

FINAL

**Report on Carcinogens
Background Document for**

Vinyl Fluoride

**Meeting of the
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee**

Prepared for the:
**U.S. Department of Health and Human Services
Public Health Services
National Toxicology Program
Research Triangle Park, NC 27709**

Prepared by:
**Technology Planning and Management Corporation
Canterbury Hall, Suite 310
4815 Emperor Blvd
Durham, NC 27703
Contract Number NOI-ES-85421**

Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

US Department of Health and Human Services National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen*, or *reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary Statement

Vinyl Fluoride

CASRN 75-02-5

Carcinogenicity

Vinyl fluoride (VF) is *reasonably anticipated to be a human carcinogen* based on evidence of tumor induction at multiple organ sites in rats and mice. Inhalation exposure of rats to vinyl fluoride resulted in increased incidences of hepatic hemangiosarcomas, hepatocellular adenomas or carcinomas, and Zymbal gland carcinomas; inhalation exposure of mice to VF resulted in increased incidences of hepatic hemangiosarcomas, bronchiolar-alveolar adenomas or adenocarcinomas, hepatocellular adenomas, mammary gland adenocarcinomas, and Harderian gland adenomas (Bogdanffy *et al.* 1995; IARC 1995). The tumor response to VF in laboratory animals is similar to the responses to vinyl chloride, a known human carcinogen (NTP 1998; IARC 1987), and to vinyl bromide, a probable human carcinogen (IARC 1986). A unique feature of vinyl chloride carcinogenicity is the induction of rare hepatic hemangiosarcomas in rats and mice and the causal association in epidemiological studies between vinyl chloride exposure and excess risk of hemangiosarcoma of the liver (NTP 1998). The fact that VF, vinyl chloride, and vinyl bromide induce rare hemangiosarcomas of the liver in experimental animals and induce the formation of similar DNA adducts suggests a possible common mechanism of carcinogenicity for these vinyl halides.

No studies on the potential carcinogenicity of VF in humans have been reported.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

VF is mutagenic in *Salmonella typhimurium* with metabolic activation (Dupont de Nemours and Co 1992a). In addition, VF induces gene mutations and chromosomal aberrations in Chinese hamster ovary cells (with metabolic activation), sex-linked recessive lethal mutations in *Drosophila melanogaster*, and micronuclei in bone marrow cells of female mice (IARC 1995).

The biotransformation pathway for VF is thought to be similar to that of vinyl chloride, that is, cytochrome P-450 mediated oxidation to the haloethylene oxide (fluoroethylene oxide), followed by rearrangement to the haloacetaldehyde (2-fluoroacetaldehyde), which is oxidized to fluoroacetic acid. Human liver microsomes metabolize VF at a rate similar to that of rat or mouse liver microsomes (Cantoreggi and Keller 1997).

VF metabolites form covalent DNA adducts. A dose-related increase in the formation of the promutagenic adduct $N^2,3$ -ethenoguanine was detected in liver DNA of rats and mice exposed to VF by inhalation (Swenberg *et al.* 1995).

No data are available that would suggest that mechanisms thought to account for tumor induction by VF in experimental animals would not also operate in humans.

Table of Contents

Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens	i
Summary Statement	iii
1 Introduction	1
1.1 Chemical identification	1
1.2 Physical-chemical properties.....	1
1.3 Identification of metabolites.....	2
2 Human Exposure.....	5
2.1 Use.....	5
2.2 Production	5
2.3 Analysis.....	5
2.4 Environmental occurrence.....	5
2.5 Environmental fate	5
2.5.1 Air	5
2.5.2 Water.....	5
2.5.3 Soil	6
2.6 Environmental exposure.....	6
2.7 Occupational exposure	6
2.8 Biological indices of exposure	6
2.9 Regulations.....	6
3 Human Cancer Studies	9
4 Studies of Cancer in Experimental Animals	11
4.1 Carcinogenesis studies of VF in mice	11
4.2 Carcinogenesis studies of VF in rats	12
4.3 Additional studies of VF carcinogenicity in animals	14
4.4 Summary	14
5 Genotoxicity	17
5.1 Prokaryotic systems.....	17
5.1.1 Induction of mutation in <i>Salmonella typhimurium</i>	17
5.2 Eukaryotic systems.....	17
5.2.1 Mutagenicity in <i>Drosophila melanogaster</i>	17
5.3 Mammalian systems.....	17
5.3.1 In vitro assays.....	17
5.3.2 In vivo assays	18
5.4 Summary	19
6 Other Relevant Data	21
6.1 Absorption, metabolism, and excretion of VF.....	21
6.2 Alkylating properties and DNA adduct formation.....	23
6.3 Effects of VF on cell proliferation	24

6.4	Structure-activity relationship	24
6.5	Summary	26
7	References	27
Appendix A: IARC. (1995). <i>Dry cleaning, Some Chlorinated Solvents and Other Industrial Chemicals</i> . Monographs on the Evaluation of the Carcinogenic Risk to Humans. Vol. 63. World Health Organization. Lyon, France. A-1 – A-11.		
		33
Appendix B: IARC. (1986). <i>Some Chemicals Used in Plastics and Elastomers</i> . Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans—Some Chemicals used in plastics and elastomers. Vol 39. World Health Organization. Lyon, France. pp. B-1 – B-10.....		
		35

List of Tables

Table 1-1.	Physical and chemical properties of VF	1
Table 2-1.	U.S. EPA Regulations.....	7
Table 4-1.	Incidences of primary tumors of the liver, lung, mammary gland and Harderian gland in mice exposed to VF gas for up to 18 months.....	12
Table 4-2.	Tumor incidences in rats exposed to VF gas for up to two years.....	14
Table 6-1.	Summary of carcinogenesis, mutagenesis, and pharmacokinetics for VF, VB, and VC.....	25

List of Figures

Figure 1-1.	Structure of VF.....	1
Figure 1-2.	Structure of fluoroethylene oxide.....	2
Figure 1-3.	Structure of fluoroacetaldehyde	2
Figure 1-4.	Structure of fluoroacetic acid	2
Figure 6-1.	Proposed metabolic pathway of VF	22

1 Introduction

Vinyl fluoride (VF) was nominated for listing in the Report on Carcinogens (RoC) by the National Institute of Environmental Health Sciences (NIEHS) RoC Review Group (RG1) based on review of the 1995 International Agency for Research on Cancer (IARC) monograph (IARC 1995) which indicates that there is sufficient evidence in experimental animals for the carcinogenicity of VF and that it is *probably carcinogenic to humans* (Group 2A).

1.1 Chemical identification

VF is a member of the vinyl halide class. VF and the other vinyl halides are used ubiquitously in industry, especially in manufacture of plastics. They are easily polymerized and copolymerized with various materials, such as acrylonitrile, vinyl acetate, and styrene, to form pliable lightweight plastics or thermoplastic resins (HSDB 1995). VF (C₂H₃F, mol wt 46.044, CASRN 75-02-5) also is known as fluoroethene. It is a colorless gas at ambient temperature and pressure and is highly flammable. VF is used in the production of polyvinyl fluoride and other fluoropolymers and as an intermediate in organic synthesis. The structure of VF is illustrated in Figure 1-1.

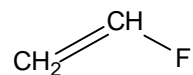


Figure 1-1. Structure of VF

1.2 Physical-chemical properties

VF's RTECS number is YZ7351000, and its UN number for shipping, is 1860. The physical and chemical properties of VF are summarized in Table 1-1.

Table 1-1. Physical and chemical properties of VF

Property	Information	Reference
Molecular weight	46.04	CRC (1993)
Color	colorless	Lewis (1993)
Odor	faint ethereal odor	NIOSH (1994)
Physical state	flammable gas	CRC (1993)
Melting point (°C)	-160.5	CRC (1993)
Boiling point (°C) at 750 mm	-72	CRC (1993)
Specific gravity, at 21°C	0.636 (liquid)	Kirk-Othmer (1991)
Relative vapor density (air = 1)	1.58	HSDB (1995)
Solubility in: Water at 20°C Alcohol Ether Acetone	insoluble soluble soluble soluble	Sax (1979) Sax (1979) Sax (1979) Lide (1994)

1.3 Identification of metabolites

The major metabolites of VF are expected to be fluoroethylene oxide and fluoroacetaldehyde, based on indirect evidence of metabolism similar to that of vinyl chloride (VC) and vinyl bromide (VB); fluoroacetaldehyde can be further metabolized to fluoroacetic acid (Cantoreggi and Keller 1997). In a manner analogous to metabolism of VC (and VB), VF may initially be oxidized by microsomal monooxygenase(s) to fluoroethylene oxide (C_2H_3FO , mol wt 122.95), the structure of which is shown in Figure 1-2 (Bolt 1988; Ballering *et al.* 1996). The structure of fluoroacetaldehyde (C_2H_3FO , mol wt 62.044) is shown in Figure 1-3, and the structure of fluoroacetic acid ($C_2H_3FO_2$, mol wt 78.043, CASRN 144-49-0) is shown in Figure 1-4.

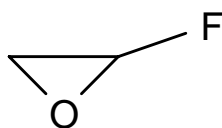


Figure 1-2. Structure of fluoroethylene oxide

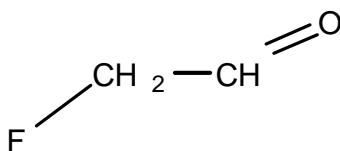


Figure 1-3. Structure of fluoroacetaldehyde

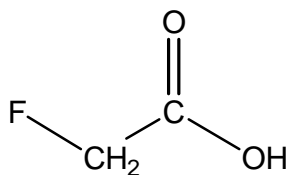


Figure 1-4. Structure of fluoroacetic acid

VF alkylates the prosthetic heme group of cytochrome P-450, and the alkylate has been identified as *N*-(2-oxoethyl)protoporphyrin IX. This observation suggests a reaction of heme with fluoroacetaldehyde (Ortiz de Montellano *et al.* 1982, cited in Cantoreggi and

Keller 1997). It also is likely that incorporation of fluoroacetate into the citric acid cycle disrupts energy metabolism and leads to increased production of mitochondrial acetylcoenzyme A and hence excretion of ketone bodies and free fluoride. Administration of VF has been shown to increase acetone exhalation by rats (Filser *et al.* 1982).

2 Human Exposure

2.1 Use

VF is used mainly in the production of polyvinyl fluoride and other fluoropolymers. Polymers of VF are resistant to weather and have great strength, chemical inertness, and low permeability to air and water. Polyvinyl fluoride is laminated with aluminum, galvanized steel, and cellulosic materials and is used as a protective surface for the exteriors of residential and commercial buildings. Polyvinyl fluoride laminated with various plastics has been used to cover walls, pipes, and electrical equipment and inside aircraft cabins (IARC 1995).

