VINYL FLUORIDE

This substance was considered by a previous Working Group in February 1995 (IARC, 1995). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

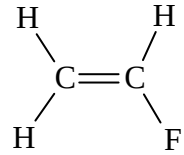
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

From IARC (1995) and IPCS-CEC (1997)
Chem. Abstr. Serv. Reg. No.: 75-02-5
Chem. Abstr. Name: Fluoroethene
IUPAC Systematic Name: Fluoroethylene
Synonyms: 1-Fluoroethene; 1-fluoroethylene; monofluoroethene; monofluoroethylene
RTECS No.: YZ7351000
UN TDG No.: 1860 (stabilized)
EINECS No.: 200-832-6

1.1.2 *Structural and molecular formulae and relative molecular mass*



C2H3F Relative molecular mass: 46.04

1.1.3 *Chemical and physical properties of the pure substance*

From IARC (1995), IPCS-CEC (1997), Ebnesajjad (2001) and Lide (2005), unless otherwise specified

(a) *Description*: Compressed liquefied gas with characteristic odour; may travel along the ground; distant ignition possible
(b) *Boiling-point*: –72.2 °C
(c) *Melting-point*: –160.5 °C
(d) *Spectroscopy data*: Infrared (prism [30864]; grating [48458P]) and mass [15] spectral data have been reported.
(e) *Solubility*: Slightly soluble in water (15.4 g/L at 6.9 MPa)
(f) *Vapour pressure*: 370 psi [2.553 MPa] at 21 °C
(g) *Relative vapour density (air = 1)*: 1.6
(h) *Reactivity*: Reacts with alkali and alkaline earth metals, powdered aluminium, zinc and beryllium.
(i) *Density:* 0.636 at 21 °C
(j) *Stability in water:* The HYDROWIN Program (v1.67) cannot estimate a hydrolysis rate constant for this chemical structure; volatilization is a major fate process for vinyl fluoride in water; volatilization half-lives of 2 and 23.5 h have been estimated for a model river (1 m deep) and a model pond (2 m deep), respectively (Lyman *et al*., 1990).
(k) *Octanol/water partition coefficient:* log P_{ow}, 1.19 (Meylan & Howard, 1995)
(l) *Flash-point:* Flammable gas
(m) *Auto-ignition temperature:* 385 °C
(n) *Explosive limits (vol. %) in air*: 2.6–21.7
(o) *Chemical danger*: The substance may polymerize freely; it decomposes on heating to produce hydrogen fluoride.
(p) *Conversion factor*: $mg/m^3 = 1.88 \times ppm$[1]

1.1.4 *Technical products and impurities*

Vinyl fluoride is available commercially at a purity of 99.9%; 0.1% *d*-limonene (see IARC, 1993) is added as a stabilizer (IARC, 1995).

1.1.5 *Analysis*

Vinyl fluoride has been determined in workplace air collected in poly(tetrafluoroethylene) bags and analysed by gas chromatography (Oser, 1980). Non-specific methods that involve fluorescence spectrophotometry and chemiluminescence have been reported (Quickert *et al*., 1975; Sutton *et al*., 1979).

[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

1.2 Production and use

1.2.1 *Production*

Vinyl fluoride was first prepared by the reaction of 1,1-difluoro-2-bromoethane with zinc. Most approaches to vinyl fluoride synthesis have employed reactions of acetylene with hydrogen fluoride either directly or utilizing catalysts. Other routes have involved ethylene and hydrogen fluoride, pyrolysis of 1,1-difluoroethane and fluorochloroethanes, reaction of 1,1-difluoroethane with acetylene and halogen exchange of vinyl chloride with hydrogen fluoride (Siegmund *et al.*, 1988; Ebnesajjad, 2001).

Use of vinyl fluoride in the Member States of the European Union in 1991 was estimated to be about 3600 tonnes (Environmental Chemicals Data and Information Network, 1993). In 1994, vinyl fluoride was produced by one company each in Japan and the USA (Chemical Information Services, 1994). Annual production in the USA was above one million pounds [454 000 kg] in 1990 and approximately 3.3 millions pounds [1.5 million kg] in 2001 (National Toxicology Program, 2005).

