Renal tubule adenoma or carcinoma (combined): 0/50*, 11/50 (22%)**, 37/50 (74%)**, 27/50 (54%)**	*$P < 0.001$ (trend), poly-3 test; **$P < 0.001$, poly-3 test	
		Liver, hepato-cholangiocarcinoma: 1/50 (2%), 2/50 (4%), 2/50 (4%), 3/50 (6%)	NS	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (F) 5–6 wk 105 wk NTP (2015)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0, 6.25, 12.5, 25 ppm, for (6 h + T_{90} (10 min))/d, 5 d/wk for 105 wk 50, 50, 50, 50 36, 25, 30, 24	*Liver* Hepatocellular adenoma: 25/50 (50%)*, 21/50 (42%), 36/50 (72%)**, 29/50 (58%) Hepatocellular carcinoma: 8/50 (16%)*, 14/50 (28%), 12/50 (24%), 17/50 (34%)** Hepatocellular adenoma or carcinoma (combined): 28/50 (56%)*, 30/50 (60%), 37/50 (74%)**, 38/50 (76%)*** Hepato-cholangiocarcinoma: 0/50, 1/50 (2%), 1/50 (2%), 2/50 (4%) Haemangiosarcoma: 1/50*, 1/50, 1/50, 6/50** *Vascular system* Haemangioma: 0/50, 2/50, 2/50, 2/50 Haemangiosarcoma: 4/50*, 4/50, 4/50, 9/50 Haemangioma or haemangiosarcoma (combined): 4/50 (8%)*, 6/50 (12%), 6/50 (12%), 11/50 (22%)** *Lung*, bronchioloalveolar carcinoma: 1/50 (2%)*, 2/50 (4%), 7/50 (14%)**, 5/49 (10%) *Ileum*, carcinoma: 1/50 (2%), 1/50 (2%), 1/50 (2%), 3/50 (6%)	 *P = 0.026 (trend), poly-3 test; **P = 0.015, poly-3 test *P = 0.022 (trend), poly-3 test; **P = 0.015, poly-3 test *P = 0.003 (trend), poly-3 test; **P = 0.041, poly-3 test; ***P = 0.009, poly-3 test NS *P = 0.007 (trend); **P = 0.041 NS *P = 0.044 (trend) *P = 0.018 (trend), poly-3 test; **P = 0.027, poly-3 test *P = 0.038 (trend), poly-3 test; **P = 0.030, poly-3 test NS	Principal strengths: well-conducted GLP study Historical incidence of hepatocellular adenoma (mean ± standard deviation): inhalation studies, 105/300 (35.0 ± 8.8%), range 28–50%; all routes, 378/948 (39.9 ± 18.7%), range 14–78% Historical incidence of hepatocellular carcinoma: inhalation studies, 44/300 (14.7 ± 5.0%), range 8–20%; all routes, 152/948 (16.0 ± 10.6%), range 4–46% Historical incidence of hepato-cholangiocarcinoma: inhalation studies, 0/300; all routes, 0/948. Historical incidence of haemangioma or haemangiosarcoma (combined) (vascular system): inhalation studies, 21/300 (7.0 ± 2.1%), range 4–10%; all routes, 55/950 (5.8 ± 3.7%), range 2–14% Historical incidence of bronchioloalveolar carcinoma: inhalation studies, 13/299 (4.4 ± 4.3%), range 0–10%; all routes, 38/949 (4.0 ± 3.6%), range 0–14% Historical incidence of ileum carcinoma: inhalation studies: 2/300 (0.7 ± 1.0%), range 0–2%; all routes, 2/950 (0.2 ± 0.6%), range 0–2%

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (M) 9 wk 104 wk NTP (1982)	Gavage Vinylidene chloride, 99% Corn oil 0, 2, 10 mg/kg bw, 1×/d, 5 d/wk for 104 wk 50, 50, 50 33, 35, 36	All sites No significant increase in tumour incidence in treated animals	NS	Principal limitations: MTD does not appear to have been achieved
Full carcinogenicity Mouse, B6C3F$_1$/N (F) 9 wk 104 wk NTP (1982)	Gavage Vinylidene chloride, 99% Corn oil 0, 2, 10 mg/kg bw, 1×/d, 5 d/wk for 104 wk 50, 50, 50 40, 32, 42	*Haematopoietic system [haematopoietic and lymphoid tissues]* Malignant lymphoma (all): 2/48 (4%), 9/49 (18%)*, 6/50 (12%) Lymphoma or leukaemia (all): 7/48 (15%), 15/49 (31%)*, 7/50 (14%)	*P = 0.028, Fisher exact test; P = 0.012, life table test *P = 0.050, Fisher exact test; P = 0.037, life table test	Principal limitations: MTD does not appear to have been achieved
Initiation–promotion (tested as initiator) Mouse, Ha:ICR Swiss (F) 6–8 wk 428–576 d Van Duuren et al. (1979)	Skin application Vinylidene chloride, NR Acetone Single application of vinylidene chloride (in 0.2 mL acetone) then 14 d later 5 µg TPA in 0.2 mL acetone 3×/wk for 428–576 d Five groups: no treatment (control); acetone only (vehicle control); 121.0 mg vinylidene chloride + TPA; TPA only (TPA-treated control); 20 µg DMBA + TPA (positive control) 100, 30, 30, 90, 30 NR, NR, NR, NR, NR	*Skin*, papilloma: 0/100, 0/30, 8/30 (27%)*, 6/90 (7%), 29/30 (97%)	*$P < 0.005$, χ^2 test vs TPA control	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, Sprague-Dawley (F) 13 wk Lifetime Cotti et al. (1988)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0, 100 ppm, 4 h/d, 5 d/wk for 7 wk, then 7 h/d, 5 d/wk for 97 wk 60, 54 NR, NR	*Mammary gland* Malignant tumours: 2/60 (3.3%), 4/54 (7.4%) Benign and malignant tumours: 24/60 (40%), 29/54 (53.7%)	 [NS] [NS]	Principal limitations: unsatisfactory study design (use of only one dose); unsatisfactory reporting (no detailed information on survival or description of observed tumours) Breeders of the Cotti et al. (1988) transplacental plus inhalation exposure experiment (see below)
Full carcinogenicity Rat, Sprague-Dawley (M) Embryo Lifetime Cotti et al. (1988)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0, 100 ppm transplacentally at d 12 of gestation, then 4 h/d, 5 d/wk for 7 wk then 7 h/d, 5 d/wk for 97 wk 158, 62 NR, NR	*Haematopoietic system*, leukaemia: 12/158 (7.6%), 10/62 (16.1%)	 [NS]	Principal limitations: unsatisfactory study design (use of only one dose); unsatisfactory reporting (no detailed information on survival or description of observed tumours) Offspring of the Cotti et al. (1988) breeders (see above)
Full carcinogenicity Rat, Sprague-Dawley (F) Embryo Lifetime Cotti et al. (1988)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0, 100 ppm transplacentally at d 12 of gestation, then 4 h/d, 5 d/wk for 7 wk then 7 h/d, 5 d/wk for 97 wk 149, 61 NR, NR	*Haematopoietic system*, leukaemia: 1/149 (0.7%), 4/61 (6.5%)*	 *[$P < 0.03$, Fisher exact test]	Principal limitations: unsatisfactory study design (use of only one dose); unsatisfactory reporting (no detailed information on survival or description of observed tumours) Offspring of the Cotti et al. (1988) breeders (see above)
Full carcinogenicity Rat, Sprague-Dawley (M) 6–7 wk 24 mo Quast et al. (1986)	Inhalation Vinylidene chloride, 99% Air 0, 25, 75 ppm for 6 h/d, 5 d/wk for 18 mo 86, 85, 86 13, 13, 8	All sites No significant increase in tumour incidence in treated animals	 NS	Principal limitations: short duration of exposure (18 mo total) Exposure to 0, 10, 75 ppm the first month

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, Sprague-Dawley (F) 6–7 wk 24 mo Quast et al. (1986)	Inhalation Vinylidene chloride, 99% Air 0, 25, 75 ppm, 6 h/d, 5 d/wk for 18 mo 84, 86, 84 19, 11, 16	*Mammary gland*, adenocarcinoma: 2/84, 7/86*, 4/84 (total no. tumours: 2, 8, 4)	*$P < 0.05$, Fisher exact test [NS; $P = 0.0898$, 1-tail Fisher exact test]	Principal limitations: short duration of exposure (18 mo total); poor survival in high-dose females Exposure to 0, 10, 40 ppm the first month
Full carcinogenicity Rat, F344/N (M) 5–6 wk 105 wk NTP (2015)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0, 25, 50, 100 ppm, for (6 h + T_{90} (10 min))/d, 5 d/wk for 105 wk 50, 50, 50, 50 25, 27, 22, 19	*Mesothelium*, malignant mesothelioma: 1/50 (2%)*, 12/50 (24%)**, 28/50 (56%)**, 23/50 (46%)** *Nose*, respiratory epithelium, adenoma: 0/49*, 0/50, 1/50 (2%), 4/50 (8%) *Kidney*, renal tubule carcinoma: 0/50, 2/50, 1/49, 1/50	*$P < 0.001$ (trend), poly-3 test; **$P < 0.001$, poly-3 test *$P = 0.004$ (trend), poly-3 test NS	Principal strengths: well-conducted GLP study Historical incidence of nasal respiratory epithelium adenoma (mean ± standard deviation): inhalation studies, 0/198; all routes: 0/697 Historical incidence of renal tubule carcinoma: inhalation studies, 0/200; all routes, 1/697