2.2 Production

E.I. du Pont de Nemours & Co. Inc. has been identified as the major manufacturer of VF (HSDB 1995). VF was first prepared in the early 1900s by a reaction of zinc with 1,1-difluoro-2-bromoethane. Modern preparation of VF involves a reaction of acetylene and hydrogen fluoride in the presence of a mercury- or aluminum-based catalyst (IARC 1995). The U.S. Environmental Protection Agency (EPA), through the Office of Pollution Prevention and Toxics, listed VF in the high production volume (HPV) chemical list in 1990. U.S. EPA estimated the annual production volume for 1990 at 3.83 to 6.96×10^6 lb (U.S.EPA 1990).

2.3 Analysis

Air samples collected in polytetrafluoroethylene bags can be sampled and analyzed for VF concentrations by gas chromatography (GC) (IARC 1995, HSDB 1995).

2.4 Environmental occurrence

VF is not known to occur naturally (IARC 1995). Industrial release of VF during its use and production may account for its presence in the environment (HSDB 1995).

2.5 Environmental fate

2.5.1 Air

VF exists in the vapor phase in the ambient atmosphere. VF reacts with photochemically produced hydroxyl radicals, with an estimated half-life of about 1.5 days. VF also reacts with atmospheric ozone, leading to its atmospheric degradation (estimated half-life of about 16 days) (HSDB 1995).

2.5.2 Water

The major fate process for VF in water is volatilization. The half-lives for volatilization from a model river (1 m deep) and a model pond (2 m deep) are 2 and 23.5 hours, respectively. VF has a bioconcentration factor (BCF) of 4.7, and therefore is not expected to bioconcentrate in aquatic organisms, as a BCF of greater than 1,000 is required for significant bioaccumulation. Adsorption to sediment is not considered to be an important fate process for VF in water (HSDB 1995).

2.5.3 Soil

Because VF remains a gas under normal conditions, it will evaporate to the atmosphere when released into soil. When dissolved in an aqueous solution, VF is very mobile in soil. There are insufficient data to predict whether biodegradation is an important fate process in soils that preclude evaporation (HSDB 1995).

2.6 Environmental exposure

Environmental exposure to VF occurs via inhalation, because VF released into the environment exists as a gas (IPCS 1993).

2.7 Occupational exposure

Occupational exposure to VF occurs through inhalation (HSDB 1995). Dermal and eye contact can occur among workers handling liquid VF; this type of contact will cause frostbite (IPCS 1993).

VF was sampled in a manufacturing and polymerization plant in the United States. In eight personal air samples taken at the manufacturing plant, concentrations of VF generally were < 2 ppm (3.76 mg/m³). In one personal sample, however, the concentration of VF was 21 ppm (39.5 mg/m³). VF concentrations in seven personal samples taken in the polymerization plant ranged from 1 to 4 ppm (1.88 to 7.52 mg/m³). In four general working areas, the VF concentrations ranged from 1 to 5 ppm (1.88 to 9.4 mg/m³) (IARC 1995).

The National Institute for Occupational Safety and Health (NIOSH) recommended an exposure limit of 1 ppm (1.88 mg/m³) as an eight-hour time-weighted average (TWA), with a ceiling value of 5 ppm (9.4 mg/m³) for short-term (15-minute) exposures (IARC 1995).

2.8 Biological indices of exposure

Simple fluoroalkenes, such as VF, are metabolized in humans, which leads to elevated urinary excretion of free fluoride (the mechanism is discussed in Section 1.3 and 6.1) (HSDB 1995).

2.9 Regulations

VF is regulated by U.S. EPA under the Clean Air Act to prevent accidental releases. It has a threshold reporting quantity of 1,000 lb. VF also is regulated by U.S. EPA under the Toxic Substances Control Act (TSCA), which requires health and safety studies to determine risk of injury to human health or the environment. U.S. EPA regulations are summarized in Table 2-1.

Table 2-1. U.S. EPA Regulations

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 68—PART 68—CHEMICAL ACCIDENT PREVENTION PROVISIONS. Promulgated: 59 FR 4493, 01/31/94. U.S. Codes: 42 U.S.C. 7412(r), 7601(a)(1), 7661-7661f.	This part lists regulated substances and thresholds, the petition process for adding or deleting substances, and specific requirements for preventing accidental releases. VF is regulated as a flammable substance with a threshold quantity of 1,000 lb for accidental release prevention.
40 CFR 716—PART 716—HEALTH AND SAFETY DATA REPORTING. Promulgated: 51 FR 32726, 09/15/86. U.S. Codes: 15 U.S.C. 2607(d). The effective date for VF is 10/04/82. The sunset date is 10/04/92.	The provisions of this part require the submission of lists and copies of health and safety studies on chemical substances and mixtures selected for priority consideration for testing rules under section 4(a) of TSCA and on other chemicals for which U.S. EPA requires health and safety information in fulfilling the purposes of TSCA.
40 CFR 799—PART 799—IDENTIFICATION OF SPECIFIC CHEMICAL SUBSTANCE AND MIXTURE TESTING. Promulgated: 49 FR 39817, 10/10/84. U.S. Codes: 15 U.S.C. 2603, 2611, and 2625.	This part identifies VF as a chemical for which data are to be developed to determine the risk of injury to human health or the environment presented by this chemical. All persons who manufacture VF, other than as an impurity, from July 22, 1987, to the end of the reimbursement period shall submit letters of intent to conduct testing or exemption applications, submit study plans, conduct tests in accordance with the TSCA Good Laboratory Practice Standards (40 CFR part 792), and submit data as specified in this section.

Source: These regulations in this table have been updated through the 1998 Code of Federal Regulations 40 CFR, July 1, 1996; 21 CFR, April 1, 1996; 29 CFR, July 1, 1996.

3 Human Cancer Studies

No studies on the relationship of VF exposure to human cancer were available.

4 Studies of Cancer in Experimental Animals

4.1 Carcinogenesis studies of VF in mice

An inhalation study in which Crl:CD-1(ICR)BR mice were exposed to VF at concentrations of 0, 200, 2,000, or 20,000 ppm (equivalent to 0, 376, 3,760, or 37,600 mg/m³) six hours/day, five days/week for approximately 90 days was used to establish doses for a cancer bioassay in mice. In the range-finding study, results of hematological assessments (after 45 and 90 days) and histopathological assessments revealed no evidence of VF-associated toxicity. On day 93, groups of five mice per sex per exposure level received infusions of [³H]thymidine followed by five additional days of VF exposure for measurement of cell proliferation in liver, kidney, lung, and nasal cavity tissues. Exposure to VF caused hepatocellular proliferation, as indicated by increased incorporation of [³H]thymidine into hepatocytes. The magnitudes of the hepatocellular proliferative responses were similar at 2,000 and 20,000 ppm. Exposure to VF at 20,000 ppm caused increased [³H]thymidine incorporation into nasal olfactory epithelium in male mice (Bogdanffy *et al.* 1990).

In the cancer bioassay (Bogdanffy *et al.* 1995), groups of 80 or 81 male and female Crl:CD-1(ICR)BR mice, approximately 47 days of age, were exposed to VF (purity > 99.94%) by inhalation at concentrations of 0, 25, 250, or 2,500 ppm (0, 47, 470, or 4,700 mg/m³) for six hours/day, five days/week for up to 18 months. Reduced survival of exposed mice necessitated sacrifice of mice at various times between 375 and 550 days. Animals in the 250- and 2,500-ppm groups were sacrificed when survival of the groups reached approximately 25% (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 both sexes were sacrificed at the scheduled study termination, 18 months. The approximate survival rates for the control and low-dose groups were 58% and 22%, respectively, for both sexes. All organs of control and high-dose-group animals were examined microscopically; only the nose, lungs, liver, kidneys, gross lesions, and target organs of animals in the other groups were subjected to microscopic evaluation.

The mice were evaluated after necropsy at intervals of 6, 12, 17 to 18, and 19 to 24 months. An early, significant increase in the incidence of lung tumors (bronchioalveolar adenoma) was observed in males in the 250- and 2,500-ppm groups and in females in the 2,500-ppm group sacrificed at 6 months. Statistical analyses of the overall tumor incidences were not conducted because of the varying durations of exposure to VF; however, observations included exposure-related increases in incidences of pulmonary, hepatic, and Harderian gland tumors in both sexes and mammary gland tumors in females. Although the incidence of hepatocellular adenomas did not exhibit dose-dependence, the increased tumor latency, increased multiplicity, and associated increase in putatively preneoplastic basophilic foci led to the conclusion that the tumors observed in males in the 25-ppm group were related to VF exposure.

Overall (aggregate) incidences of tumors in the lungs, liver, Harderian gland, and mammary gland in animals sacrificed or found dead between 7 and 18 months are summarized in Table 4-1.

Table 4-1. Incidences of primary tumors of the liver, lung, mammary gland and Harderian gland in mice exposed to VF gas for up to 18 months

Tumor type	Tumor incidence/number examined			
	Concentration (ppm)			
	0	25	250	2500
Males				
Lungs				
Primary lung tumors	11/81	45/80	52/80	56/81
Bronchioalveolar adenoma	11/81	43/80	48/80	49/81
Bronchioalveolar adenocarcinoma	1/81	1/80	4/80	4/81
Liver				
Hemangiosarcoma	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
Harderian gland adenoma	3/80	13/79	12/80	31/80
Females				
Lungs				
Primary lung tumors	9/81	24/80	47/80	53/81
Bronchioalveolar adenoma	9/81	22/80	46/80	49/81
Bronchioalveolar adenocarcinoma	0/81	1/80	1/80	3/81
Liver				
Hemangiosarcoma	0/81	13/81	25/80	32/81
Hepatocellular adenoma	0/81	0/81	1/80	0/81
Mammary gland				
Adenoma	0/79	0/80	0/78	1/79
Adenocarcinoma	0/79	22/80	20/78	19/79
Adenoma, adenocarcinoma, fibroadenoma (combined)	0/77	22/76	20/78	20/77
Harderian gland adenoma	1/81	7/81	6/79	12/81

Source: Bogdanffy *et al.* (1995)

Based on the induction of liver hemangiosarcomas and bronchioalveolar adenomas in both sexes of mice, mammary gland tumors in females, and Harderian gland adenomas in males by VF in this study, IARC concluded that VF is carcinogenic to mice of both sexes (IARC 1995).

4.2 Carcinogenesis studies of VF in rats

An inhalation study in which Sprague-Dawley rats were exposed to VF at concentrations of 0, 200, 2,000, or 20,000 ppm (equivalent to 0, 376, 3,760, or 37,600 mg/m³) six hours/day, five days/week for 90 days was used to establish doses for a cancer bioassay in rats. In the range-finding study, urinary excretion of fluoride was measured after 45 and 90 days of exposure to VF. Excretion of fluoride, indicative of VF metabolism,

appeared to reach a plateau at an exposure concentration of 2,000 ppm. Urinary excretion of fluoride was greater in both sexes after 90 days of exposure than after 45 days. Results of clinical chemical assessments, hematological assessments (after 45 or 90 days), and histopathological assessments revealed no evidence of VF-associated toxicity.

