# VINYL FLUORIDE

This substance was considered by previous working groups, in June 1985 and March 1987 (IARC, 1986, 1987a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

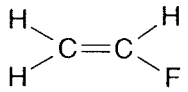
## 1. Exposure Data

### 1.1 Chemical and physical data

*1.1.1 Nomenclature*

*Chem. Abstr. Serv. Reg. No.*: 75-02-5
*Chem. Abstr. Name*: Fluoroethene
*IUPAC Systematic Name*: Fluoroethylene
*Synonyms*: 1-Fluoroethene; 1-fluoroethylene; monofluoroethene; monofluoroethylene

*1.1.2 Structural and molecular formulae and relative molecular mass*




$C_2H_3F$ Relative molecular mass: 46.04

*1.1.3 Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless gas (Ebnesajjad & Snow, 1994)

(*b*) *Boiling-point*: –72.2 °C (Lide, 1993)

(*c*) *Melting-point*: –160.5 °C (Lide, 1993)

(*d*) *Spectroscopy data*: Infrared (prism [30864]; grating [48458P]) and mass [15] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*e*) *Solubility*: Slightly soluble in water (1.1% by weight) (PCR Inc., 1994); soluble in acetone, ethanol and diethyl ether (Sax & Lewis, 1989; Lide, 1993)

(*f*) *Volatility*: Vapour pressure, 370 psi [2553 kPa] at 21 °C (Ebnesajjad & Snow, 1994); relative vapour density (air = 1), 1.6 (PCR Inc., 1994)

(*g*) *Stability*: Lower explosive limit (in air), 2.6% (PCR Inc., 1994); polymerizes freely; forms explosive mixtures with air (Buckingham, 1982); ignites in the presence of heat or sources of ignition (Sax & Lewis, 1989)

(*h*) *Reactivity*: Reacts with alkali and alkaline earth metals, powdered aluminium, zinc and beryllium (PCR Inc., 1994)

(*i*) *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 (PCR Inc., 1994).

### *1.1.5 Analysis*

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

## 1.2 Production and use

### *1.2.1 Production*

Vinyl fluoride was first prepared from 1,1-difluoro-2-bromoethane, with zinc as the catalyst, in Belgium in the early 1900s. Modern production involves direct addition of hydrogen fluoride to acetylene in the presence of mercury- or aluminium-based catalysts (Brasure, 1980). In the past, vinyl fluoride was produced by dehydrofluorination of 1,1-difluoroethane or by direct conversion of ethylene (see IARC, 1994) in the presence of a carbon catalyst impregnated with palladium and copper chloride (Brasure, 1980; Siegmund *et al.*, 1988). Dehydrochlorination of 1-chloro-1-fluoroethane and 1-chloro-2-fluoroethane is used commercially (Siegmund *et al.*, 1988).

Vinyl fluoride is produced by one company each in Japan and the United States of America (Chemical Information Services, Inc., 1994).

### *1.2.2 Use*

The main use of vinyl fluoride is in the production of polyvinyl fluoride and other fluoropolymers. Polyvinyl fluoride was first prepared in the 1930s (Brasure, 1980) and was introduced commercially in the United States in 1961 (Ebnesajjad & Snow, 1994). It is converted into a thin film by plasticized melt extrusion (Brasure, 1980) and is sold under the trademarks Tedlar PVF film and Dalvor (Siegemund *et al.*, 1988).

Polymers of vinyl fluoride are characterized by strong resistance to weather, great strength, chemical inertness and low permeability to air and water. Polyvinyl fluoride laminated with aluminium, galvanized steel and cellulosic materials has been used as a protective surfacing for the exteriors of residential and industrial buildings. Laminations with various plastics have also

[1] Calculated from: $mg/m^3$ = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

been used as protective coverings on walls, pipes and electric equipment and inside aircraft cabins (Cohen & Kraft, 1971; Brasure, 1980).

Use of vinyl fluoride in the Member States of the European Union in 1991 was estimated at about 3600 tonnes (Environmental Chemicals Data and Information Network, 1993).

### 1.3 Occurrence

#### *1.3.1 Natural occurrence*

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

#### *1.3.2 Occupational exposures*

Vinyl fluoride was determined in a manufacturing and a polymerization plant in the United States. 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).

### 1.4 Regulations and guidelines

In most countries, exposure limits have not been recommended (ILO, 1991). The United States National Institute for Occupational Safety and Health (1994) recommended an exposure limit of 1 ppm [1.88 mg/m$^3$] as an 8-h time-weighted average, with a ceiling value of 5 ppm [9.4 mg/m$^3$] for short-term (15-min) exposure.

## 2. Studies of Cancer in Humans

No data were available to the Working Group.