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, F344/N (F) 5–6 wk 105 wk NTP (2015)	Inhalation (whole-body) Vinylidene chloride, > 99.9% Air 0, 25, 50, 100 ppm, for (6 h + T_{90} (10 min))/d, 5 d/wk for 105 wk 50, 50, 50, 50 30, 26, 30, 19	*Thyroid C-cell* Adenoma: 3/50 (6%)*, 4/50 (8%), 6/48 (13%), 11/50 (22%)** Carcinoma: 0/50, 6/50 (12%)*, 2/48 (4%), 2/50 (4%) Adenoma or carcinoma (combined): 3/50 (6%)*, 10/50 (20%)**, 8/48 (17%), 13/50 (26%)*** *Haematopoietic system*, mononuclear cell leukaemia: 10/50 (20%)*, 11/50 (22%), 13/50 (26%), 25/50 (50%)** *Nose*, respiratory epithelium, adenoma: 0/50, 0/50, 0/50, 1/50 *Mesothelium*, malignant mesothelioma: 0/50, 1/50, 1/50, 0/50	 *P = 0.004 (trend), poly-3 test; **P = 0.012, poly-3 test *P = 0.011, poly-3 test *P = 0.006 (trend), poly-3 test; **P = 0.023, poly-3 test; ***P = 0.003, poly-3 test *P < 0.001 (trend), poly-3 test **P < 0.001, poly-3 test NS NS	Principal strengths: well-conducted GLP study Historical incidence of thyroid C-cell adenoma (mean ± standard deviation): inhalation studies, 13/200 (6.5 ± 1.0%), range 6–8%; all routes, 81/690 (11.7 ± 5.5%), range 6–22% Historical incidence of thyroid C-cell carcinoma: inhalation studies, 1/200 (0.5 ± 1.0%), range 0–2%; all routes, 6/690 (0.9 ± 2.0%), range 0–7% Historical incidence of thyroid C-cell adenoma or carcinoma (combined): inhalation studies, 14/200 (7.0 ± 1.2%), range 6–8%; all routes, 87/690 (12.7 ± 5.8%), range 6–22% Historical incidence of mononuclear cell leukaemia: inhalation studies, 58/200 (29.0 ± 6.2%), range 20–34%; all routes, 165/700 (23.6 ± 8.2%), range 10–36% Historical incidence of nasal respiratory epithelium adenoma: inhalation studies, 0/200; all routes, 1/697, range 0–2% Historical incidence of malignant mesothelioma: inhalation studies, 0/200; all routes, 0/700

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 9 wk 104 wk NTP (1982)	Gavage Vinylidene chloride, 99% Corn oil 0, 1, 5 mg/kg bw, 1×/d, 5 d/wk for 104 wk 50, 50, 50 20, 24, 37	*Adrenal gland*, pheochromocytoma: 6/50 (12%)*, 5/48 (10%), 13/47 (28%)**	*P = 0.010 (trend), Cochran-Armitage test, but NS by life table analysis; **P = 0.045, Fisher exact test, but NS by life table analysis	Principal strengths: well-conducted study Principal limitations: MTD does not appear to have been achieved 12 controls and 10 low-dose animals were killed accidentally during wk 82 of the study; one low-dose animal was killed accidentally during wk 42 of the study
		Pancreas, islet cell adenoma or carcinoma (combined): 4/49 (8%)*, 1/47 (2%), 8/48 (17%)	*P = 0.025 (trend), Cochran-Armitage test, but NS by life table analysis	
		Skin, subcutaneous, fibroma: 0/50*, 1/48 (2%), 4/48 (8%)	*P = 0.024 (trend), Cochran-Armitage test, but NS by life table analysis	
Full carcinogenicity Rat, F344/N (F) 9 wk 104 wk NTP (1982)	Gavage Vinylidene chloride, 99% Corn oil 0, 1, 5 mg/kg bw, 1×/d, 5 d/wk for 104 wk 50, 50, 50 27, 28, 29	*Pituitary gland*, adenoma, NOS: 16/48 (33%)*, 20/49 (41%), 24/43 (56%)**	*P = 0.017 (trend), Cochran-Armitage test, but NS by life table analysis; **P = 0.026, Fisher exact test, but NS by life table analysis	Principal strengths: well-conducted study

bw, body weight; d, day(s); DMBA, 12-dimethylbenz[*a*]anthracene; F, female; GLP, good laboratory practice; M, male; mo, month(s); MTD, maximum tolerated dose; NOS, not otherwise specified; NR, not reported; NS, not significant; T_{90}, time to achieve 90% of the target concentration after the beginning of vapour generation; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; vs, versus; wk, week(s)

6 hours per day, 5 days per week for 1, 3, or 6 months, and maintained without treatment for a further 12-month observation period. Unexposed control groups consisted of 16–28 mice of each sex. There was a decrease in survival in exposed males and females. When control groups were pooled and exposed groups were pooled, the incidence of hepatocellular tumours was 10/60 (17%) in male controls and 4/28 (14%) in exposed males. Bronchioloalveolar tumours were observed in 8/60 (13%) male controls, 8/60 (13%) female controls, 4/28 (14%) exposed males, and 1/28 (3%) exposed females. One treated male had a haemangiosarcoma of the mesentery [a rare tumour] (Hong et al., 1981). [The Working Group considered that this study was inadequate for the evaluation because of the unsatisfactory study design (e.g. the use of only one dose, the small number of mice of each sex per exposure group, the short treatment periods, the poor survival, and the limited reporting).]

Two groups of 30 male and 30 female Swiss mice (age, 16 weeks) were exposed to vinylidene chloride (purity, 99.9%; 0.04% 1,2-dichloroethylene and 0.002% mono- and dichloroacetylene; stabilized with 200 ppm paramethoxyphenol) at concentrations of 10 or 25 ppm in air for 4 hours per day, 4–5 days per week, for 52 weeks and observed for their lifespan (up to 121 weeks) (Maltoni et al., 1984). A group of 100 mice of each sex (age, 16 weeks) not kept in inhalation chambers served as one group of controls (control A). Compared with control A mice, increased tumour incidences were seen for groups exposed at 10 and 25 ppm for: kidney adenocarcinoma in male mice (0/54, 0/24, 3/21 (14.3%) [$P = 0.02$, Fisher exact]); pulmonary adenoma in male mice (3/80 (3.7%), 11/28 (39.3%; $P < 0.05$, Fisher exact), 7/28 (25%; $P < 0.05$, Fisher exact)) and female mice (4/92 (4.3%), 3/30 (10%), 7/29 (24.1%; $P < 0.05$, Fisher exact)); and mammary tumours (mainly carcinomas) in female mice (2/98 (2%), 6/30 (20%; $P < 0.05$, Fisher exact), 4/30 (13.3%; $P < 0.05$, Fisher exact)). To increase the power of the study, additional groups of 120 Swiss mice of each sex (age, 9 weeks) were then exposed to vinylidene chloride at a concentration of 25 ppm for their lifespan (up to 121 weeks) and observed concurrently with separate control groups of 90 mice of each sex (age, 9 weeks) not kept in inhalation chambers (control B). Comparisons of tumour incidences between control B mice and the groups of mice exposed concurrently at 25 ppm showed increases in the incidences of tumours at several sites: kidney adenocarcinoma in male mice (0/66 vs 25/98 (25.5%) [$P < 0.0001$, Fisher exact test]); pulmonary adenoma in male mice (3/74 (4%) vs 16/113 (14.2%); $P < 0.05$, Fisher exact test) and female mice (3/86 (3.5%) vs 11/118 (9.3%); $P < 0.05$, Fisher exact); and mammary tumours (mainly carcinomas) in female mice (1/89 (0.1%) vs 12/118 (10.2%); $P < 0.05$, Fisher exact) (Maltoni et al., 1984). [The Working Group noted the short exposure duration and the lack of a concurrent chamber control group.]

In another study, groups of 50 male and 50 female B6C3F$_1$/N mice (age, 5–6 weeks) were exposed by whole-body inhalation to vinylidene chloride (purity, > 99.9%; stabilized with 300 ppm monomethyl ether hydroquinone) vapour at concentrations of 0 (control), 6.25, 12.5, or 25 ppm, for 6 hours plus T_{90} (time to achieve 90% of the target concentration after the beginning of vapour generation; 10 minutes) per day, 5 days per week for 105 weeks (NTP, 2015). The survival of male mice exposed to the low concentration was significantly greater than that of controls; the survival of males exposed to the high concentration and the survival of females exposed to the low and high concentrations were significantly lower than that of the controls. Mean body weights of males exposed to the medium and high concentrations and females exposed to the high concentration were at least 10% lower than those of controls during the study.

The incidences of renal tubule adenoma, renal tubule carcinoma, and renal tubule adenoma or carcinoma (combined) were significantly

increased in all exposed groups of male mice, with a significant positive trend in the incidence of these tumours. The incidences of renal tubule hyperplasia were also significantly increased in all exposed groups of males. The incidences of haemangioma of the vascular system in all exposed groups of females were non-significantly increased (0/50, 2/50, 2/50, 2/50) compared with controls. There was a significant positive trend (P = 0.044) in the incidence of haemangiosarcoma of the vascular system (4/50, 4/50, 4/50, 9/50) in females. Compared with controls, the incidence of haemangioma or haemangiosarcoma (combined) of the vascular system (4/50, 6/50, 6/50, 11/50) in females exposed to the high concentration was significantly greater, and a significant positive trend was observed. Compared with controls, the incidence of liver haemangiosarcoma (1/50, 1/50, 1/50, 6/50) in females exposed to the high concentration was significantly greater, and a significant positive trend was observed. The incidences of hepatocellular adenoma in females exposed to medium concentrations, of hepatocellular carcinoma in females exposed to high concentrations, and in hepatocellular adenoma or carcinoma (combined) in females exposed to medium and high concentrations were significantly greater than those in the control groups, with significant positive trends. In addition, hepato-cholangiocarcinoma occurred in all exposed groups of females (0/50, 1/50, 1/50, 2/50). In female B6C3F$_1$ mice, this neoplasm is very rare and has not been observed in 300 inhalation controls or 948 controls from all routes of exposure in studies conducted by the National Toxicology Program (NTP). [The Working Group considered that the occurrence of hepato-cholangiocarcinomas may have been related to treatment.] The incidences of hepato-cholangiocarcinoma in exposed groups of males were also non-significantly increased compared with that in the control group (1/50, 2/50, 2/50, 3/50) and exceeded the historical control range for inhalation studies (0–2%). In males, hepato-cholangiocarcinoma has been reported in 2/299 (0.7%) inhalation controls and in 10/949 (1.1%) controls from all routes of exposure. The incidence of bronchioloalveolar carcinoma was significantly increased in females exposed to medium concentrations with a significant positive trend. In females exposed to high doses, it was also reported that the incidence of carcinoma of the small intestine (ileum) (3/50, 6%) exceeded the historical control ranges for inhalation studies and all routes of administration. Historical rates for this tumour are 2/300 (range, 0–2%) for inhalation studies and 2/950 (range, 0–2%) for all routes of administration (NTP, 2015). [The Working Group noted that this was a well-conducted good laboratory practice (GLP) study, and both sexes were used.]