Biochemical evidence of hepatocellular proliferation was observed in rats exposed to VF. On day 93, groups of five rats per sex per exposure level received infusions of [³H]thymidine followed by five additional days of VF exposure for measurement of cell proliferation in liver, kidney, lung, and nasal cavity tissues. Exposure to VF at 2,000 or 20,000 ppm caused statistically significant increases in incorporation of [³H]thymidine into hepatocytes in both sexes. The effect of VF on [³H]thymidine incorporation appeared to plateau between exposure concentrations of 2,000 and 20,000 ppm (Bogdanffy *et al.* 1990).

In the cancer bioassay (Bogdanffy *et al.* 1995), groups of 95 male and 95 female Sprague-Dawley rats (CrI:CD[®]BR), approximately 40 days of age, were exposed by inhalation to VF (purity > 99.94%) at concentrations of 0, 25, 250, or 2,500 ppm (0, 47, 470, or 4,700 mg/m³) for six hours/day, five days/week for up to two years. Ten rats per group were sacrificed on test days 275 and 276 for interim examination. Because of high mortality, rats in the 250- and 2,500-ppm groups were sacrificed when the percentage of surviving animals in each group reached approximately 25% (586 days and 657 days for all surviving animals in the 2,500- and 250-ppm groups, respectively). All surviving control and low-dose animals were sacrificed at the scheduled termination of the study (two years). The survival rates for control and low-dose groups at the end of the study were 30% and 25% (males) and 25% and 15% (females), respectively.

The rats were evaluated after necropsy at intervals of 0 to 12, 13 to 18, and 19 to 24 months. An early appearance of VF-induced tumors was observed in the 12 month evaluation. Exposure to VF at 2,500 ppm for up to 12 months was associated with the development of Zymbal gland carcinoma in both sexes. The incidence of Zymbal gland carcinoma in high-dose males was statistically significant (Fisher's exact test). Although the incidence in females (4/18, 22%) was not significantly elevated, it was unusually high for one-year-old rats and was probably due to VF administration.

Exposure of the rats to VF for up to two years caused increased incidence of hemangiosarcomas of the liver, hepatocellular adenomas and carcinomas, and Zymbal gland carcinomas. VF-associated reduced survival and/or saturation of VF metabolism likely limited the induction of neoplasms in high-dose groups. The total tumor incidences in rats exposed to VF for up to two years are summarized in Table 4-2.

Table 4-2. Tumor incidences in rats exposed to VF gas for up to two years

Tumor type	Tumor incidence/number examined			
	Concentration (ppm)			
	0	25	250	2500
Males				
Liver				
Hemangiosarcoma	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	2/51	3/49	11/80
Females				
Liver				
Hemangiosarcoma	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	0/50	1/49	12/80

Source: Bogdanffy *et al.* (1995)

Based on the increased incidence of liver hemangiosarcomas and Zymbal gland tumors in both sexes of rats and an increased incidence of hepatocellular adenomas and carcinomas in female rats resulting from exposure to VF in this study, IARC concluded that VF is carcinogenic to rats of both sexes (IARC 1995).

4.3 Additional studies of VF carcinogenicity in animals

Similarly to vinyl chloride, VF induces the formation of preneoplastic ATPase-deficient foci in newborn Wistar rats (Bolt *et al.* 1981).

4.4 Summary

VF is closely related to VC (*known to be a human carcinogen*) and VB (*nominated as reasonably anticipated to be a human carcinogen*). The strong structural similarity among the vinyl halides predicts similar biological effects. That prediction is verified by the similarity of tumor response observed in carcinogenesis experiments conducted with these agents.

Inhalation of VF increases the incidences of hemangiosarcomas in both sexes of mice and rats, tumors of the lung and Harderian gland in male and female mice, and mammary gland tumors in female mice. VF also increases the incidence of Zymbal gland carcinomas and hepatocellular neoplasms in rats of both sexes. The interpretative value of these data is strengthened by the facts that the tumor responses are dose-related and that the spectrum of VF-induced neoplasms closely resembles that reported for VC (Maltoni 1974, as cited in IARC 1979) and VB (IARC 1986). These findings, particularly

the induction of rare hemangiosarcomas of the liver by these three vinyl halides, support the conclusion that VF *is reasonably anticipated to be a human carcinogen*.

5 Genotoxicity

5.1 Prokaryotic systems

5.1.1 Induction of mutation in *Salmonella typhimurium*

VF was tested for the ability to induce *his* gene mutations in *Salmonella typhimurium*. In a series of five assays, VF was tested in various *S. typhimurium* tester strains at exposure concentrations of 0 to 52% with and without exogenous metabolic activation. VF induced statistically significant increases ($P < 0.01$) in mutation frequency (1.4 to 2.1 times negative control mutation frequencies) in three of the five assays in strain TA1535 with metabolic activation. VF did not induce reverse mutations in strains TA98, TA100, or TA1537 in the presence of metabolic activation, nor in any strain in the absence of metabolic activation (Dupont de Nemours and Co. 1992a).

5.2 Eukaryotic systems

5.2.1 Mutagenicity in *Drosophila melanogaster*

5.2.1.1 Sex-linked recessive lethal assay

VF caused excessive sex-linked recessive lethal mutations in *Drosophila melanogaster*. Males (N = 198) were exposed to VF at air concentrations of 47.6% for 24 hours and then mated with untreated females. The progeny exhibited a significant increase ($P < 0.01$) in the frequency of sex-linked recessive lethal mutations compared with controls. VF exposure resulted in the production of 100 lethal mutations (2.4%) in the F₂ progeny, compared with 5 lethal mutations (0.08%) among F₂ progeny of flies not exposed to VF. Survivability among the VF-exposed males was 86.4%. Fertility was unaffected in the surviving males (CMA 1988).

In its review of an abstract of a study conducted by Bentley *et al.* (1992, cited in IARC 1995), IARC stated that VF induced sex-linked recessive lethal mutations in *Drosophila melanogaster* at exposure concentrations of 19.1% or 38.8% for six hours.

5.3 Mammalian systems

5.3.1 In vitro assays

5.3.1.1 *hprt* locus forward mutation test

VF induced *hprt* forward mutations in Chinese hamster ovary (CHO) cells in the presence of metabolic activation by S9 liver homogenate from rats. CHO cells in uncapped tissue culture flasks were exposed to VF gas concentrations of 0 to 100% in the ambient environment of glass chambers for five hours (with S9 metabolic activation) or for 18 to 19 hours (without S9 metabolic activation). VF was not mutagenic without metabolic activation. However, VF was mutagenic at all concentrations (from 20% to 100%), causing statistically significant dose-related increases in mutant frequencies. Cell survival was 62% in a preliminary non-activated cytotoxicity test at the highest VF concentration tested (100%) (Dupont de Nemours and Co. 1992b).

In its review of an abstract of a study conducted by Bentley *et al.* (1992, cited in IARC 1995), IARC concluded that VF induced gene mutations in Chinese hamster ovary

(CHO) cells with metabolic activation at exposure concentrations of 19.1% or 38.8% for six hours.

5.3.1.2 Chromosomal aberrations

CHO cells were incubated with VF at target concentrations of 0, 10%, 40%, 70%, or 100% for five hours without rat S9 metabolic activation or with VF at target concentrations of 0, 10%, 25%, 50%, or 75% VF for two hours with rat S9 metabolic activation. Statistically significant increases in chromosomal aberrations (CA) occurred at VF levels of 10%, 25%, and 50% with metabolic activation. Significant increases in CA were observed only at the highest concentration without S9 metabolic activation. A second trial used concentrations of VF at 0, 12.3%, 35.4%, 63.3%, or 91.3% with metabolically activated CHO cells. Statistically significant increases in CA frequency were induced at the 35.4% and 63.3% VF concentrations (Dupont de Nemours and Co. 1986).

In its review of an abstract of a study conducted by Bentley *et al.* (1992, cited in IARC 1995), IARC concluded that VF induced CA in CHO cells with metabolic activation at exposure concentrations of 19.1% or 38.8% for six hours.

5.3.2 In vivo assays

5.3.2.1 Chromosomal aberrations

Dominant lethal test (rat)

Groups of 40 male Crl:CD[®]BR rats were exposed by inhalation to VF at concentrations of 0, 200, 2,000, or 20,000 ppm (0, 376, 3,760, or 37,600 mg/m³) six hours/day for five days and then mated with unexposed females. No statistically significant treatment-related differences in pre- or post-implantation losses were found in females mated with males exposed to VF at any concentration. No males died in the study (Dupont de Nemours and Co. 1988).

Mammalian bone marrow cytogenetic test (metaphase analysis)

VF gave equivocal results in males and positive results in females for induction of micronuclei in bone marrow polychromatic erythrocytes (PCEs) of 43-day-old CD-1 mice. The mice were exposed by inhalation to mean VF concentrations of 0, 50,100, 191,000, or 388,000 ppm (0, 94,348, 359,689, or 730,678 mg/m³) for 24, 48, or 72 hours. At the 24-hour sampling time, no single test resulted in a significant increase of micronucleated PCEs above control values. However in female mice, a statistically significant trend was observed of concentration-related increases in the proportion of micronucleated PCEs. No statistically significant increases in micronucleated PCEs or concentration-related trends were observed at the 48- and 72-hour sampling times. Increases in the frequency of micronucleated PCEs in males in the 50,100- and 388,000-ppm exposure groups at the 24-, 48-, and 72-hour sampling times were not statistically significant. The frequency of micronucleated PCEs in female mice showed a significant concentration-related increase at the 191,000- and 388,000- ppm exposure levels, confirmed by scoring of additional PCEs. No significant depression of the ratio of PCEs to normochromatic erythrocytes was seen in the VF-exposed mice (Dupont de Nemours and Co. 1987).

In its review of an abstract of a study conducted by Bentley *et al.* (1992, cited in IARC 1995), IARC concluded that VF induced micronuclei in bone marrow cells of female mice at exposure concentrations of 19.1% or 38.8% for six hours. VF did not induce unscheduled DNA synthesis in pachytene spermatocytes or single strand breaks or cross-links in testicular DNA of male mice.

DNA single strand breaks

Testicular-cell DNA from groups of male Sprague-Dawley rats tested by nose-only inhalation exposure to VF at 0 or (2%) 20,000 ppm (37,600 mg/m³) for six hours/day for one, two, or five consecutive days showed no significantly increased frequencies of single strand breaks or cross-links (Dupont de Nemours and Co. 1991).

In its review of an abstract of a study conducted by Bentley *et al.* (1992, cited in IARC 1995), IARC concluded that VF did not induce unscheduled DNA synthesis in pachytene spermatocytes, nor single strand breaks or cross-links in testicular DNA of male mice.