1.2.2 *Use*

Since the 1960s, vinyl fluoride has mainly been used in the production of polyvinyl fluoride (PVF) and other fluoropolymers. PVF homopolymers and copolymers have excellent resistance to degradation by sunlight, chemical attack, water absorption and solvents, and have a high solar energy transmittance rate. These properties have resulted in the utilization of PVF film and coating in outdoor and indoor functional and decorative applications. These films have found use where thermal stability, outdoor durability, stain resistance, adherence and release properties are required (Ebnesajjad, 2001).

PVF is converted to a thin film by plasticized melt extrusion and is sold under the trade marks Tedlar PVF film and Dalvor. The growing market for solar panels has increased the demand for photovoltaic materials such as Tedlar and has forced the manufacturer to boost its production of vinyl fluoride (Dupont, 2007).

1.3 Occurrence

1.3.1 *Natural occurrence*

Vinyl fluoride is not known to occur as a natural product.

1.3.2 *Occupational exposure*

No estimates of the number of workers exposed to vinyl fluoride are available.

The concentration of vinyl fluoride in air was determined at a manufacturing and at a polymerization plant in the USA. The concentrations in eight samples taken at the manufacturing plant were generally < 2 ppm [3.76 mg/m^3], but a level of 21 ppm

[39.5 mg/m^3] was reported in one personal sample. The concentrations in seven personal samples taken in the polymerization plant were 1–4 ppm [1.88–7.52 mg/m^3] and those in four general area samples were 1–5 ppm [1.88–9.4 mg/m^3] (Oser, 1980).

1.3.3 *Environmental exposure*

No data were available to the Working Group on environmental exposure to vinyl fluoride.

1.4 Regulations and guidelines

Table 1 presents the few guidelines that are available for the workplace in various countries, regions or organizations.

Table 1. Guidelines for levels of vinyl fluoride in the workplace

Country/region or Organizations	TWA (ppm)	STEL (ppm)	Carcinogenicity	Notes
Canada				
Alberta	1			
Ontario	1			
Ireland	1			
Japan-JSOH			2A	
New Zealand			A2	
USA				
NIOSH REL	1	5 (ceiling)		
ACGIH TLV	1		A2	

From ACGIH® Worldwide (2005)
2A/A2, suspected human carcinogen; ACGIH, American Conference of Governmental Industrial Hygienists; JSOH, Japanese Society of Occupational Health; NIOSH, National Institute of Occupational Safety and Health; REL, recommended exposure limit; STEL, short-term exposure limit; TLV, threshold limit value; TWA, time-weighted average