3.1.2 Oral administration

Groups of 50 male and 50 female B6C3F$_1$/N mice (age, 9 weeks) were given vinylidene chloride (purity, 99%; 0.15% *trans*-dichloroethylene and the stabilizer hydroquinone monomethyl ether [0.02%]) in corn oil by gavage at doses of 2 or 10 mg/kg bw once per day, 5 days a week for 104 weeks (NTP, 1982). Groups of 50 mice of either sex were given corn oil alone and served as vehicle controls. Compared with controls, the exposure to vinylidene chloride had no effect on survival in male and female mice. Mean body weights of the female mice given the high dose were comparable with those of controls; however, the mean body weights of male mice given either dose and of female mice given the low dose were slightly lower than those of controls. Significant increases in the incidence of tumours of the haematopoietic system [haematopoietic and lymphoid tissues] were observed in female mice given the low dose: these tumours were malignant lymphoma (2/48; 9/49, P = 0.012 by life table test, and P = 0.028 by Fisher exact test; 6/50) and lymphoma or leukaemia (combined) (7/48; 15/49, P = 0.037 by life table test, and P = 0.050

by Fisher exact test; 7/50). [The Working Group noted the absence of compound-related effects on survival or clinical signs, which suggests that the maximum tolerated dose (MTD) was not reached.]

3.1.3 Subcutaneous injection

A group of 30 female Ha:ICR Swiss mice (age, 6–8 weeks) received subcutaneous injections of 2.0 mg vinylidene chloride [purity unspecified] (Aldrich Chemical Co.) in 0.05 mL trioctanoin into the left flank once per week for 548 days [78 weeks] (Van Duuren et al., 1979). A group of 30 mice received similar treatment with trioctanoin (vehicle control) only. An additional group of 100 mice served as untreated controls. No local sarcomas were observed in the controls or mice treated with vinylidene chloride. [The Working Group noted some limitations of the study, including the use of only one dose, a lack of body weight data, and the fact that only tissues from the injection site and the liver were examined histologically.]

3.1.4 Skin application

Van Duuren et al. (1979) also tested vinylidene chloride on mouse skin. Two groups of 30 female Ha:ICR Swiss mice (age, 6–8 weeks) were treated three times per week for 440–594 days [not further reported] with skin applications of 40.0 or 121.0 mg vinylidene chloride [purity unspecified] (Aldrich Chemical Co.) in 0.2 mL acetone on the dorsal skin. Controls received no treatment (n = 100) or treatment with acetone only (n = 30). No skin papillomas were observed in the controls or mice treated with vinylidene chloride. [The Working Group noted some limitations of the study, including the lack of body weight data and the uncertain dose due to the volatility of vinylidene chloride.]

3.1.5 Initiation–promotion

Vinylidene chloride was tested for its initiating activity in a two-stage mouse-skin assay (Van Duuren et al., 1979). A group of 30 female Ha:ICR Swiss mice (age, 6–8 weeks) received a single skin application of 121.0 mg vinylidene chloride [purity unspecified] (Aldrich Chemical Co.) in 0.2 mL acetone on the dorsal skin, followed 14 days later by applications of 5 µg 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in 0.2 mL acetone three times per week for 428–576 days [not further reported]. Four other groups of mice received no treatment (n = 100), treatment with acetone only (n = 30), treatment with TPA only (n = 90), or treatment with 20 µg 7,12-dimethylbenz[*a*]anthracene (DMBA) plus TPA (n = 30), and served as untreated, vehicle, TPA-treated, or positive controls, respectively. Complete necropsies were performed at termination of the study or at death, and all abnormal-appearing tissues and organs were examined histologically. Routine sections of certain tissues and organs were examined [not further specified]. In the 90 TPA-only control mice, seven skin papillomas were observed in six mice; two mice had skin squamous cell carcinomas. In the vinylidene chloride plus TPA group of 30 mice, nine skin papillomas were observed in eight mice (P < 0.005 versus TPA controls); one mouse had a skin squamous cell carcinoma. No skin papilloma or carcinoma was observed in the untreated or acetone controls. In the positive control group (DMBA+TPA), 317 skin papillomas developed in 29 mice (P < 0.0005 vs TPA controls); 18 mice had skin squamous cell carcinomas. [The Working Group noted some limitations of the study, including the use of only one dose, a lack of body weight data, and the uncertain dose due to the volatility of vinylidene chloride.]

3.2 Rat

3.2.1 Inhalation

In an exposure experiment in utero, groups of 60 or 54 pregnant female Sprague-Dawley breeder rats (age, 13 weeks) were exposed by whole-body inhalation to 0 (controls) or 100 ppm vinylidene chloride (purity, > 99.9%; 1,2-dichloroethylene, 0.40 g/kg; mono- and dichloroethylene, 0.02 g/kg; stabilized with 200 ppm paramethoxyphenol) for 4 hours per day, 5 days per week for 7 weeks, then for 7 hours per day, 5 days per week for 97 weeks, and then kept under observation until spontaneous death. Concurrently, groups of 62 male and 61 female offspring were exposed transplacentally beginning at day 12 of gestation, and by whole-body inhalation postnatally with the same regimen as the breeders described above. Along with 158 male and 149 female rats serving as unexposed controls, all were kept under observation until spontaneous death. Exposure to vinylidene chloride did not affect survival, but caused a slight decrease in body weights in all exposed groups. In breeders, vinylidene chloride caused non-significant increases in the incidences of benign and malignant tumours of the mammary gland and malignant tumours of the mammary gland. Compared with controls, an increased incidence of leukaemia was found in exposed male (control, 12/158, 7.6%; exposed, 10/62, 16.1% [not significant]) and female (control, 1/149, 0.7%; exposed, 4/61, 6.5% [$P < 0.03$]) offspring (Cotti et al., 1988). [The Working Group noted the unsatisfactory study design with limited reporting, the use of only one dose, and the lack of detailed information on survival or observed tumours.]

Lee et al. (1977, 1978) exposed two groups of 36 male and 36 female CD rats (age, 2 months) to vinylidene chloride (purity, 99% pure) in air at 0 (controls) or 55 ppm for 6 hours per day, 5 days per week for up to 12 months (with interim terminations of 4 rats after 1, 2, 3, 6, and 9 months), at which time the experiment was terminated. Of the 36 exposed male rats, 2 developed haemangiosarcomas [not significant], 1 in a mesenteric lymph node and 1 in the subcutaneous tissue. No haemangiosarcomas were observed in 35 male controls. There was no treatment-related increase in tumour incidence in females. [The Working Group concluded this was an inadequate study for the evaluation because of the unsatisfactory study design, use of only one dose, short durations of exposure, and limited reporting.]

Groups of male and female CD rats (age, 2 months) were exposed to 55 ppm vinylidene chloride (purity, 99%) in air for 6 hours per day, 5 days per week, for 6 months (20 males and 20 females) or 10 months (14 males and 16 females). After treatment, all exposed groups were maintained without further exposure for 12 months, at which time the remaining rats were killed. Corresponding control groups of 20 and 16 rats (a total of 36 control rats per sex) were maintained on filtered air for the same treatment periods and then maintained for a further 12-month period. There was a decrease in survival in exposed males. A single hepatic haemangiosarcoma was observed in a male rat that had been exposed to vinylidene chloride for 6 months (Hong et al., 1981). [The Working Group concluded this was an inadequate study for the evaluation because of the unsatisfactory study design (e.g. the use of only one dose, the small number of rats of each sex per exposure group, and the short duration of exposure) and the limited reporting.]

Maltoni et al. (1984) exposed groups of 30 male and 30 female Sprague-Dawley rats (age, 16 weeks) to vinylidene chloride (purity, 99.9%; 0.04% 1,2-dichloroethylene and 0.002% mono- and dichloroacetylene; stabilized with 200 ppm paramethoxyphenol) at 10, 25, 50, or 100 ppm for 4 hours per day, 4–5 days per week for 52 weeks, followed by observation for lifetime (up to 137 weeks). An additional group of 60 rats of each sex was initially exposed at 200 ppm for 2 days,

then 150 ppm for 4 hours per day, 4–5 days per week for 52 weeks, followed by observation for lifetime; the dosing frequency was reduced periodically to four times per week due to toxicity. Groups of 100 rats of each sex (age, 16 weeks) not kept in inhalation chambers were used as controls. The pattern of neoplasms and their incidences were comparable among treated and control rats. [The Working Group noted the poor reporting of survival and body weight information for treated and control rats, as well as the short duration of exposure.]