5.4 Summary

VF is mutagenic and clastogenic. VF, VC, and VB are genotoxic chemicals requiring metabolic activation to similar DNA-reactive intermediates. VF is a base-pair substitution mutagen in *S. typhimurium* strain TA1535. VF induces excessive sex-linked recessive lethal mutations in *D. melanogaster*, induces *hprt* forward mutations in CHO cells with rat S9 metabolic activation, and is clastogenic in CHO cells *in vitro*. In an assay for induction of micronucleated PCEs in female mice *in vivo*, VF gave equivocal results, and it failed to induce single strand breaks or cross-links in DNA when tested *in vivo* in rats.

6 Other Relevant Data

6.1 Absorption, metabolism, and excretion of VF

VF is readily absorbed after inhalation (Filser and Bolt 1980, 1981, cited in IARC 1995).

The metabolic process appears to be saturable and dose-dependent. An early estimate indicated that metabolic saturation occurred at inhalation concentrations in excess of 75 ppm (140 mg/m³) in rats (Filser and Bolt 1980, cited in IARC 1995). Pharmacokinetic data imply that the rate of biotransformation of VF is about one-fifth that of VC (Bolt *et al.* 1981). VF is metabolized faster than VB, but slower than VC (Bolt *et al.* 1982).

Available evidence suggests that VF is metabolized via the same pathway as VC and VB. VC and VB are metabolized to haloacetaldehydes. Based upon VC metabolism, it is also likely that fluoroacetaldehyde is metabolized to fluoroacetic acid, a potent inhibitor of the Krebs cycle. Incorporation of fluoroacetate into the citric acid cycle disrupts energy metabolism and leads to increased production of mitochondrial acetyl coenzyme A and, hence, excretion of ketone bodies. Administration of VF has been shown to increase acetone exhalation by rats (Filser *et al.* 1982). The results of experiments reported by Cantoreggi and Keller (1997) are consistent with hepatic oxidative metabolism of VF. In the study, mice and rats were exposed to VF in a closed chamber gas uptake system. VF uptake was monitored from the chamber. Mice were observed to have a higher metabolic rate for VF than rats (6.5 vs. 2.2 $\mu\text{mol/hr}$ per kilogram body weight). Inhibition of the cytochrome P-450 enzyme CYP 2E1 by administration of 4-methylpyrazole completely impaired VF metabolism in both species. CYP 2E1 induction in rats (by administration of ethanol) increased metabolic capacity.

The proposed metabolic pathway for VF, similar to the pathways for its vinyl halide analogs VC and VB, is illustrated in Figure 6-1 (Bolt 1988; Ballering *et al.* 1996).

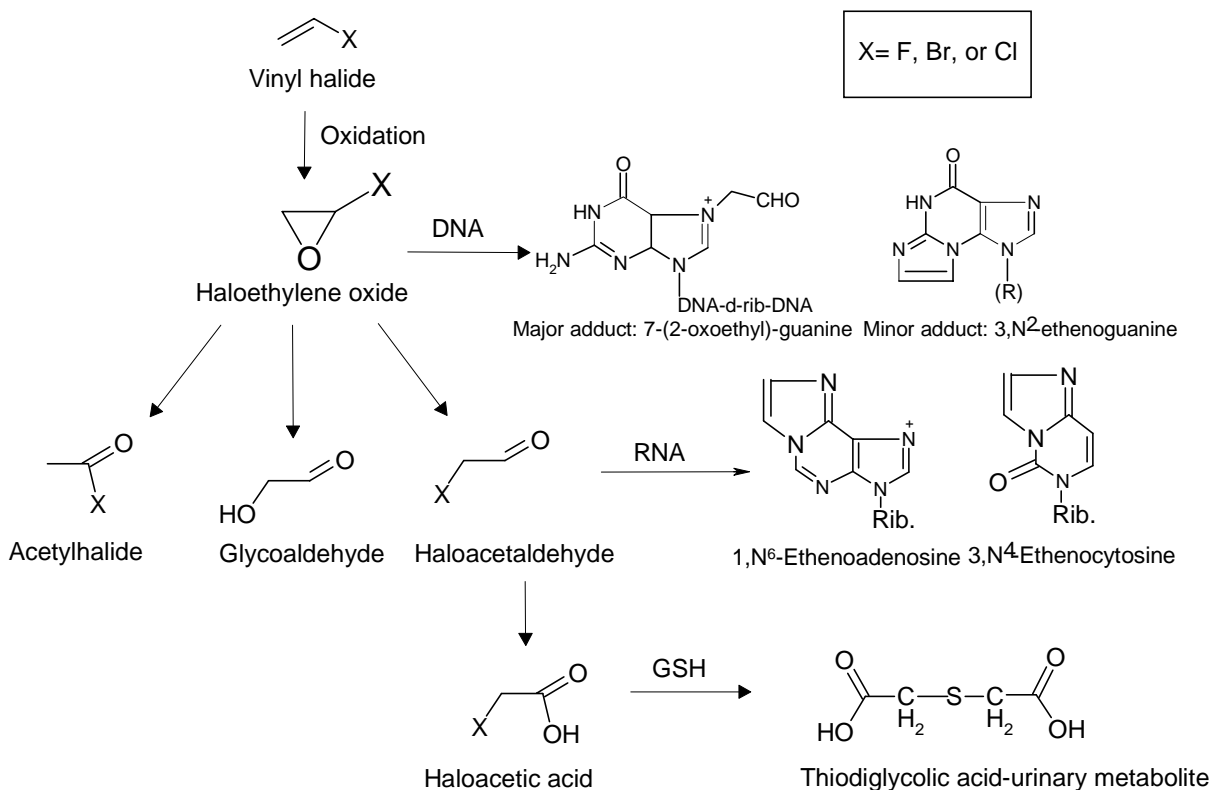


Figure 6-1. Proposed metabolic pathway of VF

Source: Bolt 1986, 1988 and Ballering *et al.* 1996.

VF toxicity is mediated via epoxide formation. Oxidative metabolism of inhaled VF in the presence of Aroclor 1254 (a hepatic cytochrome P-450 inducer) resulted in enhanced toxicity (Conolly *et al.* 1978, cited in Cantoreggi and Keller 1997). In addition, administration of trichloropropylene oxide (an inhibitor of epoxide hydrolase) also increased VF toxicity (Conolly and Jaeger 1977, cited in Cantoreggi and Keller 1997).

Cantoreggi and Keller (1997) demonstrated that microsomes from mice metabolized VF more rapidly than those from rats ($V_{\max} = 3.5$ and 1.1 nmol/hr per milligram protein, respectively) when rat or mouse liver hepatic microsomes were exposed to VF gas in closed chambers in the presence of an NADPH-regenerating system. Disappearance of VF gas from the incubation headspace was monitored, which was consistent with the results from the *in vivo* experiment. Microsomes from human livers were found to metabolize VF at a rate similar to that for rat or mouse liver microsomes. Among ten human livers tested, V_{\max} ranged from 0.57 to 3.3 nmol/hr per milligram protein. V_{\max} values were directly related to microsomal content of CYP 2E1.

Urinary excretion of fluoride was determined in rats exposed to 0, 200, 2,000 or 20,000 ppm VF (0, 376, 3,760, or 37,600 mg/m³) for six hours/day, five days/week, after 45 and 90 days of exposure. Urinary fluoride concentrations were dose-related at both time

periods, but were nonlinear, with a plateau appearing at approximately 2,000 ppm (for both sexes). The appearance of a plateau was taken as evidence of metabolic saturation. It also was noted that urinary fluoride concentrations were consistently higher, after 90 days of exposure to VF than after 45 days. Increased excretion of fluoride after 90 days of VF exposure may reflect hepatic enzyme induction or saturation of deposition sites (Bogdanffy *et al.* 1990).

6.2 Alkylating properties and DNA adduct formation

Although the metabolism of VF is largely unknown, it has been demonstrated that the action of monooxygenase on VF produces fluoroethylene (fluorooxirane, a reactive epoxide intermediate) (see Figure 6-1) (Bolt *et al.* 1982; Cantoreggi and Keller 1997). This is analogous to the mechanism for the metabolic production of chloroethylene (chlorooxirane) from the VF analog VC (Bolt *et al.* 1982).

Comparative molecular orbital studies show that the three-membered ring of fluorooxirane has more tension and is less stable than that of chlorooxirane, although it is less reactive to tissue macromolecules than chlorooxirane. The order of reactivity of vinyl halide-derived haloethylene oxides (halooxiranes) with tissue macromolecules has been proposed to be VC > VF > VB (Bolt *et al.* 1982).

VF alkylates the prosthetic heme group of cytochrome P-450, and the alkylate has been identified as *N*-(2-oxoethyl)protoporphyrin IX. This observation suggests a reaction of heme with fluoroacetaldehyde (Ortiz de Montellano *et al.* 1982, cited in Cantoreggi and Keller 1997).

The VF analog VC induces the formation of DNA adducts 7-(2'-oxoethyl)guanine, *N*²,3-ethenoguanine, 3,*N*⁴-ethenocytosine, and 1,*N*⁶-ethenoadenine (Bartsch *et al.* 1994, Guengerich 1994, both cited in La and Swenberg 1996). Similarly, inhaled VF in both rats and mice results in the formation of *N*²,3-ethenoguanine in liver DNA. The formation of this adduct reaches a plateau at exposure concentrations of approximately 250 ppm in both species, indicating metabolic saturation at this exposure (Swenberg *et al.* 1995). The transition mutation in the *K-ras* gene, activated by a GC to AT transition at the second base of codon 13 in five of six VC-induced tumors in humans, is consistent with the known miscoding properties of *N*²,3-ethenoguanine and 3,*N*⁴-ethenocytosine (La and Swenberg 1996). Accordingly, VF-DNA adducts are analogous to those identified as promutagenic adducts resulting from exposure to VC (Bolt *et al.* 1982). The adduct predominantly formed is 7-(2'-oxoethyl)guanine (over 98%). However, the mutagenic effects of VC may be driven by the formation of the minor DNA adducts *N*²,3-ethenoguanine, 3,*N*⁴-ethenocytosine, and 1,*N*⁶-ethenoadenine. These adducts efficiently induce GC to AT, GC to TA, and AT to GC transitions, respectively (Barbin *et al.* 1981, Spengler and Singer 1981, Singer *et al.* 1984, 1987, 1991, Cheng *et al.* 1991, Mroczkowska and Kusmieriek 1991, and Basu *et al.* 1993 all cited in La and Swenberg 1996). Although the major DNA adduct, 7-(2'-oxoethyl)guanine, is not involved in base pairing, its removal may result in an apurinic site that can lead to a mutation (La and Swenberg 1996).

6.3 Effects of VF on cell proliferation

Male and female rats and female mice exposed to VF by inhalation exhibited small but significantly increased rates of [³H]thymidine incorporation into hepatocytes. This observation indicates a proliferative response to the chemical (Bogdanffy *et al.* 1990).