## 3. Studies of Cancer in Experimental Animals

### Inhalation

*Mouse:* Groups of 95 male and 95 female Swiss-derived mice, 47 days of age, were exposed 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 five days per week for up to 550 days. Ten mice per group were killed at six months for interim evaluation. All surviving mice were killed at various times between 375 and 550 days because of early, dose-related mortality. Animals were necropsied, and all organs were preserved for histological examination. All organs of control animals and those at the high dose were examined; only the nose, lungs, liver, kidneys, gross lesions and target organs of animals in the

other groups were examined microscopically. The overall incidences of primary lung tumours (predominantly alveolar–bronchiolar adenomas) were 11/81 male controls, 45/80 at 25 ppm, 52/80 at 250 ppm and 56/81 at 2500 ppm; and 9/81 female controls, 24/80 at 25 ppm, 47/80 at 250 ppm and 53/81 at 2500 ppm. Fatal hepatic haemangiosarcomas occurred in 1/81, 16/80, 42/80 and 42/81 males and 0/81, 13/81, 25/80 and 32/81 females in the four groups, respectively. Mammary gland neoplasms (adenoma, adenocarcinoma and fibroadenoma) occurred in 0/77 control females, 22/76 at 25 ppm, 20/78 at 250 ppm and 20/77 at 2500 ppm. Harderian gland adenomas occurred in 3/66 control males, 13/68 at 25 ppm, 12/66 at 250 ppm and 31/62 at 2500 ppm (killed between 7 and 18 months). The authors did not perform statistical analyses because of the differences in the times of killing in the various groups (Bogdanffy *et al.*, 1995).

*Rat*: Groups of 95 male and 95 female Sprague-Dawley-derived rats, 40 days of age, were exposed 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 five days per week for 725 days. Ten rats per group were killed at 271–276 days (although the interim kill had been scheduled for 12 months), and surviving rats were killed at various times between 552 and 725 days. Animals were necropsied, and organs were preserved for histological examination. All organs of control animals and those at the high dose were examined; only the nose, lungs, liver, kidneys, gross lesions and target organs of animals in the other groups were examined microscopically. Increased incidences of tumours were seen at several sites (Table 1). The authors did not perform statistical analyses because of the differences in the times of killing in the various groups (Bogdanffy *et al.*, 1995).

**Table 1. Tumour incidences in Fischer 344 rats exposed to vinyl fluoride by inhalation for two years**

| Sex | Target organ | Control | 25 ppm [47 mg/m$^3$] | 250 ppm [470 mg/m$^3$] | 2500 ppm [4700 mg/m$^3$] |
|---|---|---|---|---|---|
| Males | Hepatic haemangiosarcomas | 0/81 | 5/80 | 30/80 | 20/80 |
| | Zymbal gland tumours | 0/80 | 2/80 | 3/80 | 11/80 |
| | Hepatocellular adenomas and carcinomas | 5/80 | 10/80 | 10/80 | 7/80 |
| Females | Hepatic haemangiosarcomas | 0/80 | 8/80 | 19/80 | 15/80 |
| | Zymbal gland tumours | 0/80 | 0/80 | 1/80 | 12/80 |
| | Hepatocellular adenomas and carcinomas | 0/80 | 4/80 | 9/80 | 8/10 |

From Bogdanffy *et al.* (1995)

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

## 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 metabolism and toxicity of vinyl fluoride have been reviewed (Kennedy, 1990).

Vinyl fluoride is readily absorbed after its inhalation and reaches a tissue concentration in rats that is 90% of that in the inhaled air (Filser & Bolt, 1979, 1981). The metabolism is saturable and dose-dependent, saturation occurring at concentrations > 75 ppm (> 140 mg/m$^3$) (Filser & Bolt, 1979). Pharmacokinetic data imply that the rate of biotransformation of vinyl fluoride is about one-fifth that of vinyl chloride (Bolt *et al.*, 1981).

Fluoride appears to be a metabolite of vinyl fluoride as it is found in the urine six days after exposure (Dilley *et al.*, 1974). The fluoride concentrations in the urine of rats were found to be increased 45 and 90 days after exposure by inhalation to 0, 200, 2000 or 20 000 ppm [373, 3733 or 37 333 mg/m$^3$] vinyl fluoride for 6 h per day, five days per week for about 90 days. A plateau was observed at about 2000 ppm [3733 mg/m$^3$], suggesting 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 two years and 18 months, respectively, a plateau of urinary fluoride excretion was seen at ≥ 250 ppm (Bogdanffy *et al.*, 1995).

## 4.2 Toxic effects

### *4.2.1 Humans*

Vinyl fluoride may burn the skin and eyes and may cause headache or dizziness (United States National Library of Medicine, 1994).