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 80 or 81 male and 80 or 81 female Crl:CD-1(ICR)BR mice, approximately 47 days of age, were exposed by inhalation to 0, 25, 250 or 2500 ppm [0, 47, 470 or 4700 mg/m^3] vinyl fluoride (purity > 99.94%) for 6 h per day on 5 days per week for up to 18 months. Animals in the 250- and 2500-ppm groups were killed when survival of the groups reached approximately 25% (after 375 and 450 days for high-dose males and females and 412 and 459 days for mid-dose males and females, respectively). Surviving control and low-dose mice of each sex were killed at the scheduled termination of the study at 18 months. The survival rates for the control and low-dose groups were 58% and 22%, respectively, for both sexes. All organs of control and high-dose animals were examined microscopically; only nose, lungs, liver, kidneys, gross lesions and target organs of animals in all other groups underwent microscopic evaluation. The mice were evaluated after necropsy at intervals of 0–6 and 7–18 months. Statistical analyses of the overall tumour incidence were not conducted because of the varying durations of exposure to vinyl fluoride. An early, significant increase in the incidence of lung tumours (bronchioalveolar adenomas) was observed in males in the 250- and 2500-ppm groups and in females in the 2500-ppm group that were killed at 6 months ($p < 0.05$). The overall incidence of primary lung tumours (alveolar-bronchiolar adenomas and adenocarcinomas) in males was 11/81 controls, 45/80 at 25 ppm, 52/80 at 250 ppm and 56/81 at 2500 ppm and that in females was 9/81 (controls), 24/80 at 25 ppm, 47/80 at 250 ppm and 53/81 at 2500 ppm. Hepatic angiosarcomas occurred in 1/81 control, 16/80 low-dose, 42/80 mid-dose and 42/81 high-dose males and in 0/81 control, 13/81 low-dose, 25/80 mid-dose and 32/81 high-dose females. Mammary gland adenocarcinomas were seen only in female mice that were necropsied between 7 and 18 months of observation and occurred in 0/62 controls and 22/60, 20/65 and 19/64 animals exposed to 25, 250 and 250 ppm, respectively. Two fibroadenomas and one mammary adenoma also occurred in the high-dose group. The incidence of Harderian gland adenomas was increased in both sexes of exposed animals that survived beyond 6 months. The incidence in males was 3/66 controls and 13/68, 12/66 and 31/62 mice exposed to 25, 250 and 2500 ppm, respectively; in females, the incidence was 1/64 controls and 7/61, 6/66 and 12/66 mice exposed to increasing concentrations of vinyl fluoride, respectively. No carcinomas of the Harderian gland were seen. The overall (aggregate) incidence of tumours in the lungs, liver (haemangiosarcomas and hepatocellular tumours), Harderian gland and mammary gland is summarized in Table 2. Although the incidence of hepatocellular adenomas was not dose-dependent, the decreased tumour latency, increased multiplicity and associated increase in putatively preneoplastic basophilic foci led to the conclusion that the tumours

observed in males in the 25 ppm-treated group were related to exposure to vinyl fluoride (Bogdanffy *et al*., 1995).

Table 2. Incidence of primary tumours of the liver, lung, mammary gland and Harderian gland in mice exposed to vinyl fluoride by inhalation for up to 18 months

Tumour type	Tumour-bearing mice/no. examined			
	Concentration (ppm) [mg/m^3]			
	0	25 [47]	250 [470]	2500 [4700]
Males				
Liver				
Haemangiosarcoma	1/81	16/80	42/80	42/81
Hepatocellular adenoma	7/81	15/80	5/80	3/81
Hepatocellular carcinoma	2/81	2/80	1/80	0/81
Lung				
Primary lung tumour	11/81	45/80	52/80	56/81
Bronchioalveolar adenoma	11/81	45/80	52/80	56/81
Bronchioalveolar adenocarcinoma	1/81	1/80	4/80	4/81
Harderian gland adenoma	3/81	13/80	12/80	31/81
Females				
Liver				
Haemangiosarcoma	0/81	13/80	25/80	32/81
Hepatocellular adenoma	0/81	0/81	1/80	0/81
Lung				
Primary lung tumour	9/81	24/80	47/80	53/81
Bronchioalveolar adenoma	9/81	24/80	47/80	53/81
Bronchioalveolar adenocarcinoma	0/81	1/80	1/80	3/81
Mammary gland				
Adenocarcinoma	0/81	22/81	20/80	19/81
Harderian gland adenoma	1/81	7/81	6/80	12/81

From Bogdanffy *et al*. (1995)

3.1.2 *Rat*

Groups of 95 male and 95 female Sprague-Dawley (Crl:CD®BR) rats, approximately 40 days of age, were exposed by inhalation to 0, 25, 250 or 2500 ppm [0, 47, 470 or 4700 mg/m^3] vinyl fluoride (purity > 99.94%) for 6 h per day on 5 days per week for up to 2 years. Ten rats per group were killed on test days 275 and 276 for interim examination. Because of high mortality, rats in the 250- and 2500-ppm groups were killed when the percentage of surviving animals in each group reached approximately 25% (657 days and 586 days for all surviving animals in the 250-and 2500-ppm groups, respectively). All surviving control and low-dose animals were killed at the scheduled termination of the study (2 years). The survival rates for control and low-dose groups at