In this experiment, animals were exposed to VF in air at concentrations of 0, 200, 2,000 or 20,000 ppm (0, 376.6, 3,766.4, or 37,664 mg/m³) for six hours/day, five days/week for 90 days. On day 93, the animals were implanted with osmotic mini-pumps containing [³H]thymidine and exposed for five more days. Tritium incorporation into trachea, lungs, nose, liver, and kidneys was measured. High-dose female mice exhibited a significant increase in mean labeling index of hepatocytes whereas high-dose male mice had a significantly elevated labeling index of the olfactory nasal epithelium. Although the mean hepatocyte-labeling index in high-dose male mice was elevated relative to controls, the range of measurements was highly variable, and the difference was not statistically significant. Exposure of male and female rats to VF at 2,000 or 20,000 ppm caused significant increases in hepatocyte labeling. The magnitude of response at 20,000 ppm was similar to that observed at 2,000 ppm.

During assessment of VF carcinogenicity, Bogdanffy *et al.* (1995) attempted to confirm their earlier demonstration of the cellular proliferative effect of VF in mice and rats. In these experiments, a pulse label with 5-bromodeoxyuridine (BrdU) revealed no evidence of cellular proliferation. The researchers concluded that the proliferative response reported earlier might have been too subtle for detection with the less sensitive BrdU pulse labeling technique.

6.4 Structure-activity relationship

The metabolism of VF probably proceeds through the same pathway as that of VC (a known human carcinogen) and the probable human carcinogen VB. VF is less rapidly metabolized than either VC or VB (Bolt *et al.* 1982). The metabolic process appears to be saturable, as observed for VC. Pharmacokinetic data imply that the rate of biotransformation of VF in rats is about one fifth that of VC (Bolt *et al.* 1981).

The spectrum of neoplasms produced by the three vinyl halides in mice and rats is strikingly similar. Table 6-1 summarizes the information available on carcinogenesis, mutagenesis, and metabolism of the three vinyl halides.

Table 6-1. Summary of carcinogenesis, mutagenesis, and pharmacokinetics for VF, VB, and VC

Study	VF	VB	VC
Animal carcinogenicity			
<i>Types of tumors formed</i>			
Hepatic hemangiosarcoma	rats, mice ^a	rats ^b	rats, mice ^c
Extrahepatic hemangiosarcoma	—	—	rats, mice ^d
Hepatocellular carcinoma	rats ^e	rats ^b	—
Hepatocellular adenoma	rats, mice ^e	—	rats ^d
Zymbal gland carcinoma	—	rats ^b	rats ^d
Bronchioalveolar adenoma and adenocarcinoma	rats, mice ^e	—	—
Harderian gland adenocarcinomas	mice ^e	—	—
Mammary gland adenocarcinomas	mice ^e	—	mice ^d
<i>Oncogene activation</i>			
Oncogenicity (formation of ATPase-deficient hepatic foci in newborn rats)	positive ^f	positive ^g	positive ^h
Mutagenicity			
Prokaryotic cells <i>in vitro</i>	positive ⁱ	positive ^j	positive ^d
<i>D. melanogaster in vivo</i>	positive ^k	positive ^l	positive ^d
Mammalian cells <i>in vitro</i>	positive ^m	na	positive ^d
Mammalian bone marrow test <i>in vivo</i>	positive ⁿ	na	positive ^o
Pharmacokinetics			
<i>Metabolism</i>			
Metabolism by rat liver microsomes	V _{max} = 1.1 nmol/hr-mg protein ^p	na	V _{max} = 280.4 nmol/hr-mg protein ^q
Metabolism by mouse liver microsomes	V _{max} = 3.5 nmol/hr-mg protein ^p	na	na
Metabolism by human liver microsomes	V _{max} = 0.5-3.3 nmol/hr-mg protein ^p	na	na
Detection of free ions in urine	positive ^r	positive ^r	positive ^r
Detection of acetone in exhaled air in rats	positive ^s	positive ^s	positive ^s
<i>Distribution (air partition coefficients)^p</i>			
Blood (rats)	0.75 ± 0.09	4.05 ± 0.16	1.68 ± 0.18
Liver (rats)	0.83 ± 0.58	3.33 ± 0.38	1.60 ± 0.17
Muscle (rats)	0.54 ± 0.28	2.26 ± 0.13	2.10 ± 0.45
Fat	1.82 ± 0.15	49.2 ± 1.3	20.0 ± 0.7

Study	VF	VB	VC
<i>Alkylating properties</i>			
Reactive intermediates and formation of DNA adducts	7-(2'-oxoethyl)guanine, <i>N</i> ² , 3-ethenoguanine ^f	7-(2'-oxoethyl)guanine; <i>N</i> ² , 3-ethenoguanine ^u	7-(2'-oxoethyl)guanin e; <i>N</i> ² , 3-ethenoguanine ^v ; 3, <i>N</i> ⁴ -ethenocytosine; 1, <i>N</i> ⁶ -ethenoadenine ^u

—, Not reported; na, Not available

^aBogdanffy *et al.* 1995, IARC 1995

^bIARC 1986

^cIARC 1979, NTP 1998

^dIARC 1979

^eBogdanffy *et al.* 1995

^fBolt *et al.* 1981

^gBolt *et al.* 1979

^hLaib *et al.* 1985

ⁱDupont de Nemours and Co 1992a

^jIARC 1986, Roldan-Arjona *et al.* 1991

^kCMA 1988, IARC 1995

^lVogel and Nivard 1993, Ballering *et al.* 1996.

^mDupont de Nemours and Co 1992b, IARC 1995

ⁿDupont de Nemours and Co 1987, IARC 1995

^oRichardson *et al.* 1983

^pCantonreggi and Keller 1997

^qel Ghisassi *et al.* 1998

^rDilley *et al.* 1974

^sFilser *et al.* 1982

^tSwenberg *et al.* 1995

^uBolt *et al.* 1988

^vSwenberg *et al.* 1992

6.5 Summary

The information available on VF metabolism, DNA reactivity of its metabolites, and the spectrum of tumor induction in rats and mice suggests that VF is a genotoxic carcinogen. The metabolism of VF probably proceeds through the same pathway as that of the known human carcinogen VC and the probable human carcinogen VB. Metabolism of VC and VB results in the production of reactive metabolites that bind to proteins and nucleic acids. All three vinyl halide congeners are active in genotoxicity assays. Inhalation exposure to each congener produces unequivocal carcinogenicity in rats and mice of both sexes. The three vinyl halides produce a similar array of neoplasms in mice and rats.

7 References

1. Ballering, L.A., M.J. Nivard, and E.W. Vogel. (1996). Characterization by two-endpoint comparisons of the genetic toxicity profiles of vinyl chloride and related etheno-adduct forming carcinogens in *Drosophila*. *Carcinogenesis* 17:1083-1092.
2. Barbin, A.J., H. Bartsch, P. Leconte, and M. Radman. (1981). Studies on the miscoding properties of 1,N6-ethenoadenine and 3,N4-ethenocytosine, DNA reaction products of vinyl chloride metabolites, during in vitro DNA synthesis. *Nucleic Acids Res* 9:375-387.
3. Bartsch, H., A. Barbin, M.J. Marion, J. Nair, and Y. Guichard. (1994). Formation, detection, and role in carcinogenesis of ethenobases in DNA. *Drug Metab Rev* 26:349-371.
4. Basu, A.K., M.L. Wood, L.J. Niedernhofer, L.A. Ramos, and J.M. Essigmann. (1993). Mutagenic and genotoxic effects of 3 vinyl chloride-induced DNA lesions - 1,n(6)-ethenoadenine, 3,n(4)-ethenocytosine, and 4-amino-5-(imidazol-2-yl)imidazole. *Biochemistry* 32:12793-12801.
5. Bentley, K.S., L.S. Mullin, L.B. Rickard, D.A. Vlachos, A.M. Sarrif, R.C. Sernau, D.J. Brusick, and R.D. Curren. (1992). Vinyl fluoride mutagenic in mammalian somatic cells in-vitro and in-vivo and in *Drosophila* germ cells but nongenotoxic in germ cells of mammals. *Environ Mol Mutagen* 20:Suppl. 5.(Abstract).
6. Bogdanffy, M.S., C.R. Kee, D.P. Kelly, M.C. Carakostas, and G.P. Sykes. (1990). Subchronic inhalation study with vinyl fluoride: effects on hepatic cell proliferation and urinary fluoride excretion. *Fundam Appl Toxicol* 15:394-406.
7. Bogdanffy, M.S., G.T. Makovec, and S.R. Frame. (1995). Inhalation oncogenicity bioassay in rats and mice with vinyl fluoride. *Fundam Appl Toxicol* 26:223-238.
8. Bolt, H.M., R.J. Laib, and G. Stockle. (1979). Formation of pre-neoplastic hepatocellular foci by vinyl bromide in newborn rats. *Arch Toxicol* 43:83-84.
9. Bolt, H.M., R.J. Laib, and K.P. Klein. (1981). Formation of pre-neoplastic hepatocellular foci by vinyl fluoride in newborn rats. *Arch Toxicol* 47:71-73.
10. Bolt, H.M., R.J. Laib, and J.G. Filser. (1982). Reactive metabolites and carcinogenicity of halogenated ethylenes. *Biochem Pharmacol* 31:1-4.
11. Bolt, H.M. (1988). Roles of etheno-DNA adducts in tumorigenicity of olefins. *Crit Rev Toxicol* 18:299-309.
12. Cantoreggi, S. and D.A. Keller. (1997). Pharmacokinetics and metabolism of vinyl fluoride in vivo and in vitro. *Toxicol Appl Pharmacol* 143:130-139.
13. Cheng, K.C., B.D. Preston, D.S. Cahill, M.K. Dosanjh, B. Singer, and L.A. Loeb. (1991). The vinyl-chloride DNA derivative n2,3-ethenoguanine produces g-ja transitions in *Escherichia-coli*. *Proc Natl Acad Sci U S A*. 88:9974-9978.