### *4.2.2 Experimental systems*

The acute lethality of vinyl fluoride is so low that concentrations can be increased to the point at which oxygen becomes limiting (Lester & Greenberg, 1950; Kopecný *et al.*, 1964; Clayton, 1967).

Rats were exposed to vinyl fluoride at 3000 ppm [5640 mg/m$^3$] for 30 min and followed for seven days thereafter. Increased urine output and potassium excretion were observed at various times (Dilley *et al.*, 1974). [The Working Group noted that the control values on some days were similar to those that were significantly different from control values on other days.]

Groups of 15 male and 15 female rats and mice were exposed to vinyl fluoride at concentrations of 0, 200, 2000 or 20 000 ppm [0, 375, 3750 or 37 500 mg/m$^3$] for 6 h per day, on five days per week for 90 days. No significant changes in histopathological or haematological parameters or in clinical chemistry were found at 45 days or at the end of the 90-day exposure

(Bogdanffy *et al.*, 1990). Rats and mice exposed to vinyl fluoride by inhalation at 0, 25, 250 or 2500 ppm [47, 470 or 4700 mg/m$^3$] also showed no changes in these measures (Bogdanffy *et al.*, 1995). The survival of the exposed mice and rats was decreased, however, such that, after early sacrifices, only control animals and those receiving the lowest dose were available for clinical evaluation. Liver-cell proliferation, measured as the labelling index in animals implanted with osmotic minipumps containing $^3$H-thymidine, was increased in rats and mice of each sex at all concentrations in one study (Bogdanffy *et al.*, 1990) but not in a subsequent study with interim sampling for cell proliferation (Bogdanffy *et al.*, 1995), owing perhaps to use of a less sensitive technique in the later study.

Increased exhalation of acetone has been reported to be due to the effects of vinyl fluoride on intermediary metabolism (Filser *et al.*, 1982). Intermediate metabolites of vinyl fluoride have been shown to alkylate the haem group of cytochrome P450 enzymes *in vitro*, suggesting potential inhibition of the metabolism of other substances (Ortiz de Montellano *et al.*, 1982).

Exposure of rats to vinyl fluoride at 10 000 ppm [18 800 mg/m$^3$] after pretreatment with Aroclor 1254 resulted in liver damage (Conolly *et al.*, 1978). Treatment of newborn rats with 2000 ppm [3760 mg/m$^3$] vinyl fluoride for 8 h per day, on five days per week for 14 weeks resulted in increased numbers of preneoplastic foci in their livers (Bolt *et al.*, 1981).

### 4.3 Reproductive and prenatal effects

No data were available to the Working Group.

### 4.4 Genetic and related effects

As reported in an abstract, vinyl fluoride induced gene mutations and chromosomal aberrations in Chinese hamster ovary cells in the presence of an exogenous metabolic system, sex-linked recessive lethal mutations in *Drosophila melanogaster* and micronuclei in polychromatic erythrocytes from the bone marrow of female mice exposed to 19.1 or 38.8% vinyl fluoride for 6 h. No unscheduled DNA synthesis was seen in pachytene spermatocytes, no single strand breaks or cross-links in testicular DNA and no dominant lethal mutations in male rats (Bentley *et al.*, 1992).

### 4.5 Structure–activity relationship

Vinyl fluoride bears a close structural relationship to vinyl chloride (see IARC, 1987b).

## 5. Summary and Evaluation

### 5.1 Exposure data

Vinyl fluoride has been produced commercially since the 1960s for use in the production of polyvinylfluoride and fluoropolymers. Human exposure may occur during its production and use.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Vinyl fluoride was tested for carcinogenicity in one experiment in mice and one experiment in rats by inhalation. It produced haemangiosarcomas in the liver and alveolar–bronchiolar adenomas in mice of each sex, mammary tumours in females and Harderian gland adenomas in males. In rats, it produced haemangiosarcomas of the liver and Zymbal gland tumours in animals of each sex and an increased incidence of hepatocellular adenomas and carcinomas in females.

### 5.4 Other relevant data

Vinyl fluoride is readily absorbed after administration by inhalation. Its metabolism is saturable and dose-dependent. Vinyl fluoride has very low acute toxicity. High doses produced no measurable toxic effects after subchronic exposure. Survival was decreased after chronic exposure, but no other toxic effects were seen in surviving animals.

### 5.5 Evaluation[1]

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

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

#### Overall evaluation

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

In making the overall evaluation, the Working Group took into account the following evidence: Vinyl fluoride is closely related structurally to the known human carcinogen, vinyl chloride. The two chemicals cause the same rare tumour (hepatic haemangiosarcoma) in experimental animals, which is also a tumour caused by vinyl chloride in humans.

## 6. References

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[1] For definition of the italicized terms, see Preamble, pp. 22–26.

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