Vinylidene Fluoride
(CAS No. 75-38-7)

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CONTENTS

EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of data on the toxicity, ecotoxicity and environmental fate and impact of vinylidene fluoride (VDF). A hazard/risk assessment is required under current OECD/EU schemes [a,b]. In the USA, VDF is included in the Environmental Protection Agency (EPA) Chemical Right-to-Know Initiative [c].

VDF, a colourless gas, is used mainly in the manufacture of polyvinylidene fluoride and of copolymers with chlorotrifluoroethylene or hexafluoropropylene; it is also used in smaller quantities in the manufacture of other fluorinated copolymers. VDF is sparingly soluble in water and any VDF released to the environment will distribute to the atmosphere, where it will degrade to formaldehyde and carbonyl fluoride. Formaldehyde occurs naturally in the atmosphere and is broken down to carbon dioxide and water; carbonyl fluoride, once absorbed into cloud droplets, will be hydrolysed to carbon dioxide and hydrogen fluoride. VDF does not cause depletion of the stratospheric ozone layer and it makes a comparatively negligible contribution to global warming and the formation of ground-level ozone (except for the additional carbon dioxide from breakdown).

Model calculations predict that VDF will not be toxic to environmental organisms. No bioaccumulation and biomagnification in the food chain is expected. Biodegradation of VDF in water, sediment or soil is unknown, but is not considered of relevance since VDF will partition rapidly into the air.

VDF has a low acute toxicity in laboratory animals, with no signs of cardiac sensitisation following short-term inhalation of high doses; longer-term exposure also results in a low level of toxicity. The effects are weak and relate to changes in blood chemistry (increased haemoglobin), degeneration of the vomeronasal organ, and mineralisation of the kidneys at high doses. VDF is metabolised to fluoroacetic acid, which could interfere with the citric acid cycle.

VDF is not genotoxic either *in vitro* or *in vivo,* apart from some activity in a bacterial test. Although rats developed carcinomas in an early one-year oral study, subsequent lifetime inhalation studies in rats and mice showed no adverse effects at high doses. It is therefore unlikely that VDF has significant long-term toxic or carcinogenic properties.

[a] OECD Existing Chemicals Programme [www1.oecd.org/ehs/hazard.htm]
[b] EU Existing Chemicals Work Area [ecb.ei.jrc.it/existing-chemicals/]
[c] US-EPA high production volume (HPV) challenge list [www.epa.gov/oppt/chemrtk/]

VDF has no effects on rat fertility or reproduction. Signs of impaired spermatogenesis found in an early study remained unconfirmed in two subsequent studies. A teratology study did not indicate any embryotoxic, foetotoxic or teratogenic effects at high concentrations.

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple uses) are jointly reviewed by experts from a number of companies with knowledge of the chemicals. Only the chemical itself is considered in a JACC review; products in which it appears as an impurity are not normally taken into account.

This document presents a critical evaluation of the toxicology, ecotoxicology, environmental fate and impact of vinylidene fluoride (CAS No. 75-38-7).

Where relevant, the Task Force has graded the studies by means of a "code of reliability" (CoR) (Appendix A) to reflect the degree of confidence that can be placed on the reported results.

1. SUMMARY AND CONCLUSIONS

Vinylidene fluoride (VDF) is a colourless, odourless, flammable gas that is sparingly soluble in water. It is used mainly in the manufacture of VDF polymers, and with chlorotrifluoroethylene and hexafluoropropylene, in the manufacture of thermoplastic or elastomeric copolymers. Smaller quantities are used in the manufacture of terpolymers based on tetrafluoroethylene and hexafluoropropylene, and in the production of 1,1,1-trifluoroethane (HFC-143a). The total global VDF consumption for fluoropolymers and fluoroelastomers is nearly 23 kt/year. Manufacturers of VDF either polymerise the compound on-site, or sell and transport the substance in bulk quantities as a liquefied gas under pressure.

Any VDF released to the environment ("fugitive emissions") is expected to partition preferentially to the atmosphere on account of its high volatility and limited solubility in water. Environmental modelling shows that VDF remains predominantly in the aqueous phase only while there is continuous accidental emission to water; it will volatilise fairly rapidly to the atmosphere once emission ceases. When released into soil, VDF has a moderate mobility; most of any VDF present in soil will evaporate into the atmosphere. Under the natural conditions prevailing in soil and in natural water under ambient conditions, VDF will partition to air before any significant degradation can take place.

No bioaccumulation or biomagnification in the food chain is expected. No experimental data are available on the biodegradation of VDF in water, sediment or soil.