14. CMA. (1988). Mutagenicity test on vinyl fluoride: *Drosophila Melanogaster* sex-linked recessive lethal test (Final Report) with attachments and cover letter dated 8/15/88. NTIS/OTS0522809 Washington, D.C., U.S. EPA/ Office of Toxic Substances.
15. Conolly, R.B. and R.J. Jaeger. (1977). Acute hepatotoxicity of ethylene and halogenated ethylenes after PCB pretreatment. *Environ Health Perspect* 21:131-135.
16. Conolly, R.B., R.J. Jaeger, and S. Szabo. (1978). Acute hepatotoxicity of ethylene, vinyl fluoride, vinyl chloride, and vinyl bromide after Aroclor 1254 pretreatment. *Exp Mol Pathol* 28:25-33.
17. CRC. (1993). CRC Handbook of Chemistry and Physics. Weast, R. C. and Astle, M. J. Boca Raton, FL., CRC Press, Inc.
18. Dilley, J.V., V.L.J. Carter, and E.S. Harris. (1974). Fluoride ion excretion by male rats after inhalation of one of several fluoroethylenes or hexafluoropropene. *Toxicol Appl Pharmacol* 27:582-590.
19. Dupont de Nemours and Co. (1986). Evaluation of vinyl fluoride in the *in vitro* assay for chromosomal aberrations in Chinese hamster ovary (CHO) cells. U.S. EPA-OTS Document Id. No. 40-8834277 Washington, D.C., U.S. EPA/ Office of Toxic Substances.
20. Dupont de Nemours and Co. (1987). Mouse bone marrow micronucleus assay of vinyl fluoride. U.S. EPA-OTS Document Id. No.87- 0515661 Washington, D.C., U.S. EPA/ Office of Toxic Substances.
21. Dupont de Nemours and Co. (1988). Dominant lethal mutation study of vinyl fluoride in rats. U.S. EPA-OTS Document Id. No. 40-8834277 Washington, D.C., U.S. EPA/ Office of Toxic Substances.
22. Dupont de Nemours and Co. (1991). Detection of DNA damage in the rat testicular DNA by alkaline elution following *in vivo* inhalation exposure to vinyl fluoride. U.S. EPA-OTS Document Id. No. 40-9134424 Washington, D.C., U.S. EPA/ Office of Toxic Substances.
23. Dupont de Nemours and Co. (1992a). Mutagenic activity of fluoroethylene in the Salmonella/Microsome Assay. U.S. EPA-OTS Document Id. No. 88-920002842 Washington, D.C., U.S. EPA/ Office of Toxic Substances.
24. Dupont de Nemours and Co. (1992b). Mutagenicity evaluation of vinyl fluoride in the CHO/prt assay. U.S. EPA-OTS Document Id. No. 88-920002841 Washington, D.C., U.S. EPA/ Office of Toxic Substances.
25. el Ghissassi, F., A. Barbin, and H. Bartsch. (1998). Metabolic activation of vinyl chloride by rat liver microsomes: low- dose kinetics and involvement of cytochrome P450 2E1. *Biochem Pharmacol* 55:1445-1452.
26. Filser, J.G. and H.M. Bolt. (1980). Characteristics of haloethylene-induced acetonemia in rats. *Arch Toxicol* 45:109-116.
27. Filser, J.G. and H.M. Bolt. (1981). Inhalation pharmacokinetics based on gas uptake studies: 1. Improvement of kinetic models. *Arch Toxicol* 47:279-292.

28. Filser, J.G., P. Jung, and H.M. Bolt. (1982). Increased acetone exhalation induced by metabolites of halogenated C1 and C2 compounds. *Arch Toxicol* 49:107-116.
29. Guengerich, F. (1994). Mechanisms of formation of DNA-adducts from ethylene dihalides, vinyl halides, and arylamines. *Drug Metab Rev* 26:47-66.
30. HSDB. (1995). Hazardous Substances Data Bank -- CAS# 75-02-5. MEDLARS Online Information Retrieval System, National Library of Medicine.
31. IARC. (1979). *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 19. Lyon, France, World Health Organization.
32. IARC. (1986). *Some Chemicals Used in Plastics and Elastomers. Vinyl Fluoride*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 39, pp. 147-154 Lyon, France, World Health Organization.
33. IARC. (1987). *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Suppl 7. Lyon, France. World Health Organization.
34. IARC. (1995). *Dry cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. Vinyl Fluoride*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 63, pp. 467-475. Lyon, France, World Health Organization.
35. IPCS. (1993). Vinyl Fluoride. International Chemical Safety Cards. <http://www.cdc.gov/niosh/ipcs/ipcs0598.html> , International Programme on Chemical Safety & the Commission of the European Communities.
36. Kirk-Othmer. (1991). Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed.(1), -p.684 New York, NY., John Wiley and Sons.
37. La, D.K. and J.A. Swenberg. (1996). DNA adducts: Biological markers of exposure and potential applications to risk assessment. *Mutat Res* 365:129-146.
38. Laib, R.J., K.P. Klein, and H.M. Bolt. (1985). The rat liver foci bioassay: I. Age-dependence of induction by vinyl chloride of ATPase-deficient foci. *Carcinogenesis* 6:65-68.
39. Lewis, R. J., Sr. (1993). Hawley's Condensed Chemical Dictionary. Lewis, R. J., Sr. 12th ed. New York, Van Nostrand Reinhold.
40. Lide, D. R. (1994). CRC Handbook of Chemistry and Physics. Lide, D. R. 75th ed., - p.163 Boca Raton, Fl, CRC Press, Inc.
41. Maltoni, C. (1974). Vinyl chloride carcinogenesis: current results and perspectives. *Med Lav* 65:421-444.
42. Mroczkowska, M. and J.T. Kusmierk. (1991). Miscoding potential of n-2,3-ethenoguanine studied in an Escherichia-coli DNA-dependent RNA-polymerase in vitro system and possible role of this adduct in vinyl chloride-induced mutagenesis. *Mutagenesis* 6:385-390.

43. NIOSH. (1994). NIOSH Pocket Guide to Chemical Hazards. (94-116) Washington, D.C., U.S. Department of Health and Human Services.
44. NTP. (1998). *Eighth Report on Carcinogens (Summary)*. Vinyl Chloride (CAS No. 75-01-4). http://ntp-server.niehs.nih.gov/htdocs/8_RoC/KC/VinylChloride.html , National Toxicology Program.
45. Ortiz de Montellano, P., K.L. Kunze, H.S. Beilan, and C. Wheeler. (1982). Angiosarcoma of the liver in workers exposed to vinyl chloride. First two cases found in Italy (Ital.). *Med Lav* 65:445-450.
46. Richardson, C.R., J.A. Styles, and I.P. Bennett. (1983). Activity of vinyl chloride monomer in the mouse micronucleus assay. *Mutat Res* 122:139-142.
47. Roldan-Arjona, T., P.M. Garcia, R.F. Luque, C. Hera, and C. Pueyo. (1991). An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. *Mutagenesis* 6:199-205.
48. Sakai, K., M. Fukuba, Y. Hasui, K. Moriyoshi, T. Ohmoto, T. Fujita, and T. Ohe. (1998). Purification and characterization of an esterase involved in poly(vinyl alcohol) degradation by *Pseudomonas vesicularis* PD. *Biosci Biotechnol Biochem* 62:2000-2007.
49. Sax. (1979). *Dangerous Properties of Industrial Materials*. Sax, N. I. and Lewis, R. J., Sr. 5th ed. New York, Van Nostrand Reinhold.
50. Scheller, N.A., A. Ranasinghe, S. Kim, S. Holt, M.S. Bogdanffy, and J.A. Swenberg. (1995). High resolution GC/MS detection of N2,3-ethenoguanine in livers of control and vinyl fluoride exposed B6C3F1 mice. *Int Toxicologist* 7:21.(Abstract)
51. Singer, B., L.G. Abbott, and S. Spengler. (1984). Assessment of mutagenic efficiency of two carcinogen-modified nucleosides, 1,N6-ethenodeoxyadenosine and O4-methyldeoxythymidine, using polymerases of varying fidelity. *Carcinogenesis* 5:1165-1171.
52. Singer, B., J.T. Kusmierek, W. Folkman, F. Chavez, and M.K. Dosanjh. (1991). Evidence for the mutagenic potential of the vinyl-chloride induced adduct, n-2, 3-etheno-deoxyguanosine, using a site- directed kinetic assay. *Carcinogenesis* 12:745-747.
53. Singer, B., S.J. Spengler, F. Chavez, and J.T. Kusmierek. (1987). The vinyl chloride-derived nucleoside, n2,3-ethenoguanosine, is a highly efficient mutagen in transcription. *Carcinogenesis* 8:745-747.
54. Spengler, S. and B. Singer. (1981). Transcriptional errors and ambiguity resulting from the presence of 1,N6-ethenoadenosine or 3,N4-ethenocytidine in polyribonucleotides. *Nucleic Acids Res* 9:365-373.
55. Swenberg, J., T.R.F. N.Fedtke, and V.E.Walker. (1990). Relationships between carcinogen exposure, DNA adducts and carcinogenesis. In D.B.Clayson, I.C.Munro, P.Shubik, and J.A.Swenberg, editors. Elsevier, Amsterdam. 161-184.

56. Swenberg, J.A., N. Fedtke, F. Ciroussel, A. Barbin, and H. Bartsch. (1992). Etheno adducts formed in DNA of vinyl chloride-exposed rats are highly persistent in liver. *Carcinogenesis* 13(4):727-729.
57. Swenberg, J.A., D.K. La, N.A. Scheller, and K.-Y. Wu. (1995). Dose-Response Relationships for Carcinogens. *Toxicol Lett* 82/83:751-756.
58. U.S. EPA. (1990). Vinyl Fluoride (CAS# 75-02-5). <http://www.epa.gov/opptintr/chemrtk/opptsrch.htm> Washington, DC., U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.
59. U.S. EPA. (1996). Toxic Release Inventory for 1996. <http://toxnet.nlm.nih.gov/servlets/simple-search?1.15.1.2358> (& type CAS# 75-02-5), U.S. EPA TRIFacts.
60. Vogel, E.W. and M.J. Nivard. (1993). Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. *Mutagenesis* 8:57-81.
61. Walles, S.A., B. Holmberg, K. Svensson, S. Osterman-Golkar, K. Sigvardsson, and K. Lindblom. (1988). Induction of single-strand breaks in liver DNA of mice after inhalation of vinyl chloride. *IARC Sci Publ* 227-231.

Appendix A: IARC. (1995). *Dry cleaning, Some Chlorinated Solvents and Other Industrial Chemicals*. Monographs on the Evaluation of the Carcinogenic Risk to Humans. Vol. 63. World Health Organization. Lyon, France. pp. 467-475.

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

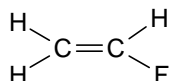
Chem. Abstr. Serv. Reg. No.: 75-02-5

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



$\text{C}_2\text{H}_3\text{F}$

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:* $-72.2\text{ }^\circ\text{C}$ (Lide, 1993)
- (c) *Melting-point:* $-160.5\text{ }^\circ\text{C}$ (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 $21\text{ }^\circ\text{C}$ (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*: $\text{mg/m}^3 = 1.88 \times \text{ppm}^1$

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 (Ebnasajjad & 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 (Siegmund *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: $\text{mg/m}^3 = (\text{relative molecular mass}/24.45) \times \text{ppm}$, 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/m³], but a level of 21 ppm [39.5 mg/m³] 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/m³], and those in four general area samples were 1–5 ppm [1.88–9.4 mg/m³] (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/m³] as an 8-h time-weighted average, with a ceiling value of 5 ppm [9.4 mg/m³] 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/m³] 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/m³] 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/m³) (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/m³] 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/m³], 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/m³] 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/m³] 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/m³] 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/m³] 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 ³H-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/m³] after pretreatment with Aroclor 1254 resulted in liver damage (Conolly *et al.*, 1978). Treatment of newborn rats with 2000 ppm [3760 mg/m³] 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 Evaluation¹

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

- Bentley, K.S., Mullin, L.S., Rickard, L.B., Vlachos, D.A., Sarrif, A.M., Sernau, R.C., Brusick, D.J. & Curren, R.D. (1992) Vinyl fluoride: mutagenic in mammalian somatic cells in vitro and in vivo and in *Drosophila* germ cells but nongenotoxic in germ cells of mammals (Abstract). *Environ. mol. Mutag.*, **19** (Suppl. 20), 5

¹ For definition of the italicized terms, see [Preamble](#).