the end of the study were 25% and 20% (males) and 25% and 15% (females), respectively. The rats were evaluated after necropsy at intervals of 0–12, 13–18 and 19–24 months. Statistical analyses of the overall tumour incidence were not conducted because of the varying durations of exposure to vinyl fluoride. An early appearance of liver and Zymbal gland tumours was observed at the 12-month evaluation. Exposure of the rats to vinyl fluoride for up to 2 years caused an increase in the incidence of haemangiosarcomas of the liver and Zymbal gland carcinomas in males and females and hepatocellular adenomas and carcinomas in females. The overall incidence of tumours in rats exposed to vinyl fluoride for up to 2 years is summarized in Table 3 (Bogdanffy *et al*., 1995).

Table 3. Incidence of primary tumours of the liver and Zymbal gland in rats exposed to vinyl fluoride by inhalation for up to 2 years

Tumour type	Tumour-bearing rats/no. examined			
	Concentration (ppm) [mg/m^3]			
	0	25 [47]	250 [470]	2500 [4700]
Males				
Liver				
Haemangiosarcoma	0/80	5/80	30/80	20/80
Hepatocellular adenoma	1/80	4/80	4/80	4/80
Hepatocellular carcinoma	4/80	6/80	6/80	3/80
Zymbal gland				
Carcinoma, sebaceous/squamous-cell	0/80	2/80	3/80	11/80
Females				
Liver				
Haemangiosarcoma	0/80	8/80	19/80	15/80
Hepatocellular adenoma	0/80	4/80	9/80	5/80
Hepatocellular carcinoma	0/80	0/80	0/80	3/80
Zymbal gland				
Carcinoma, sebaceous/squamous-cell	0/80	0/80	1/80	12/80

From Bogdanffy *et al*. (1995)

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The limited available data on the absorption, distribution, metabolism and excretion of vinyl fluoride in experimental systems have been reviewed previously (IARC, 1995). The following section summarizes the salient features of the studies reviewed at that time, as well as significant new information on the metabolism and pharmacokinetics of vinyl fluoride in experimental animals.

Vinyl fluoride is readily absorbed after inhalation (Filser & Bolt, 1979, 1981). The very low solubility of vinyl fluoride in tissues and blood suggests that it rapidly equilibrates within the body during inhalation exposures. The low blood:air and tissue:air partition coefficients (0.54–1.82 in rats) indicate a low volume of distribution for vinyl fluoride. Moreover, a fat:blood partition coefficient of 2.4 for this chemical indicates that it is unlikely to be stored to a significant extent in the adipose tissues (Cantoreggi & Keller, 1997).

The metabolic pathways of vinyl fluoride are thought to be similar to those of vinyl chloride and vinyl bromide (National Toxicology Program, 1999). The initial oxidation of vinyl fluoride results in the formation of fluoroethylene oxide and is probably mediated by cytochrome P450 (CYP) 2E1, as indicated by the inhibition of the metabolism of vinyl fluoride by 4-methylpyrazole (Cantoreggi & Keller, 1997). Vinyl fluoride, similarly to vinyl chloride, is shown to mediate in-vitro nicotinamide adenine dinucleotide phosphate-dependent inactivation of CYP (Ortiz de Montellano *et al*., 1982).

In-vitro studies with human liver microsomes indicated that the apparent affinity for the metabolism of vinyl fluoride (Michaelis-Menten constant, 0.5 μM) and the maximum velocity (0.57–3.3 nmol/h/mg protein) were in the same range as those found in rodents (Cantoreggi & Keller 1997). However, considerable interindividual variation in maximum velocity (sixfold) was observed in 10 human samples (Cantoreggi & Keller,1997).