Atmospheric degradation of VDF, with a mean half-life of 3.3 days, is initiated mainly by reaction with hydroxyl radicals in the troposphere; this process yields carbonyl fluoride and formaldehyde. Formaldehyde occurs naturally in the atmosphere and is broken down to carbon dioxide and water. Carbonyl fluoride, once absorbed into cloud droplets, will be hydrolysed to carbon dioxide and hydrogen fluoride. VDF does not deplete stratospheric ozone. It makes a negligible contribution to global warming, although its global warming potential is believed to be comparable to that of carbon dioxide, while its emissions are many orders of magnitude lower. In view of the low emissions, the contribution of VDF to the formation of tropospheric ozone is not expected to be significant.

In the absence of experimental data, a modelling approach has been used to assess the effects of VDF on aquatic and terrestrial organisms. From this, and because of its rapid partitioning into the air, it may be concluded that VDF will not be of concern for the aquatic or terrestrial environment.

Laboratory rats exposed to VDF at high concentrations (2,200 ppm; 5,800 mg/m^3) for 30 minutes showed an increased urinary fluoride excretion. In other studies, metabolism seemed to be

saturated at 100 or 400 ppm (260 or 1,050 mg/m^3). There is some evidence that VDF is metabolised to fluoroacetic acid; the latter could interfere with the citric acid cycle.

Following short-term exposure of rats and mice by inhalation to 800,000 ppm VDF (2,100,000 mg/m^3), LC_{50} values were from 128,000 (335,000 mg/m^3) to greater than 800,000 ppm (2,100,000 mg/m^3). These studies, although not conducted according to current guidelines, indicate that VDF has a low acute toxicity. Since VDF is a gas at ambient temperature, no specific skin or eye irritation studies have been carried out. Dogs and cats primed with adrenalin and exposed to 250,000 to 500,000 ppm VDF (650,000 - 2,100,000 mg/m^3) for 5 to 15 minutes showed no signs of cardiac sensitisation.

In the mouse, the mean corpuscular haemoglobin concentration was increased following repeated exposure to 40,000 ppm VDF (100,000 mg/m^3) for 13 weeks. The no-observed adverse effect level (NOAEL) was 7,000 ppm (18,000 mg/m^3). In another 13-week mouse study, mild renal regenerative changes were observed in males at all concentrations and in females at 50,000 ppm (130,000 mg/m^3). In this study, the NOAEL was < 500 ppm (1,300 mg/m^3).

In the rat, reversible degeneration of the vomeronasal organ was observed following exposure to 7,000 ppm VDF (18,000 mg/m^3) for 13 weeks. The NOAEL was 1,000 ppm (2,600 mg/m^3). In an earlier study, rats exposed up to 50,000 ppm (130,000 mg/m^3) for 13 weeks showed changes in haematology, clinical chemistry and in organ weights, without a clear relationship to dose or sex. Histopathology revealed one animal with rhinitis and nasal epithelial erosion. The NOAEL in this study was < 500 ppm (1,300 mg/m^3).

In another study, rats exposed to concentrations of up to 40,000 ppm VDF (100,000 mg/m^3) for 13 weeks showed transient changes in haematology, clinical chemistry and organ weights; these were not dose related. In the 7,000 and 40,000 ppm (18,000, 100,000 mg/m^3) males, there were histological signs of impaired spermatogenesis. Increased mineralisation of the kidneys in the 40,000 ppm males and vomeronasal degeneration at all concentrations were observed at the end of the study. The NOAEL was < 1,000 ppm (2,600 mg/m^3).

VDF has been tested in a number of genotoxicity assays. VDF does not significantly interfere with the genome of organisms. A marginally positive finding in the *Salmonella typhimurium* strain TA1535 at 100,000 ppm VDF and above (≥ 260,000 mg/m^3) in the presence of a metabolic activation system, cannot be explained. It may be that some metabolite of VDF interfered directly or indirectly with the genomic integrity of the test organism.

In a 1-year gavage study in rats, lipomas and liposarcomas were observed in treated animals at autopsy following natural death. As the study design was not compatible with current protocols for these endpoints and the observations were inadequately reported, the results are difficult to

interpret. Two subsequent lifetime inhalation studies in rats (2 years) and mice (18 months) showed no significant treatment-related adverse non-carcinogenic or carcinogenic effect at the highest concentration tested (10,000 ppm; 26,000 mg/m^3). It is therefore considered unlikely that VDF has significant long-term toxic or carcinogenic properties.

The potential effect of VDF on male and female fertility and reproduction has been studied in rats. In a 13-week inhalation study there was an effect on the testes, indicating impaired spermatogenesis. However, a subsequent 13-week study, with emphasis on male fertility, failed to confirm this earlier finding. A combined male/female fertility and reproduction study in the rat did not reveal any effect on these endpoints at up to 7,000 ppm VDF (18,000 mg/m^3). A teratology study in the rat did not indicate any embryotoxic, foetotoxic or teratogenic effect at the highest concentration tested (10,000 ppm; 26,000 mg/m^3).