- Bogdanffy, M.S., Kee, C.R., Kelly, D.P., Carakostas, M.C. & Sykes, G.P. (1990) Subchronic inhalation study with vinyl fluoride: effects on hepatic cell proliferation and urinary fluoride excretion. *Fundam. appl. Toxicol.*, **15**, 394–406
- Bogdanffy, M.S., Makovec, G.T. & Frame, S.R. (1995) Inhalation oncogenicity bioassay in rats and mice with vinyl fluoride. *Fundam. appl. Toxicol.* (in press)
- Bolt, H.M., Laib, R.J. & Klein, K.-P. (1981) Formation of pre-neoplastic hepatocellular foci by vinyl fluoride in newborn rats. *Arch. Toxicol.*, **47**, 71–73
- Brasure, D.E. (1980) Poly(vinyl fluoride). In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk-Othmer Encyclopaedia of Chemical Technology*, 3rd Ed., Vol. 11, New York, John Wiley & Sons, pp. 57–64
- Buckingham, J., ed. (1982) *Dictionary of Organic Compounds*, 5th Ed., Vol. 3, New York, Chapman and Hall, p. 2649
- Chemical Information Services, Inc. (1994) *Directory of World Chemical Producers 1995/1996 Standard Edition*, Dallas, TX, p.706
- Clayton, J.W., Jr (1967) Fluorocarbon toxicity and biological action. *Fluorine Chem. Rev.*, **1**, 197–252
- Cohen, F.S. & Kraft, P. (1971) Vinyl fluoride polymers. In: Bikales, N.M., ed., *Encyclopedia of Polymer Science and Technology*, Vol. 14, New York, Wiley Interscience, pp. 522–540
- Conolly, R.B., Jaeger, R.J. & Szabo, S. (1978) Acute hepatotoxicity of ethylene, vinyl fluoride, vinyl chloride, and vinyl bromide after Aroclor 1254 pretreatment. *Exp. mol. Pathol.*, **28**, 25–33
- Dilley, J.V., Carter, V.L., Jr & Harris, E.S. (1974) Fluoride ion excretion by male rats after inhalation of one of several fluoroethylenes or hexafluoropropene. *Toxicol. appl. Pharmacol.*, **27**, 582–590
- Ebnesajjad, S. & Snow, L.G. (1994) Poly(vinyl fluoride). In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 11, New York, John Wiley & Sons, pp. 683–694
- Environmental Chemicals Data and Information Network (1993) *Fluoroethene*, Ispra, JRC-CEC, last update: 02.09.1993
- Filser, J.G. & Bolt, H.M. (1979) Pharmacokinetics of halogenated ethylenes in rats. *Arch. Toxicol.*, **42**, 123–136
- Filser, J.G. & Bolt, H.M. (1981) Inhalation pharmacokinetics based on gas uptake studies. I. Improvement of kinetic models. *Arch. Toxicol.*, **47**, 279–292
- Filser, J.G., Jung, P. & Bolt, H.M. (1982) Increased acetone exhalation induced by metabolites of halogenated C₁ and C₂ compounds. *Arch. Toxicol.*, **49**, 107–116
- IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 39, *Some Chemicals used in Plastics and Elastomers*, Lyon, pp. 147–154
- IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1–42*, Lyon, p. 73
- IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1–42*, Lyon, pp. 373–376
- IARC (1993) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 56, *Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins*, Lyon, pp. 135–162
- IARC (1994) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 45–71

- ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva
- Kennedy, G.L., Jr (1990) Toxicology of fluorine-containing monomers. *Crit. Rev. Toxicol.*, **21**, 149–170
- Kopečný, J., Lúčanská, N., Šipka, F., Cerný, E. & Ambros, D. (1964) Toxicity of vinyl fluoride. *Pracov. Lék.*, **16**, 310–311 (in Polish)
- Lester, D. & Greenberg, L.A. (1950) Acute and chronic toxicity of some halogenated derivatives of methane and ethane. *Arch. ind. Hyg. occup. Med.*, **2**, 335–344
- Lide, D.R., ed. (1993) *CRC Handbook of Chemistry and Physics*, 74th Ed., Boca Raton, FL, CRC Press, pp. 3–518, B-25
- Ortiz de Montellano, P.R., Kunze, K.L., Beilan, H.S. & Wheeler, C. (1982) Destruction of cytochrome P-450 by vinyl fluoride, fluorene, and acetylene. Evidence for a radical intermediate in olefin oxidation. *Biochemistry*, **21**, 1331–1339
- Oser, J.L. (1980) Extent of industrial exposure to epichlorohydrin, vinyl fluoride, vinyl bromide and ethylene dibromide. *Am. ind. Hyg. Assoc. J.*, **41**, 463–468
- PCR Inc. (1994) *Material Safety Data Sheet: Vinyl Fluoride*, Gainesville, FL
- Quickert, N., Findlay, W.J. & Monkman, J.L. (1975) Modification of a chemiluminescent ozone monitor for the measurement of gaseous unsaturated hydrocarbons. *Sci. total Environ.*, **3**, 323–328
- Sadtler Research Laboratories (1980) *1980 Cumulative Index*, Philadelphia, PA
- Sax, N.I. & Lewis, R.J. (1989) *Dangerous Properties of Industrial Materials*, 7th Ed., New York, Van Nostrand Reinhold, p. 3476
- Siegmund, G., Schwertfeger, W., Feiring, A., Smart, B., Behr, F., Vogel, H. & McKusick, B. (1988) Fluorine compounds. In: Gerhartz, W., Yamamoto, Y.S., Elvers, B., Rounsville, J.F. & Schulz, G., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th Ed., Vol. A11, New York, VCH Publishers, pp. 349–392
- Sutton, D.G., Westberg, K.R. & Melzer, J.E. (1979) Chemiluminescence detector based on active nitrogen for gas chromatography of hydrocarbons. *Anal. Chem.*, **51**, 1399–1401
- United States National Institute for Occupational Safety and Health (1994) *NIOSH Pocket Guide to Chemical Hazards* (DHHS (NIOSH) Publ. No. 94-116), Cincinnati, OH, pp. 330–331
- United States National Library of Medicine (1994) *Hazardous Substances Data Bank (HSDB)*, Bethesda, MD
- Weast, R.C. & Astle, M.J. (1985) *CRC Handbook of Data on Organic Compounds*, Vols I & II, Boca Raton, FL, CRC Press, pp. 433, 624 (I), 591, 770 (II)

Appendix B: IARC. (1986). *Some Chemicals Used in Plastics and Elastomers*. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans – Some Chemicals used in plastics and elastomers. Vol 39. World Health Organization. Lyon, France. pp. 147 – 154.

VINYL FLUORIDE

1. Chemical and Physical Data

1.1 Synonyms and trade names

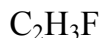
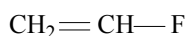
Chem. Abstr. Services Reg. No.: 75-02-5

Chem. Abstr. Name: Ethene, fluoro-

IUPAC Systematic Name: Fluoroethylene

Synonyms: Monofluoroethylene; VF; vinyl fluoride, monomer

1.2 Structural and molecular formulae and molecular weight



Mol. wt: 46.05

1.3 Chemical and physical properties of the pure substance

(a) *Description:* Colourless gas with an ethereal odour (Brasure, 1980); Sax, 1984)

(b) *Boiling-point:* -72.2°C (Weast, 1984)

(c) *Melting-point:* -160.5°C (Weast, 1984)

(d) *Density:* Liquid density, 0.620 g/cm^3 at 25°C (Brasure, 1980)

(e) *Spectroscopy data:* Infrared (Sadtler Research Laboratories, 1980; prism [30864^a], grating [48458P]) and mass spectral data (NIH/EPA Chemical Information System, 1983) have been reported.

^a Spectrum number in Sadtler compilation

- (f) *Solubility*: Insoluble in water; soluble in ethanol and diethyl ether (Hawley, 1981; Sax, 1984, Weast, 1984); soluble in acetone (Weast, 1984)
- (g) *Volatility*: Vapour pressure, 25 atm (19 000 mg Hg) at 21°C (Brasure, 1980)
- (h) *Stability*: Polymerizes freely; forms explosive mixtures with air (Buckingham, 1982); ignites in presence of heat or sources of ignition (Sax, 1984)
- (i) *Conversion factor*: $\text{mg/m}^3 = 1.88 \times \text{ppm}^a$

1.4 Technical products and impurities

Vinyl fluoride is not available commercially in bulk quantities, although it is produced and used internally by one company in the USA (US Environmental Protection Agency, 1981). It is relatively unreactive, in comparison to other monomers, and requires high pressure, temperatures of 60-140°C and free radical catalysts for polymerization. However, for storage purposes, stabilizers such as terpenes (D-limonene) are added to prevent spontaneous polymerization (Cohen & Kraft, 1971; Grayson, 1985). Vinyl fluoride is available with a purity of 99% (Weiss, 1980)

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Vinyl fluoride is produced by the addition of hydrogen fluoride to acetylene in the presence of mercury catalysts. In another method, 1,1-difluoroethane (also formed by the addition of hydrogen fluoride to acetylene) is pyrolysed to vinyl fluoride. Vinyl fluoride has been produced in the USA since 1962 (US Environmental Protection Agency, 1980). No data were available on the quantities of vinyl fluoride produced in 1983.

(b) Use

Vinyl fluoride is used to produce polyvinyl fluoride and other fluoropolymers. Since vinyl fluoride is less reactive than vinyl chloride, free-radical polymerization with peroxide-type catalysts requires high pressures (4350-14500 psi; 300-1000 atm) and moderate

^a Calculated from: $\text{mg/m}^3 = (\text{molecular weight}/24.45) \times \text{ppm}$, assuming standard temperature (25°C) and pressure (760 mm Hg)

temperatures (60-140°C) (Grayson, 1985). The introduction of commercial polyvinyl fluoride by E. I. duPont de Nemours, Inc. in 1962 (US Environmental Protection Agency, 1980) was aided by the development of a Ziegler-Natta catalyst that allowed polymerization at lower temperatures and pressures (Cohen & Kraft, 1971).