Groups of 85–86 male and 84–86 female Sprague-Dawley rats (age, 6–7 weeks) were exposed to vinylidene chloride (purity, 99%; stabilized with hydroquinone monomethyl ether) at 0 (control), 10, or 40 ppm for 6 hours per day, 5 days per week for 1 month. Exposure was then increased to 25 or 75 ppm vinylidene chloride for 17 months because of the lack of treatment-related effects at 10 and 40 ppm after 1 month of treatment. Surviving rats were held for an additional 6 months. There were no treatment-related effects on body weight gain or survival, except for a significant increase in mortality among females exposed at 75 ppm during months 14–24 of the study. Compared with controls, vinylidene chloride caused a [non-significant] increase in the incidence of mammary gland adenocarcinoma in the females exposed at low concentrations (2/84; 7/86, $P < 0.05$, Fisher exact test [$P = 0.0898$, 1-tail Fisher exact test]; 4/84). There was no significant increase in the incidence of any tumours in males (Quast et al., 1986). [The Working Group noted some limitations of the study, including the short duration of exposure, incorrect statistics, and poor survival in females exposed at high concentrations.]

In another study (NTP, 2015), groups of 50 male and 50 female F344/N rats (age, 5–6 weeks) were exposed by whole-body inhalation to vinylidene chloride (purity, > 99.9%; stabilized with 300 ppm monomethyl ether hydroquinone) vapour at concentrations of 0 (control), 25, 50, or 100 ppm for 6 hours plus T_{90} (10 minutes) per day, 5 days per week for 105 weeks. The survival of exposed groups of males was similar to that of controls. The survival of females exposed at 100 ppm was significantly less than that of controls. Mean body weights of exposed groups of male and female rats were similar to those of controls throughout the study. In male rats, the incidences of malignant mesothelioma (mainly from the tunica vaginalis, then pleura, pericardium, and peritoneum) occurred with a significant positive trend and were significantly increased in all exposed groups compared with the control group. A significant positive trend in the incidence of adenoma of the nasal respiratory epithelium was observed in male rats (0/49, 0/50, 1/50, 4/50); no nasal respiratory epithelium adenomas have been seen in male historical controls. The incidence of adenoma of the nasal respiratory epithelium in females exposed to the high concentration (1/50, 2%) also exceeded the historical control range for inhalation studies (0/200; all routes, 1/697, 0–2%). Significantly increased incidences, with significant positive trends, were seen for C-cell adenoma of the thyroid gland in females exposed to the high concentration, and for C-cell adenoma or carcinoma (combined) of the thyroid gland in females exposed to low and high concentrations. Significantly increased incidence was seen for C-cell carcinoma of the thyroid gland in females exposed to the low concentration. The incidence of mononuclear cell leukaemia was significantly increased in females exposed to the high concentration, with a significant positive trend. Renal tubule carcinomas were observed in four males exposed to vinylidene chloride (0/50, 2/50, 1/49, 1/50); these neoplasms are rare in male F344/N rats (historical incidence: inhalation studies, 0/200; all routes, 1/697). Rare malignant mesotheliomas occurred in one female exposed to the low concentration (pleura and pericardium) and one female exposed to the medium concentration (peritoneum) (historical incidence:

inhalation studies, 0/200; all routes, 0/700) (NTP, 2015). [The Working Group noted that this was a well-conducted GLP study, and that both sexes were used.]

3.2.2 Oral administration

A group of 24 female BD IV rats [age unspecified] were given a single dose of 150 mg/kg bw vinylidene chloride (purity, 99%; containing 0.03% 4-methoxyphenol) in olive oil by gavage on day 17 of gestation. Their progeny (89 males and 90 females) were given doses of 50 mg/kg bw vinylidene chloride in 0.3 mL olive oil once per week for life, beginning at weaning. A vehicle-control group of 14 dams were given 0.3 mL olive oil on day 17 of gestation, and their progeny (53 males and 53 females) were given 0.3 mL olive oil once per week for life, beginning at weaning. All survivors were killed at 120 weeks or when moribund. Litter sizes, pre-weaning mortality, survival rates, and body weight gain were similar between the group treated with vinylidene chloride and the vehicle-control group. No statistically significant increase in the incidence of any tumours was noted in exposed male or female offspring or in exposed dams (Ponomarkov & Tomatis, 1980). [The Working Group noted the use of only one dose.]

The NTP (1982) exposed groups of 50 male and 50 female Fischer 344/N rats (age, 9 weeks) to vinylidene chloride (purity, 99%; 0.15% *trans*-dichloroethylene and the stabilizer, hydroquinone monomethyl ether [0.02%]) at doses of 0 (control), 1, or 5 mg/kg bw in corn oil by gavage once a day, 5 days per week for 104 weeks. Survival and body weight throughout the study were similar in all treated and control groups. Twelve control male rats and 10 male rats exposed to the low dose were killed accidentally during week 82 of the study, and one male exposed to the low dose was killed accidentally during week 42. [The absence of compound-related effects on survival or clinical signs suggests that the rats could have tolerated higher doses.] No significant increase in tumour incidence was observed in male and female rats treated with vinylidene chloride in this study. [The Working Group noted that the ability of this study to assess the carcinogenicity of vinylidene chloride was limited by the accidental deaths of the control rats and male rats exposed to the low dose, and by not achieving the MTD.]

Maltoni et al. (1984) exposed groups of 50 male and 50 female Sprague-Dawley rats (age, 9–10 weeks) to vinylidene chloride (purity, 99.9%; 0.04% 1,2-dichloroethylene and 0.002% mono- and dichloroacetylene; stabilized with 200 ppm paramethoxyphenol) at 0.5, 5, 10, or 20 mg/kg bw in olive oil by gavage once per day for 4–5 days per week for 52 weeks, followed by observation for their lifespan (up to 147 weeks). A group of 82 males and 77 females served as vehicle controls for the group exposed to the lowest dose, and a separate group of 100 rats of each sex served as vehicle controls for the remaining exposed groups. The pattern and incidences of tumours observed in this study were comparable among treated and control rats. [The Working Group noted the poor reporting on survival and body weight information for treated and control rats, and the short duration of exposure.]

Groups of 47–48 male and 48 female Sprague-Dawley rats (age, 6–7 weeks) were given vinylidene chloride (purity, ≥ 99.5%; with 1–5 mg/L hydroquinone monomethyl ether) at 50, 100, or 200 mg/L in drinking-water ad libitum for 2 years. A group of 80 male and 80 female controls received drinking-water only. Mortality and body weight gain were similar in the treated and control groups; no statistically significant increase in tumour incidence was reported in treated rats (Quast et al., 1983). [The Working Group noted that the stability of drinking-water solutions was not determined. The MTD does not appear to have been achieved.]

3.3 Hamster

3.3.1 Inhalation

Groups of 30 male and 30 female Chinese hamsters (age, 29 weeks) were exposed to vinylidene chloride (purity, 99.9%; with 0.04% 1,2-dichloroethylene and 0.002% mono- and dichloroacetylene; stabilized with 200 ppm para-methoxyphenol) at 25 ppm in air for 4 hours per day, 4–5 days per week for 52 weeks, and observed for their lifetime (up to 164 weeks). A group of 18 males and 17 females, not housed in inhalation chambers, were used as controls. The pattern of neoplasms and their incidences were comparable among treated and control hamsters (Maltoni et al., 1984). [The Working Group noted the use of only one dose, the short duration of exposure, and the small number of controls, making this study inadequate for evaluating the carcinogenicity of vinylidene chloride.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

The toxicokinetics of vinylidene chloride have been reviewed by several groups over the past 30 years, including *IARC Monographs* Working Groups in 1985 and 1998 (IARC, 1986, 1999). Several major vinylidene chloride review documents (EPA, 2002; WHO, 2003; ATSDR, 2009; Health Canada, 2015) have been published since 1999.

4.1.1 Absorption

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Rodents

Vinylidene chloride is well absorbed from the lungs and gastrointestinal (GI) tract as it is a small, uncharged, lipophilic molecule. The lungs are an optimal site for absorption of the volatile organic chemical (VOC), due to their large surface area, high blood perfusion rate, and intimate alveolar–capillary interfaces (Bruckner et al., 2013). Arterial blood levels rapidly reach and remain at near steady-state for the duration of inhalation exposures of rats. Percentage systemic uptake of a series of vapour concentrations in rats was as high as 80% (Dallas et al., 1983). Equivalent vapour exposures should result in higher systemic doses of VOCs in rodents than in humans because of the higher alveolar ventilation rate, blood:air partition coefficient, cardiac output, and metabolic rate of rodents (NAS, 2009). Vinylidene chloride is also well absorbed from the GI tract (Putcha et al., 1986), but the administration of equivalent oral and inhaled doses to rats results in significantly higher arterial blood levels and nephrotoxicity in animals inhaling the chemical (Bruckner et al., 2010). Fatty foods retard its GI absorption, and the VOC is subject to extensive first-past hepatic and pulmonary elimination as it is extensively metabolized and volatile (Bruckner et al, 2010, 2013).

4.1.2 Distribution and excretion

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Rat

Vinylidene chloride was rapidly distributed to all tissues examined following a single oral dose of the [^{14}C]-labelled compound to rat. The highest levels of radioactivity were found in the liver and kidneys 30 minutes after dosing (Jones

& Hathway, 1978a). Preferential distribution to the liver, kidneys, and lungs was seen in rats following inhalation of vinylidene chloride at 10 or 200 ppm (McKenna et al., 1978).

Vinylidene chloride is rapidly eliminated by rats. Putcha et al. (1986) reported the half-life of vinylidene chloride in rats to be up to 60 minutes. Metabolic clearance is primarily responsible for systemic elimination. Metabolic saturation was manifest at an oral dose of 50 mg/kg bw by reduction in exhaled carbon dioxide and urinary metabolites, and increased vinylidene chloride exhalation (Jones & Hathway, 1978b).