The saturation of vinyl fluoride metabolism occurs at about 75 ppm [143 mg/m^3] in rats (Filser & Bolt, 1979). Both in-vitro and in-vivo metabolism studies indicated that the rate of metabolism of vinyl fluoride is about three times greater in mice than in rats (3.5 versus 1.1 nmol/h/mg protein) (Cantoreggi & Keller, 1997). Pharmacokinetic data also indicate that the rate of biotransformation of vinyl fluoride in rats is about one-fifth that of vinyl chloride (Filser & Bolt, 1979). Administration of vinyl fluoride to rats results in increased exhalation of acetone, which implies an inhibition of Krebs cycle by the fluoroacetate that results from vinyl fluoride metabolism (Filser *et al*., 1982).

Fluoride appears to be a metabolite of vinyl fluoride since it is found in the urine of rats 6 days after exposure. The concentrations of fluoride in the urine of rats were found to be increased 45 and 90 days after exposure by inhalation to 200 or 2000 ppm [382 or 3820 mg/m^3] vinyl fluoride for 6 h per day on 5 days per week for about 90 days. A plateau was observed at about 2000 ppm [3820 mg/m^3], which suggests saturation of vinyl fluoride metabolism (Bogdanffy *et al*., 1990). When rats and mice were exposed to 0, 25, 250 or 2500 ppm [0, 47, 470 or 4700 mg/m^3] vinyl fluoride for 18 months, a plateau of urinary excretion of fluoride was seen at ≥ 250 ppm (Bogdanffy *et al*., 1995).

4.2 Genetic and related effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.1 *Experimental systems*

(a) DNA adducts

Vinyl fluoride metabolites form covalent DNA adducts that are similar to those formed by metabolites of vinyl chloride. These include *N*7-(2′-oxoethyl)guanine (7-OEG), N^2,3-ethenoguanine (N^2,3-εG), 1,N^6-ethenoadenine and 3,N^4-ethenocytosine. Target cell populations for angiosarcomas in vinyl fluoride-exposed rats are non-parenchymal cells, which contain more N^2,3-εG than hepatocytes and have lower expression of the associated DNA-repair enzyme *N*-methylpurine–DNA glycosylase (Swenberg *et al*., 1999; Holt *et al*., 2000). Other vinyl fluoride-induced DNA adducts were not measured in these animals.

During a 2-year study, rats and mice were exposed by whole-body inhalation to 0, 25, 250 or 2500 ppm [0, 47, 470 or 4700 mg/m^3] vinyl fluoride for 6 h per day on 5 days per week. Tissues were collected after 12 months for detection of 7-OEG and εG adducts in liver DNA. Similarly to vinyl chloride, a supralinear response was observed for εG as well as 7-OEG due to saturation of metabolic activation. The number of 7-OEG adducts in preweanling rats was two to three times greater than that in adults. Exposure for 12 months to 25 ppm vinyl fluoride caused a 2.5-fold increase in εG in mice and a 3.5-fold increase in rats compared with controls. In mice, a linear relationship between the incidence of angiosarcomas and the number of εG adducts was observed, while rats showed a sublinear relationship between 250 and 2500 ppm due to an increase in cell proliferation. Hepatocytes and non-parenchymal cells were isolated: non-parenchymal cells contain little or no CYP2E1; however, after 4 weeks of exposure, non-parenchymal cells contained 1.2 ± 0.9 pmol εG/μmol guanine while hepatocytes contained 0.4 pmol εG/μmol guanine which was due to a lower expression of *N*-methylpurine–DNA glycosylase (a DNA-repair enzyme) in non-parenchymal cells (Swenberg *et al*., 1999).

(b) Mutations and other related effects

Vinyl fluoride is mutagenic in *Salmonella typhimurium*, Chinese hamster ovary cells and *Drosophila melanogaster* and induces micronucleus formation in the bone-marrow cells of female mice *in vivo* (IARC, 1995).