Homopolymers and copolymers made from vinyl fluoride show exceptional resistance to chemical attack and water absorption. They are quite stable at relatively high temperatures and are highly stable when exposed to sunlight. Polyvinyl fluoride is used as a protective and decorative surface for building panels and sidings, as a protective cover for pipes (Cohen & Kraft, 1971) and electrical equipment (US Environmental Protection Agency, 1980), for insulating storage tanks, as a top coat on wall coverings, on interior finish in commercial aeroplanes, and as a surface for highway markers. Polyvinyl fluoride film does not fracture when the material to which it is bonded expands or contracts (Cohen & Kraft, 1971).

(c) Regulatory status and guidelines

The US National Institute for Occupational Safety and Health (1978, 1983) has recommended that exposure to vinyl halides be restricted to the minimum detectable level, with the eventual goal of zero exposure. It has recommended an exposure limit of 2 mg/m³ as an eight-hour time-weighted average, with a ceiling value of 10 mg/m³ for any 15-min sampling period.

2.2 Occurrence

(a) Natural occurrence

It is not known whether vinyl fluoride occurs as a natural product.

(b) Occupational exposure

Surveys made at a vinyl fluoride manufacturing plant and a vinyl fluoride polymerization plant (Table 1) showed that exposure levels for production and control operations were generally < 4 mg/m³, while exposures associated with polymer operations ranged from 2-9 mg/m³, with a time-weighted average of 3.6 mg/m³ (Bales, 1978; Oser, 1980).

2.3 Analysis

Vinyl fluoride has been determined in workplace air (1-9 mg/m³) by collection in poly(tetrafluoroethylene) bags and analysis by gas chromatography (Bales, 1978).

Table 1. Occupational exposures to vinyl fluoride at manufacturing and polymerization plants^a

Industry	Job classification	Type of sample	Concentration (mg/m ³) ^b
Manufacturing	Plant operator	Personal	< 4
	Control room	Area	< 4
	Plant operator(start-up)	Personal	40
Polymerization	Polymer operator	Personal	2-8
	Supervisor	Area	2-4
	Pumproom	Area	9

^aFrom Bales (1978); Oser (1980)

^bEight-hour time-weighted average samples

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

No data on the carcinogenicity of vinyl fluoride were available to the Working Group.

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The available data indicate that the acute inhalation toxicity of vinyl fluoride in rats and mice cannot be determined due to the occurrence of asphyxia (Lester & Greenberg, 1950; Kopečný *et al.*, 1964; Clayton, 1967).

Rats pretreated with Aroclor 1254 for three consecutive days and then exposed to 18 000 mg/m³ (10 000 ppm) vinyl fluoride for 4 h had significantly increased serum levels of alanine- α -ketoglutarate transaminase and histological signs of acute hepatotoxicity (Conolly *et al.*, 1978).

Newborn Wistar rats exposed to 4000 mg/m³ (2100 ppm) vinyl fluoride for 8 h per day on five days per week for 4-14 weeks developed ATPase-deficient foci in the liver (Bolt *et al.*, 1981), but to an extent about 20-fold lower than was seen after similar exposure to vinyl

chloride (Bolt *et al.*, 1979). This may be attributable to the slower metabolism of vinyl fluoride under inhalation conditions.

Effects on reproduction and prenatal toxicity

No data were available to the Working Group.

Absorption, distribution, excretion and metabolism

In rats, vinyl fluoride was readily taken up *via* the pulmonary route and, at equilibrium, reached a concentration in the entire organism which was 90% of that in the gas phase. Metabolism was saturable after exposure to concentrations greater than 140 mg/m³ (75 ppm) (Filser & Bolt, 1979, 1981) and was associated with the release of fluoride into the urine (Dilley *et al.*, 1974). The rate of metabolism was much slower than that of vinyl chloride or vinyl bromide under similar exposure conditions (Filser & Bolt, 1979).

When incubated with liver microsomes from phenobarbital-treated rats, vinyl fluoride alkylates the prosthetic group (haem) of cytochrome P-450. The alkylated moiety has been identified as the dimethyl ester of *N*-(2-oxoethyl)protoporphyrin IX (Ortiz de Montellano *et al.*, 1982).

Like other halogenated C₁ and C₂ compounds that are transformed to reactive metabolites, vinyl fluoride causes changes in rat intermediary metabolism which lead to increased exhalation of acetone (Filser *et al.*, 1982).

Mutagenicity and other short-term tests

No data were available to the Working Group.

(b) Humans

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Vinyl fluoride has been produced commercially since 1962 by a single company, as an intermediate, for use within the company. It is used to produce polyvinyl fluoride and other fluoropolymers. Occupational exposure is limited to the manufacture of the monomer and its conversion polymers.

4.2 Experimental data

No data were available to evaluate the carcinogenicity, reproductive effects or prenatal toxicity of vinyl fluoride to experimental animals or the activity of vinyl fluoride in short-term tests.

4.3 Human data

No data were available to evaluate the reproductive effects or prenatal toxicity of vinyl fluoride to humans.

No case report or epidemiological study was available to evaluate the carcinogenicity of vinyl bromide to humans.

4.4 Evaluation

No data were available to evaluate the carcinogenicity of vinyl fluoride to experimental animals or to humans.

5. References

- Bales, R.E. (1978) *Vinyl Halides Carcinogenicity (Current Intelligence Bulletin No. 28; DHEW (NIOSH) Pub. No. 79-102)*, Cincinnati, OH, National Institute for Occupational Safety and Health
- Bolt, H.M., Laib, R.J. & Stockle, G. (1979) Formation of pre-neoplastic hepatocellular foci by vinyl bromide in newborn rats. *Arch. Toxicol.*, *43*, 83-84
- Bolt, H.M., Laib, R.J. & Klein, K.-P. (1981) Formation of pre-neoplastic hepatocellular foci by vinyl fluoride in newborn rats. *Arch. Toxicol.*, *47*, 71-73
- Brasure, D.E. (1980) *Polyvinyl fluoride*. In: Mark, H.F., Othmer, D.F., Overberger, C.B. & Seaborg, G.T., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 11, New York, John Wiley & Sons, pp. 57-64
- Buckingham, J., ed. (1982) *Dictionary of Organic Compounds*, 5th ed., Vol. 3, New York, Chapman and Hall, p. 2649 [F-00396]
- Clayton, J.W., Jr (1967) Fluorocarbon toxicity and biological action. *Fluorine Chem. Rev.*, *1*, 197-252

- Cohen, F.S. & Kraft, P. (1971) *Vinyl fluoride polymers*. In: Bikales, N.M., ed., *Encyclopedia of Polymer Science and Technology*, Vol. 14, New York, Wiley Interscience, pp. 522-540
- Conolly, R.B., Jaeger, R.J. & Szabo, S. (1978) Acute hepatotoxicity of ethylene, vinyl fluoride, vinyl chloride, and vinyl bromide after Aroclor 1254 pretreatment. *Exp. mol. Pharmacol.*, 28, 25-33
- Dilley, J.V., Carter, V.L., Jr & Harris, E.S. (1974) Fluoride ion excretion by male rats after inhalation of one of several fluoroethylenes or hexafluoropropene. *Toxicol. appl. Pharmacol.*, 27, 582-590
- Filser, J.G. & Bolt, H.M. (1979) Pharmacokinetics of halogenated ethylenes in rats. *Arch. Toxicol.*, 42, 123-136
- Filser, J.G. & Bolt, H.M. (1981) Inhalation pharmacokinetics based on gas uptake studies. I. Improvement of kinetic models. *Arch. Toxicol.*, 47, 279-292
- Filser, J.G., Jung, P. & Bolt, H.M. (1982) Increased acetone exhalation induced by metabolites of halogenated C₁ and C₂ compounds. *Arch. Toxicol.*, 49, 107-116
- Grayson, M., ed. (1985) *Kirk-Othmer Concise Encyclopedia of Chemical Technology*, New York, John Wiley & Sons, pp. 516-517
- Hawley, G.G., ed. (1981) *The Condensed Chemical Dictionary*, 10th ed., New York, Van Nostrand Reinhold Co., p. 1086
- Kopečný, J., Lúčanská, N., Šipka, F., Černý, E. & Ambros, D. (1964) Toxicity of vinyl fluoride (Pol.). *Pracov. Lék.*, 16, 310-311
- Lester, D. & Greenberg, L.A. (1950) Acute and chronic toxicity of some halogenated derivatives of methane and ethane. *Arch. ind. Hyg. occup. Med.*, 2, 335-344
- National Institute for Occupational Safety and Health (1978) *Vinyl Fluoride and Vinyl Bromide Industrial Hygiene Survey Report (DHEW (NIOSH) Pub. No. 79-111; US NTIS PB80-190150)*, Cincinnati, OH, pp. 13-18
- National Institute for Occupational Safety and Health (1983) NIOSH recommendations for occupational health standards. *Morb. Mortal. Wkly Rep.*, 32, Suppl., 22S
- NIH/EPA Chemical Information System (1983) *Carbon-13 NMR Spectral Search System, Mass Spectral Search System and Infrared Spectral Search System*, Arlington, VA, Information Consultants, Inc.
- Ortiz de Montellano, P.R., Kunze, K.L., Beilan, H.S. & Wheeler, C. (1982) Destruction of cytochrome P-450 by vinyl fluoride, fluorene, and acetylene. Evidence for a radical intermediate in olefin oxidation. *Biochemistry*, 21, 1331-1339
- Oser, J.L. (1980) Extent of industrial exposure to epichlorohydrin, vinyl fluoride, vinyl bromide and ethylene dibromide. *Am. ind. Hyg. Assoc. J.*, 41, 463-468
- Sadtler Research Laboratories (1980) *The Sadtler Standard Spectra Collection, Cumulative Index*, Philadelphia, PA
- Sax, N.I. (1984) *Dangerous Properties of Industrial Materials*, 6th ed., New York, Van Nostrand Reinhold, Co., p. 2730

- US Environmental Protection Agency (1980) *TSCA Chemical Assessment Series, Chemical Information Profiles (CHIPs), August 1976–August 1978 (EPA-560/11-80-011)*, Washington DC, Office of Pesticides and Toxic Substances, pp. 277-289
- US Environmental Protection Agency (1981) Fluoroalkenes; response to the interagency testing committee. *Fed. Regist.*, 46, 53704-53708
- US International Trade Commission (1984) *Synthetic Organic Chemicals, US Production and Sales, 1983 (USITC Publication 1588)*, Washington DC, US Government Printing Office
- Weast, R.C., ed. (1984) *CRC Handbook of Chemistry and Physics*, 65th ed., Boca Raton, FL, CRC Press, p. C-571
- Weiss, G., ed. (1980) *Hazardous Chemicals Data Book*, Park Ridge, NJ, Noyes Data Corp., p. 913