4.1.3 Metabolism

(a) Humans

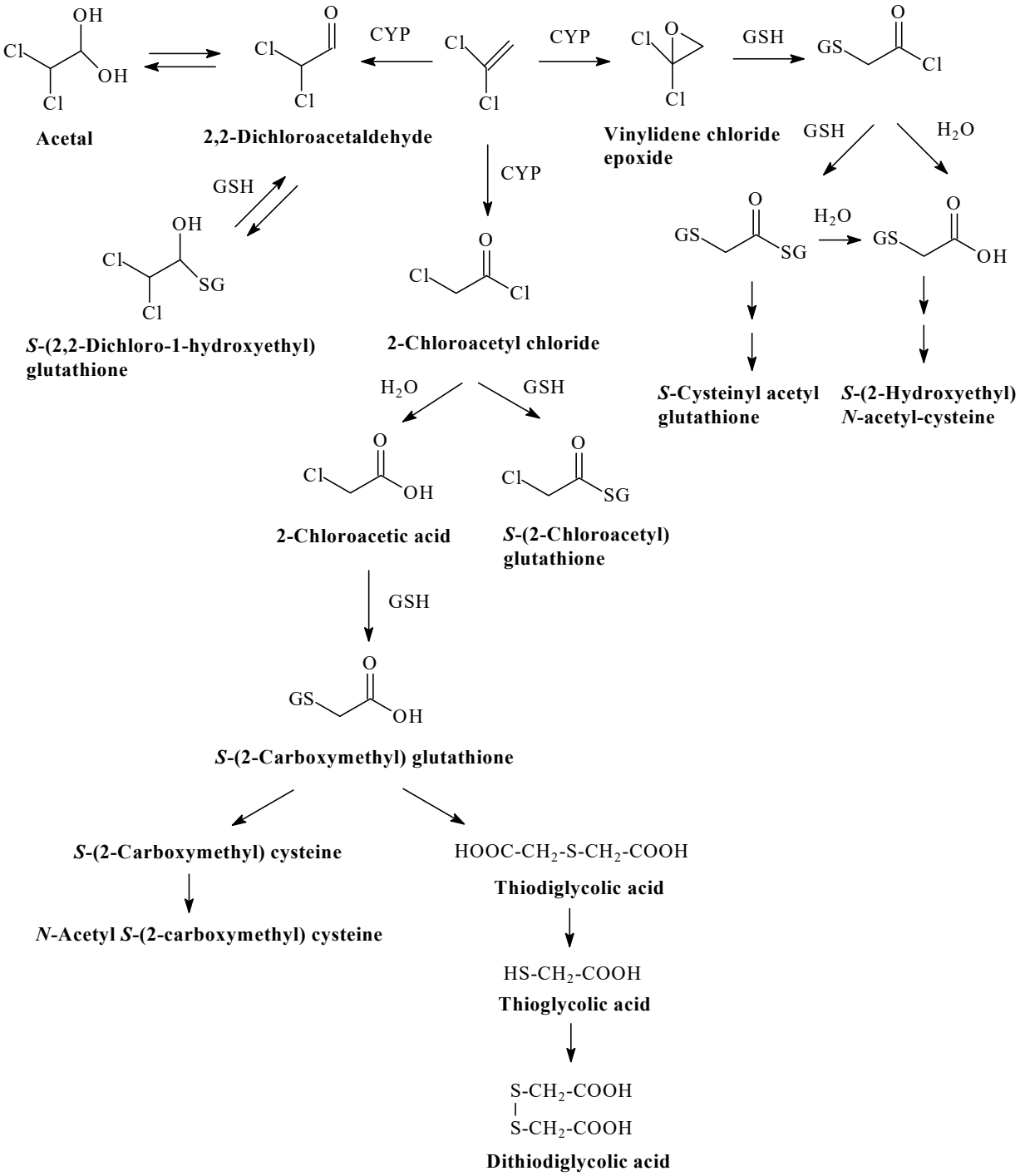
Cytochrome P450 (CYP) 2E1 is the predominant enzyme in liver (Hakkola et al., 1994), lung, and kidney responsible for the oxidation of vinylidene chloride. The formation of vinylidene chloride epoxide and 2,2-dichloroacetaldehyde was demonstrated in human lung and liver microsomes (Dowsley et al., 1999). Human lung has low and variable levels of CYP2E1 activity (Shimada et al., 1996), primarily because of the rarity of Clara cells (Forkert, 2001). CYP2E1 activity was low or not detectable in human kidney microsomal samples (Amet et al., 1997; Caro & Cederbaum, 2004; Sasso et al., 2013).

(b) Experimental systems

Vinylidene chloride is metabolized largely by CYP-catalysed oxidation in rat and mouse liver as illustrated in Fig. 4.1 (NTP, 2015). CYP2E1 is primarily responsible for the oxidative metabolism and metabolic activation of vinylidene chloride in rodents. The enzyme inducers enhance both the metabolic activation of vinylidene chloride and cytotoxicity, while certain inhibitors decrease its biotransformation and toxicity as described in Section 4.5.2. Vinylidene chloride is metabolized by CYP2E1 in rodents to at least three reactive metabolites, including vinylidene chloride epoxide, 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde (Forkert, 2001; Forkert et al., 2001). These products undergo glutathione (GSH) conjugation and/or hydrolysis. Relatively high levels of CYP2E1 are present in three primary target organs of vinylidene chloride in rodents: liver, kidney, and lung. The epoxide, an electrophilic intermediate, is an important cytotoxic metabolite of vinylidene chloride (Forkert, 2001; Forkert et al., 2001; Simmonds et al., 2004); it binds covalently to proteins and nucleic acids, and can damage hepatocytes (Jones & Liebler, 2000) and renal tubular cells (Brittebo et al., 1993).

Variance in the expression of CYP2E1 is an important factor in tissue, species, and sex susceptibility to vinylidene chloride. Levels of GSH and epoxide hydrolase are also important determinants of the extent of injury. For example, human kidney has very low or non-detectable renal CYP2E1 activity. The rate of formation of vinylidene chloride epoxide and 2,2-dichloroacetaldehyde was much lower in human lung and liver microsomes compared with that of mouse. Vinylidene chloride cytotoxicity and covalent binding are greatest in murine cells with the highest CYP2E1 content, namely centrilobular hepatocytes, followed by bronchiolar Clara cells and renal proximal tubular cells (Speerschneider & Dekant, 1995; Forkert, 2001). Biotransformation of vinylidene chloride, and presumably its metabolic activation, is about six times higher in liver microsomes from mice compared with those from rats (Dowsley et al., 1995). Sex difference in CYP2E1-mediated metabolism of vinylidene chloride correlates with the occurrence of renal tumours induced by vinylidene chloride (Speerschneider & Dekant, 1995). Metabolism of vinylidene chloride by kidney microsomes from male mice was six times greater than that by females. The rank order (adult female > weanling male = weanling female > adult male) of CYP2E1-catalysed metabolic activation of vinylidene chloride in mouse

Fig. 4.1 Proposed metabolic pathway of vinylidene chloride in rodents



CYP, cytochrome P450; GSH, glutathione
Adapted from NTP (2015)

lung microsomes (Lee & Forkert, 1995; Forkert et al., 1996a) correlates with the severity of injury of mouse bronchiolar Clara cells (Forkert et al., 1996a). Simmonds et al. (2004) subsequently demonstrated that CYP2F2, as well as CYP2E1, was capable of bioactivation of vinylidene chloride in murine lung. Expression of CYP2F in the lung is much higher in mice than in humans (Chen et al., 2002).

GSH plays an important role in the metabolism of vinylidene chloride (Fig. 4.1). This is consistent with the observation that exposure to vinylidene chloride depletes liver GSH levels (Jaeger et al., 1974; Reichert et al., 1978; Reynolds et al., 1980). GSH depletion by fasting or xenobiotics permits reactive oxidative metabolites, such as vinylidene chloride epoxide, 2-chloroacetyl chloride, and 2,2-dichloroacetyl chloride, to bind to and alkylate cellular macromolecules instead of being detoxified (Jaeger et al., 1974; Reynolds et al., 1980; Kanz et al., 1988). GSH conjugates formed in the liver can also reach target cells in the kidney, where they undergo metabolic activation by β-lyase to reactive, cytotoxic thiols (Ban et al., 1995). Pretreatment with aminooxyacetic acid, an inhibitor of cysteine conjugate β-lyase, decreased the number of damaged tubules in the kidneys of mice given a single oral dose of vinylidene chloride at 200 mg/kg bw (Ban et al., 1995). Aminooxyacetic acid pretreatment also protected rats exposed to vinylidene chloride vapour at 150–180 ppm for 4 hours from liver and kidney injury (Cavelier et al., 1996). [The Working Group noted that the metabolism of vinylidene chloride is similar to that of other vinyl halides such as vinyl chloride.]

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

Metabolic transformation of vinylidene chloride in the liver produces a highly reactive and short-lived epoxide, along with other reactive metabolites.

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Mammalian systems in vivo

See Table 4.1.