Ten rat and 10 mouse liver angiosarcomas from the 2-year study of Bogdanffy *et al*. (1995) were analysed for the presence of point mutations in Ki-*ras* exon 1 and Ha-*ras* exon 2 by polymerase chain reaction, single-strand conformational polymorphism and sequencing. No specific hot-spot mutation could be identified, although some samples

displayed a shifted band of low intensity in the single-strand conformational polymorphism analysis (Boivin-Angèle *et al*., 2000).

4.3 Mechanisms of carcinogenesis

The metabolism of vinyl fluoride is thought to be similar to that of vinyl chloride and vinyl bromide, and occurs at similar rates in human, rat and mouse livers (Cantoreggi & Keller, 1997). Vinyl fluoride is probably activated by CYP2E1 to 2-fluoroethylene oxide, which rearranges to 2-fluoroacetadehyde (Holt *et al*., 2000). Exposure of mice and rats to vinyl fluoride results in the formation of $N^{2,}$3-εG, one of the promutagenic adducts that may be implicated in the mutagenicity and carcinogenicity of vinyl chloride.

5. Summary of Data Reported

5.1 Exposure data

Vinyl fluoride is a flammable gas that is produced in a limited number of countries. It is used predominantly for the production of polyvinyl fluoride and other fluoride polymers. The use of vinyl fluoride is increasing. Workers may be exposed during the manufacture of vinyl fluoride monomer and during production of the polymers.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Vinyl fluoride was tested by inhalation in one study in rats and one study in mice. It increased the incidence of haemangiosarcomas in both sexes of mice and rats. Vinyl fluoride also increased the incidence of tumours of the lung and Harderian gland adenomas in male and female mice and mammary gland tumours in female mice, and that of Zymbal gland carcinomas in male and female rats and of hepatocellular neoplasms in female rats.

5.4 Mechanistic and other relevant data

Vinyl fluoride is readily absorbed after inhalation. The metabolic pathways of vinyl fluoride are thought to be similar to those of vinyl chloride and vinyl bromide. The initial oxidation results in formation of fluoroethylene oxide, a reaction that is probably mediated by cytochrome P450 2E1. In-vitro studies indicate that the rate of vinyl fluoride

metabolism in human liver microsomes is comparable with that in rodent cells. Pharmacokinetic data indicate that the metabolism of vinyl fluoride is saturated at about 75 ppm (~140 mg/m^3) in rats.

Fluoroethylene oxide and fluoroacetaldehyde are metabolites of vinyl fluoride that can form DNA adducts that are similar to those formed by metabolites of vinyl chloride. These include *N*7-(2-oxoethyl)guanosine and the cyclic adducts ethenodeoxyguanosine, ethenodeoxyadenosine and ethenodeoxycytidine, which can cause miscoding by modifying base-pairing sites. *N*7-(2-Oxoethyl)guanosine and ethenodeoxyguanosine adducts were found in the liver of rats and mice after 1 year of exposure to vinyl fluoride. In addition, a correlation between the amount of the ethenodeoxyguanosine adducts and the incidence of vinyl fluoride-induced angiosarcomas was observed in both species.

Vinyl fluoride was shown to be mutagenic in bacteria, Chinese hamster ovary cells and *Drosophila*.

6. Evaluation and Rationale

6.1 Carcinogenicity in humans

There is *inadequate evidence* in humans for the carcinogenicity of vinyl fluoride.

6.2 Carcinogenicity in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of vinyl fluoride.

6.3 Overall evaluation

Vinyl fluoride is *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

In making the overall evaluation, the Working Group took into consideration the fact that all available studies showed a consistently parallel response between vinyl fluoride and vinyl chloride. In addition, both vinyl chloride and vinyl fluoride are activated via a cytochrome P450 2E1-dependent pathway to their corresponding epoxides. For both vinyl chloride and vinyl fluoride, the covalent binding of these compounds to DNA yields promutagenic etheno adducts. The weight of positive evidence for both compounds was also noted among the studies for genotoxicity, although the number and variety of tests for vinyl fluoride were fewer. For practical purposes, vinyl fluoride should be considered to act similarly to the human carcinogen, vinyl chloride.

7. References

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