No evidence of genotoxicity was seen with vinylidene chloride in vivo. Bone marrow micronucleus tests (24 hours after treatment) in ddY male mice following a single exposure (25–200 mg/kg bw) or multiple exposures (25–100 mg/kg bw per day for 4 days) to vinylidene chloride by gavage were negative (Sawada et al., 1987). In a transplacental exposure study in pregnant ICR mice given vinylidene chloride at 25–100 mg/kg bw by a single intraperitoneal injection on gestational day 18, no increases in micronucleated cells in fetal liver and blood cells were seen 24 hours after treatment (Sawada et al., 1987). [The Working Group noted that these studies assessed micronuclei in 1000 binucleated lymphocytes, whereas 2000 are recommended (OECD, 2016).] Similarly, no increases in the frequencies of micronucleated erythrocytes were observed in the peripheral blood of male or female B6C3F$_1$/N mice exposed to 100 ppm vinylidene chloride for 3 months by inhalation (NTP, 2015). Negative results were also reported in dominant lethal tests (assays for mutagenicity in germ cells) in male CD-1 mice exposed to vinylidene chloride by inhalation at 10–50 ppm for 6 hours per day for 5 days, followed by mating (Anderson et al., 1977), and in male Crl:CD(SD) rats exposed to vinylidene chloride by inhalation at 55 ppm for 6 hours per

Table 4.1 Genetic and related effects of vinylidene chloride and its metabolite 2,2-dichloroacetaldehyde in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Reference
Vinylidene chloride						
Dominant lethal test	Mouse, CD-1 (M)	Sperm	–	50 ppm	Inhalation, 6 h/d for 5 d	Anderson et al. (1977)
Dominant lethal test	Rat, Crl:CD(SD) (M)	Sperm	–	55 ppm	Inhalation, 6 h/d, 5 d/wk for 11 wk	Short et al. (1977)
DNA alkylation, DNA repair	Mouse, CD-1 (M); rat, Sprague-Dawley (M)	Liver and kidney	–	50 ppm	Inhalation, 6 h	Reitz et al. (1980)
Micronuclei	Mouse, ddY (M)	Bone marrow	–	25–200 mg/kg bw (1×) or 25–100 mg/kg bw (4×)	Gavage, sampling after 24 h	Sawada et al. (1987)
Micronuclei	Mouse, ICR (F)	Fetal liver/ blood (transplacental MN test)	–	25–100 mg/kg bw	Intraperitoneal injection (in pregnant mice), 1×; sampling after 24 h	Sawada et al. (1987)
Micronuclei	Mouse, B6C3F_1/N (M, F)	Peripheral blood erythrocytes	–	100 ppm	Inhalation, 5 d/wk for 3 mo	NTP (2015)
2,2-Dichloroacetaldehyde						
DNA strand breaks (alkaline unwinding assay)	Mouse, B6C3F_1 (M); rat, F344 (M)	Liver	–	Mouse, 5 mmol/kg bw [565 mg/kg]; rat, 10 mmol/kg bw [1130 mg/kg]	Oral, single dose, 4 h duration	Chang et al. (1992)

bw, body weight; d, day(s); F, female; h, hour(s); HID, highest ineffective dose; LED, lowest effective dose; M, male; MN, micronuclei; mo, month(s); ppm, parts per million; wk, week(s)

[a] –, negative

day, 5 days per week for 11 weeks before mating (Short et al., 1977).

Alkylated DNA was recovered from the livers and kidneys of CD-1 mice and Sprague-Dawley rats exposed by inhalation to radiolabelled vinylidene chloride (10 or 50 ppm for 6 hours). However, compared with animals exposed to intraperitoneal injection of dimethylnitrosamine, few alkylated nucleotides were recovered and DNA repair synthesis was only modestly elevated (to 6% of the level induced by dimethylnitrosamine) (Reitz et al., 1980). [The Working Group noted the low specific activity of the test article, limiting the sensitivity of the assay.]

(ii) Mammalian systems in vitro

See Table 4.2.

Inconsistent mutagenic responses were seen in L5178Y mouse lymphoma cells with vinylidene chloride in the absence of metabolic activation; with activation, both cytotoxicity and mutagenicity were consistently positive in repeat experiments (McGregor et al., 1991).

Vinylidene chloride (2 and 10% in air) did not induce 8-azaguanine and ouabain resistance in Chinese hamster V79 cells in the presence of S15 (15 000 *g* liver supernatant) from phenobarbital-treated rats and mice; although exposures were conducted within a closed environment to control for volatility, no mutagenic activity was reported in this assay with either species with or without S15 (Drevon & Kuroki, 1979).

Strong, dose-related increases in chromosomal aberrations were seen in cultured Chinese hamster lung cells exposed to vinylidene chloride in tightly sealed bottles over a concentration range of 0.125–1.5 mg/mL in the presence of S9 from Kanechlor 400-induced male F344 rat liver. In addition, sister-chromatid exchanges were increased in the presence of S9 at 0.075 mg/mL (Sawada et al., 1987).

Vinylidene chloride (exposure period, 2.5 hours) induced unscheduled DNA synthesis in isolated rat hepatocytes using a method that does not require the blocking of semi-conservative DNA synthesis (Costa & Ivanetich, 1984). [The Working Group noted the sparse experimental details.]

(iii) Non-mammalian systems

See Table 4.3.

Vinylidene chloride did not induce increases in sex-linked recessive lethal mutations in germ cells of adult male *Drosophila melanogaster* exposed via feeding or injection (Foureman et al., 1994).

In bacterial test systems, vinylidene chloride consistently demonstrated mutagenic activity when tested in the presence of a metabolic activation system, in a closed environment to control for volatility (Jacobson-Kram, 1986). Vinylidene chloride (0.2, 2, and 20% in air (v/v) in a closed environment) was mutagenic in *Salmonella typhimurium* strains TA100 and TA1530 in the presence of non-induced rat or mouse liver S9. Mutagenicity was higher in the presence of mouse S9, but lower when mouse kidney or lung S9 fractions were used (Bartsch et al., 1975). Phenobarbital induction increased mutagenic responses in tests using mouse liver, kidney, and lung S9 (Bartsch et al., 1975). Similarly, vinylidene chloride is mutagenic in strains TA100 and TA1535 (Baden et al., 1978, 1982), in which pretreatment with CYP inducers increased the effectiveness of mouse liver and kidney S9, with mouse liver S9 also being more effective than rat liver S9 (Jones & Hathway, 1978c).Vinylidene chloride (2.5 mM) also induced a mutagenic response in *Escherichia coli* K-12 in the presence, but not the absence, of mouse S9 (Greim et al., 1975). Positive results were also observed in *S. typhimurium* strains TA92, TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 *uvrA* in the presence of human S9 or Swiss mouse liver S9 (uninduced or induced by vinylidene chloride) (Oesch et al., 1983). In the absence of S9, comparable and low responses were observed in

Table 4.2 Genetic and related effects of vinylidene chloride and its metabolite 2,2-dichloroacetaldehyde in mammalian cells in vitro

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Vinylidene chloride						
Gene mutation	Chinese hamster, fibroblast V79 cells	–	–	10% (v/v) in air	Exposures carried out in a desiccator	Drevon & Kuroki (1979)
Unscheduled DNA synthesis	Rat, Long Evans, hepatocytes	+	NT	2.1 mM [203 µg/mL]	Sparse experimental details; unclear reporting of results	Costa & Ivanetich (1984)
Chromosomal aberrations, sister-chromatid exchange	Chinese hamster, lung	–	+	0.125–1.5 mg/mL (CA); 0.075 mg/mL (SCE)	Sealed bottles to control for volatility	Sawada et al. (1987)
Gene mutation	Mouse, L5178Y lymphoma cells	+/–	+	0.16% (v/v) in air		McGregor et al. (1991)
2,2-Dichloroacetaldehyde						
DNA strand breaks, alkaline unwinding assay	Human, CCRF-CEM, lymphoblastic leukaemia cell line	+	NT	1 mM [113 µg/mL]		Chang et al. (1992)
DNA strand breaks, alkaline unwinding assay	Rat, Fischer F334, primary hepatocytes	–	NT	10 mM [1130 µg/mL]	Cells treated for 4 h	Chang et al. (1992)

CA, chromosomal aberration; h, hour(s); HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested; SCE, sister-chromatid exchange; v/v, volume per volume

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study)

Table 4.3 Genetic and related effects of vinylidene chloride and its metabolite 2,2-dichloroacetaldehyde in non-mammalian systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Vinylidene chloride						
Salmonella typhimurium TA100, TA1530	Reverse mutation	NT	+	0.2, 2, 20% (v/v) in air	S9 from uninduced BDVI female rat, and uninduced and PB-induced male OF-1 mouse liver, kidney, or lung	Bartsch et al. (1975)
Escherichia coli K-12	Reverse mutation	–	+	2.5 mM [242 µg/mL]	3 reverse mutation targets were tested: arg+, gal+, nad+; only the arg+ system produced a positive response	Greim et al. (1975)
Salmonella typhimurium TA100, TA1535	Reverse mutation	NT	+	3%		Baden et al. (1978)
Salmonella typhimurium TA100, TA1535	Reverse mutation	NT	+	5% (v/v) in air	Tested as a vapour in a closed system	Jones & Hathway (1978c)
Saccharomyces cerevisiae D7	Gene conversion	–	+	20 mM [1939 µg/mL]		Bronzetti et al. (1981)
Saccharomyces cerevisiae D7, host-mediated assay	Reverse mutation and gene conversion, host-mediated assay	+	NA	400 mg/kg bw, single oral dose; 100 mg/kg bw/d for 5 d/wk, total of 23 dosings		Bronzetti et al. (1981)
Salmonella typhimurium TA100, TA1535	Reverse mutation	(+)	+	3%	Few experimental details	Baden et al. (1982)
Salmonella typhimurium TA92, TA98, TA100, TA1535, TA1537; *E. coli* WP2 *uvrA*	Reverse mutation	–	+	375 ppm	In TA100, various species (mouse, rat, hamster, human) and tissue (kidney, liver) sources of S9 examined	Oesch et al. (1983)
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation	–	–	6666 µg/plate	No controls for volatility	Mortelmans et al. (1986)
Saccharomyces cerevisiae D7	Gene conversion	–	+	50.3 µM [4876 µg/mL]	S9 from Aroclor 1254-induced male mice	Koch et al. (1988)
Saccharomyces cerevisiae D7	Reverse mutation	–	+	25.1 mM [2433 µg/mL]	S9 from Aroclor 1254-induced male mice	Koch et al. (1988)
Saccharomyces cerevisiae D61.M	Aneuploidy	+	+	25.1 mM [2433 µg/mL]		Koch et al. (1988)

Table 4.3 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Drosophila melanogaster Canton-S	Sex-linked recessive lethal mutations	–	NA	25 000 ppm (feeding); 5000 ppm (injection)		Foureman et al. (1994)
Salmonella typhimurium RSJ100, TPT100	Reverse mutation	(+)	NT	500 ppm		Granville et al. (2005)
2,2-Dichloroacetaldehyde						
Salmonella typhimurium TA100, TA1535	Reverse mutation	+ (TA100)	+ (TA100)	10 µL/plate	Controlled for volatility	Bignami et al. (1980)
Streptomyces coelicolor A3	Reverse mutation	+	NT	10 µL/plate	Controlled for volatility	Bignami et al. (1980)
Aspergillus nidulans Haploid strain 35	Forward mutation	+	NT	10 µL/plate		Bignami et al. (1980)
Aspergillus nidulans diploid strain 35 × 17	Chromosomal damage	+	NT	10 mM [1130 µg/mL]	+, mitotic non-disjunction and haploidization; –, mitotic crossing-over	Crebelli et al. (1984)

bw, body weight; d, day; HIC, highest ineffective concentration; LEC, lowest effective concentration; NA, not applicable; NT, not tested; PB, phenobarbital; ppm, parts per million; v/v, volume per volume; wk, week

[a] +, positive; –, negative; (–), negative in a study of limited quality

S. typhimurium strains that express rat *GSTT1–1* (strain RSJ100) or contain an unexpressed rat *GSTT1–1* gene (strain TPT100), indicating a lack of activation of vinylidene chloride by rat GSTT1–1 (Granville et al., 2005). Vinylidene chloride (tested at up to 6666 µg/plate) was not mutagenic in strains TA98, TA100, TA1535, or TA1537, with or without induced S9, when a preincubation protocol was used (Mortelmans et al., 1986), illustrating the importance of controlling for volatility.

Vinylidene chloride was toxic but not mutagenic in the diploid yeast *Saccharomyces cerevisiae* strain D7 in the absence of exogenous metabolic activation. However, in the presence of Aroclor-1254-induced liver S10 (10 000 *g* supernatant) from male Swiss albino CD mice, dose-related increases in both point mutations and mitotic gene conversions were observed (Bronzetti et al., 1981). Vinylidene chloride also induced significant increases in both point mutations and mitotic gene conversion in logarithmic phase *S. cerevisiae* D7 cells with a high level of CYP (Koch et al., 1988), and vinylidene chloride induced a highly significant, dose-related increase in aneuploidy in *S. cerevisiae* D7 strain D61.M, with and without S9 mix (Koch et al., 1988).

Point mutations and mitotic gene conversion were seen in *S. cerevisiae* D7 recovered from kidney and liver, but not lung, tissues in a host-mediated assay in male Swiss albino mice treated with vinylidene chloride (Bronzetti et al., 1981).

(iv) Metabolites

See Table 4.1, Table 4.2, and Table 4.3.

Vinylidene chloride is metabolized in isolated hepatocytes to several reactive metabolites (Costa & Ivanetich, 1984), including vinylidene chloride epoxide, 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde (NTP, 2015).

2,2-Dichloroacetaldehyde induced DNA strand breaks in cultured CCRF-CEM human lymphoblastic leukaemia cells in the absence of S9, but not in primary rat hepatocytes or in livers of rats and mice treated orally (Chang et al., 1992). Positive results were reported in *S. typhimurium* TA100 (but not TA1535) with and without induced rat liver S9; S9 markedly attenuated the response (Bignami et al., 1980). 2,2-Dichloroacetaldehyde was also mutagenic in assays for forward (streptomycin resistance) and reverse (histidine independence) mutation in the bacterium *Streptomyces coelicolor* in the absence of S9 (Bignami et al., 1980). In a haploid strain of the mould *Aspergillus nidulans*, methionine suppression, requiring multilocus point mutations, was induced by 2,2-dichloroacetaldehyde in the absence of S9, and 8-azaguanine resistance, which results from a single locus point mutation, was weakly positive (Bignami et al., 1980). Mitotic nondisjunction and haploidization, but not mitotic crossing-over, was induced by 2,2-dichloroacetaldehyde in a diploid strain of *A. nidulans* in the absence of S9 (Crebelli et al., 1984).

4.2.2 Altered cell proliferation or death

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

In male CD-1 mice, whole-body exposure to vinylidene chloride vapour at 10 or 50 ppm for 6 hours stimulated the incorporation of [^{3}H]-labelled thymidine in kidney DNA, but not in liver DNA. A lesser extent of [^{3}H]-labelled thymidine incorporation was induced in kidney DNA of male Sprague-Dawley rats (Reitz et al., 1980).

In the lungs of male CD-1 mice given a single intraperitoneal injection of [^{14}C]-labelled vinylidene chloride at 125 mg/kg bw, there was higher macromolecular binding in the Clara cells (associated with higher CYP activity (7-ethoxycoumarin deethylase activity) and cellular damage) than that in the alveolar type II cells

(Forkert et al., 1990). Following a rapid exfoliation of non-ciliated Clara cells from the bronchiolar epithelium in male C57BL/6 mice treated with a single oral dose of vinylidene chloride at 200 mg/kg bw, [^{3}H]-labelled thymidine incorporation was transiently increased primarily in non-ciliated bronchiolar epithelial cells (Forkert et al., 1985).

In female CD-1 mice, vinylidene chloride given by intraperitoneal injection at 75 or 125 mg/kg bw decreased the membrane potential of hepatic as well as lung mitochondria, accompanied by activation of caspase-3 and DNA fragmentation characteristic of apoptosis (Martin & Forkert, 2004, 2005).

4.2.3 Other mechanisms

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Global gene expression profiles of mesotheliomas (mainly testicular) induced in male F344/N rats by whole-body exposure to vinylidene chloride vapour at 25, 50, or 100 ppm for 6 hours per day, 5 days per week for 2 years revealed overrepresentation of DNA damage and repair, as well as of pathways associated with immune dysfunction and inflammation, that were not observed in spontaneous mesotheliomas arising in control male F344/N rats from several NTP studies (NTP, 2015). The overexpressed pathways included pro-inflammatory pathways (e.g. the nuclear factor κ-light-chain-enhancer of activated B-cells (NF-κB) signalling pathway), interleukin responses (IL-8, IL-12, and IL-17), Fc receptor signalling, dendritic and natural killer cell signalling, and phosphatidylinositol 3/protein kinase B (PI3/AKT) signalling (Blackshear et al., 2015).

Global gene expression profiles of renal cell carcinoma induced in male B6C3F$_1$ mice by whole-body exposure to vinylidene chloride vapour at 6.25, 12.5, or 25 ppm for 6 hours per day, 5 days per week for 2 years (NTP, 2015) demonstrated overrepresented gene categories associated with oxidative stress, including the nuclear factor-erythroid-related factor 2 (Nrf2) pathway (Hayes et al., 2016). A trend analysis showed a correlation of oxidative stress pathway modulation between exposed non-tumour and tumour tissue in the mice. Several other pathways, including those associated with cell cycle checkpoint regulation, cell growth, and cell proliferation, were overexpressed in non-tumour kidney tissue of exposed mice compared with unexposed mice (Hayes et al., 2016).

A significant increase in T helper cell type 2 (Th2) cytokine production (IL-4, IL-5, IL-13, and interferon-γ) in single-cell suspensions obtained on day 25 from lung-associated lymph nodes and cultured in the presence of concanavalin A was seen after whole-body exposure of female BALB/c mice to vinylidene chloride vapour at 10 ppm for 6 hours per day for 4 days. Vinylidene chloride had no effect on blood levels of immunoglobulin E, on the influx of inflammatory cells into alveolar spaces, or on goblet cell proliferation (Ban et al., 2006).

Serum levels of cytokines (tumour necrosis factor α (TNFα) and IL-6) increased by 6 hours and then tended to decrease with time in male Swiss OF1 mice given a single dose of vinylidene chloride at 100, 150, or 200 mg/kg bw by gavage. Maximum renal and hepatic damage occurred at 16 and 24 hours, respectively, after treatment. There was an inverse correlation between renal tubule damage percentage and serum antibody-forming cell response and natural killer cell activity (Ban et al., 1998).

4.3 Data relevant to comparisons across agents and end-points

For the results of high-throughput screening assays of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013; EPA, 2016a, b; Filer et al., 2017), see Section 4.3 of the *Monograph* on 1-*tert*-butoxypropan-2-ol in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Humans

Acute, high-level (~4000 ppm) exposures to vinylidene chloride can cause neurological effects including depression of the central nervous system in humans, while long-term exposures to lower concentrations may cause liver and kidney toxicity (ATSDR, 1994; IARC, 1999; EPA, 2002; NTP, 2015).

4.5.2 Experimental systems

The primary target organs of toxicity induced by vinylidene chloride in experimental animals are the liver, lungs, and kidneys. Liver toxicity was induced in mice and rats by inhalation (Lee et al., 1977; Plummer et al., 1990; NTP, 2015) or by oral (Forkert & Reynolds, 1982; NTP, 1982; Wang et al., 1999) exposure; liver inflammation and degeneration was observed in rats (NTP, 2015). [Despite the hepatotoxic effects of vinylidene chloride in both sexes of rats and mice, increased incidences of liver tumours were detected only in exposed female mice.] Mechanistic studies using inducers and inhibitors of vinylidene chloride metabolism, or agents that deplete hepatic GSH levels, demonstrate the important role of biotransformation in the hepatotoxicity of vinylidene chloride (Siegers et al., 1979, 1985; Kanz et al., 1988; Wijeweera et al., 1998). A dose–response relationship is apparent between hepatocellular necrosis, reduced levels of GSH, and covalent binding of vinylidene chloride metabolites to liver tissue (Gram, 1997).

The toxic effects of vinylidene chloride in the lung were observed in mice exposed at 25 ppm or more by inhalation for 3 months (females) or for 2 years (males) (NTP, 2015). Lung toxicity (primarily in Clara cells) was also observed in orally exposed mice (Forkert & Reynolds, 1982; Forkert et al., 1985). The severity of Clara cell injury is associated with increased covalent binding to lung tissue and reduction in GSH content (Forkert et al., 1986a, b), while decreased bioactivation of vinylidene chloride prevented Clara cell toxicity (Dowsley et al., 1996; Forkert et al., 1996a, b).

Renal tubular necrosis was observed in mice and rats exposed to vinylidene chloride by inhalation (Lee et al., 1977; NTP, 2015). Mechanistic studies with metabolic modulators indicated that kidney toxicity in orally exposed mice occurs independently of an anion transport system or γ-glutamyltranspeptidase activity, but does require γ-glutamylcysteine synthetase, β-lyase, and cysteine conjugate *S*-oxidase activities (Brittebo et al., 1993; Ban et al., 1995).

Turbinate atrophy, hyperostosis, olfactory epithelium respiratory metaplasia, and respiratory epithelium hyperplasia occurred in all exposure groups of both sexes of rats (25, 50, and 100 ppm) and mice (6.25, 12.5, and 25 ppm) in 2-year inhalation studies (NTP, 2015). [Despite these findings, the incidence of nasal tumours was increased only in male rats.]

5. Summary of Data Reported

5.1 Exposure data

Vinylidene chloride is not naturally occurring and is not generally detected in the environment. The substance is used in the production of polyvinylidene chloride copolymers, the major application of which is in the production of flexible films for food packaging where vinylidene chloride may persist as an unintended manufacturing residue. Vinylidene chloride is a high production volume chemical; the global production capacity was estimated at 502 000 tonnes in 2012. Current and future demand have been impacted by the phasing-out of 1,1-dichloro-1-fluoroethane (HCFC-141b), which used significant quantities of vinylidene chloride as a precursor in its manufacture. The general population may be exposed from ambient air, indoor air, drinking-water, foods and beverages, and soil, with a maximum estimated total intake (in Canada) of less than 1.34 μg/kg body weight per day.

Small numbers of workers in the chemical industry are exposed to vinylidene chloride. Although exposure levels historically ranged up to about 8000 mg/m^3, workers have been exposed to concentrations of less than 20 mg/m^3 since the 1980s.

5.2 Human carcinogenicity data

A good-quality cohort study of mortality from cancer of the lung among workers in a plastics manufacturing plant in the USA found no association between cancer of the lung and exposure to vinylidene chloride. Two smaller occupational cohort studies had significant limitations and were considered uninformative.

5.3 Animal carcinogenicity data

Vinylidene chloride was tested for carcinogenicity in three different strains of male and/or female mice in four inhalation studies, one gavage study, one skin-application study, and one subcutaneous-injection study, and was tested as an initiator in one skin-application initiation–promotion study. Vinylidene chloride was tested in four different strains of male and female rats in six inhalation studies, three gavage studies, and one drinking-water study. The substance was also tested in male and female hamsters in one inhalation study.

In one well-conducted inhalation study conducted under good laboratory practice (GLP) conditions in mice, vinylidene chloride caused a significant increase in the incidence of, and positive trend in the incidence of, renal tubule adenoma, renal tubule carcinoma, and renal tubule adenoma or carcinoma (combined) in males, and a significant increase in the incidence of, and positive trend in the incidence of, hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) in females. In this same study in females, vinylidene chloride caused significant increases in the incidence of, and positive trend in the incidence of, liver haemangiosarcoma, and haemangioma or haemangiosarcoma (combined) of the vascular system, and a significant positive trend in the incidence of haemangiosarcoma of the vascular system. Vinylidene chloride also caused a significant increase in the incidence of, and positive trend in the incidence of, bronchioloalveolar carcinoma of the lung in females.

In a second inhalation study in mice including two experiments, vinylidene chloride caused a significant increase in the incidence of pulmonary adenoma in males and females, adenocarcinoma of the kidney in males, and tumours (mostly carcinomas) of the mammary gland in females.

In one study in male and female mice exposed to vinylidene chloride by gavage, in which the maximum tolerated dose was not reached, vinylidene chloride caused a significant increase in the incidence of malignant lymphoma in females.

There was a significant increase in the incidence of skin papilloma in the initiation–promotion study in female mice. The skin-application and subcutaneous-injection studies in mice gave negative results. The two remaining inhalation studies in mice were inadequate for the evaluation of the carcinogenicity of vinylidene chloride.

In one well-conducted GLP inhalation study in rats, vinylidene chloride caused a significant increase in the incidence of, and positive trend in the incidence of, malignant mesothelioma, and a significant positive trend in the incidence of adenoma of the nasal respiratory epithelium in males. Vinylidene chloride caused a significant increase in the incidence of, and positive trend in the incidence of, thyroid C-cell adenoma and thyroid C-cell adenoma or carcinoma (combined), and a significant increase in the incidence of thyroid C-cell carcinoma in females. Vinylidene chloride also caused a significant increase in the incidence of, and positive trend in the incidence of, mononuclear cell leukaemia in females.

In another inhalation study in male and female rats, vinylidene chloride caused a significant increase in the incidence of leukaemia in females after in utero exposure followed by lifetime exposure.

Two inhalation studies, three gavage studies, and one drinking-water study in rats gave negative results. Two inhalation studies in rats were inadequate for the evaluation of the carcinogenicity of vinylidene chloride.

The inhalation study of vinylidene chloride in hamsters was inadequate for the evaluation of the carcinogenicity of vinylidene chloride.

5.4 Mechanistic and other relevant data

No data on the absorption, distribution, or excretion of vinylidene chloride were available from humans. Inhaled or ingested vinylidene chloride is rapidly and extensively absorbed from the lungs and gastrointestinal tract of rats, and is widely distributed to tissues. Vinylidene chloride is extensively oxidized in human liver microsomes and in rodents by cytochrome P450 (CYP) 2E1.

Three of the primary oxidation products (vinylidene chloride epoxide, 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde) are associated with covalent binding, GSH depletion, and cytotoxicity in the liver, kidney, and lung. Each of these metabolites is conjugated with GSH in the liver of rats. Variation in CYP2E1 expression is an important factor in tissue, species, and sex susceptibility to vinylidene chloride. Relative levels of GSH and epoxide hydrolase are also determinants of toxic response.

With regard to the key characteristics of carcinogens, there is *moderate* evidence that vinylidene chloride is genotoxic. No data were available in exposed humans. In experimental systems, vinylidene chloride was not genotoxic in the few available in vivo assays. Vinylidene chloride was mutagenic in tests conducted in vitro with an exogenous metabolic activation system in a closed environment to control for volatility. Positive responses were seen in mammalian cells for induction of gene mutations, chromosomal aberrations, sister-chromatid exchanges, and unscheduled DNA synthesis, and in assays for mutagenicity in bacteria.

Vinylidene chloride causes liver, lung (primarily in Clara cells in mice), and kidney toxicity in rats and mice after inhalation or oral exposure. The toxicity of vinylidene chloride is largely dependent on metabolism, that is, activation to electrophilic metabolites by CYP-mediated oxidation, detoxification of reactive metabolites

by GSH conjugation, and, in the kidney, activation by β-lyase.

There was inconsistency between the induction of toxicity and the occurrence of tumours in the liver, lung, and nose in the 2-year carcinogenicity bioassays. Specifically, (i) inflammation and degeneration in the liver was observed in male and female rats but liver tumour induction was detected in only female mice; and (ii) in the case of nasal respiratory epithelium toxicity, toxicity occurred in male and female rats but tumours were observed only in male rats.

6. Evaluation

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

Vinylidene chloride is *possibly carcinogenic to humans (Group 2B)*.

6.4 Rationale

A minority group opined that a higher classification for vinylidene chloride – *probably carcinogenic to humans (Group 2A)* – is warranted based on the similarity with vinyl chloride, which is classified as *carcinogenic to humans (Group 1)*.

1. Vinyl chloride and vinylidene chloride are metabolized by CYP2E1 to electrophilic metabolites chloroethylene epoxide and vinylidene chloride epoxide, respectively.
2. There is robust evidence for the mutagenic activity for vinylidene chloride in studies in vitro that include exogenous metabolic activation systems. Negative in vivo genotoxicity studies of vinylidene chloride were primarily based on studies of rodent sperm, blood, and bone marrow cells, which are not targets of vinylidene chloride carcinogenicity. Chromosomal damage has been observed in several studies of mammalian cells incubated with vinylidene chloride. Further, vinylidene chloride was mutagenic in *Salmonella* when incubated with human S9 metabolic activation system. DNA damage by a vinylidene chloride metabolite has been observed in human lymphoblastic leukaemia cells.
3. Vinylidene chloride was carcinogenic at multiple organ sites in experimental animals, including the liver (hepatocytes and endothelial cells), kidney (renal tubule cell), lung, mammary gland, mesothelium, haematopoietic system, and thyroid (C-cell). There is similarity between two mesoderm-derived tumours of the endothelium (haemangiosarcoma) and mesoderm-derived mesothelium (malignant mesothelioma). Both the endothelium and mesothelium are single-cell layers and are derived from the mesodermal layer of the embryo, and both vinyl chloride and vinylidene chloride induce haemangiosarcoma.
4. Tumour induction by vinylidene chloride in rodents shows many similarities to that of vinyl chloride, that is, both compounds induced tumours of the lung, tumours of the mammary gland, and hepatic haemangiosarcomas in mice. The induction of hepatic haemangiosarcomas in mice has also been observed with other vinyl halides (vinyl fluoride and vinyl bromide) that are metabolized by CYP2E1 to DNA-reactive haloethylene oxide intermediates. Hepatic haemangiosarcomas are extremely rare in the general

population, but significantly elevated in workers exposed to vinyl chloride.

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