An occupational exposure limit value of 500 ppm (1,300 mg/m^3) as a time-weighted average concentration has been set for VDF by the American Conference of Governmental Industrial Hygienists. VDF is included, with a specific migration limit of 5 mg/kg, on the European Commission's positive list of monomers and other starting substances for plastics materials and articles intended to come into contact with foodstuffs.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name: Vinylidene fluoride

IUPAC name: 1,1-Difluoroethylene

Synonyms: CA 16
1,1-Difluoroethene
FC-1132a
Fluorovinylidene
Genetron-1132a
HFC-1132a
R-1132a
VF2
Vinyl difluoride
Vinylidene difluoride

CAS name: Ethene, 1,1-difluoro-

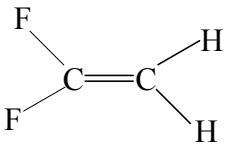
CAS registry number: 75-38-7

EC (EINECS) number: 200-867-7

Formula: $C_2H_2F_2$

Molecular mass: 64.04

Chemical structure:



2.2 EC classification and labelling

To date VDF has not been classified by the European Commission under the Dangerous Substances Directive 67/548/EEC and its subsequent amendments (EC, 2001).

VDF should be provisionally classified and labelled as follows:

Classification:	R 12	Extremely flammable	
Labelling:	Symbol	F+	Extremely flammable
	Risk phrases	R 12	Extremely flammable
	Safety phrases	S 16	Keep away from ignition sources - No smoking
		S 33	Take precautionary measures against static discharges

2.3 Physical and chemical properties

At normal (ambient) temperature and pressure, VDF is a colourless, odourless, flammable gas that is only slightly soluble in water. Physical and chemical properties are listed in Table 1.

Typically, commercial VDF has a purity of ≥ 99.7%. Common impurities are various other fluorocarbons, depending on the conditions of the production process (Section 3.1).

Table 1: Physical and chemical properties

Parameter, units	Value, unit	Reference
Freezing point	–144°C	Solvay, 2003
Boiling point at 1,013 hPa	–83°C	Solvay, 2003
Relative density of liquid D_4^{25}	0.6	Solvay, 2003
(density of water at 4°C is 1,000 kg/m^3)	0.594	Yaws, 1999
at 23.6°C	0.617	Mears *et al*, 1955
Viscosity at 20°C	No data	
Refractive index n_D at 20°C	No data	
Vapour pressure, at 20°C	35,700 hPa [a]	Solvay, 2003
	35,900 hPa [b]	Mears *et al*, 1955
	36,100 hPa [c]	Air Liquide, 2002
at 21°C	35,720 hPa [d]	Matheson-Trigas, 2002
at 25°C	40,000 hPa [e]	Mears *et al*, 1955
Vapour density at 25°C (air = 1)	2.2	Solvay, 2003
Threshold odour concentration	No data	
Surface tension at 20°C	No data	

Table 1: Physical and chemical properties (cont'd)

Parameter, units	Value, unit	Reference
Solubility in water at 1,013 hPa		
at 20°C	442 mg/l [f]	Veretennikov *et al*, 1984
at 25°C	180 mg/l [g]	NTP, 2001
at 25°C	180 mg/l [f,h]	Matheson-Trigas, 2002
at 25°C	165 mg/l [I]	Horvath, 1982
at 25°C	165 mg/l [f,j]	Yaws, 1999
at 28°C	254 mg/l	Ausimont, 2001
at 40°C	314 mg/l [f]	Veretennikov *et al*, 1984
Partition coefficient, log K_{ow} (octanol/water) at 20°C	1.24 [k]	Chou and Jurs, 1979; Yaws, 1999
Partition coefficient, log K_{oc} (organic carbon/water) at 20°C	1.54 [k]	US-EPA, 2003
Henry's Law constant, at 25°C	38,080 Pa·m^3/mol [l]	Yaws, 1999
Flash point, closed cup	≤ –65°C	Pohanish, 2002
Explosion/flammability limits in air at 1,013 hPa	4.7 - 21% (v/v)	Solvay, 2003
	4.7 - 25.1% (v/v)	Air Liquide, 2002
	5.5 - 21.3% (v/v)	NTP, 2001
	5.8 - 20.3% (v/v) [m]	Dohany, 1994; Matheson-Trigas, 2002
Auto-flammability, ignition temperature	380°C	Air Liquide, 2002
	640°C	Yaws, 1999; Matheson-Trigas, 2002

[a] Reported as 35.7 bar

[b] Reported as 521.2 psia [35.9 bar]

[c] Reported as 36.1 bar

[d] Reported as 26,790 mm Hg [35.72 bar]

[e] Reported as 579.5 psia [40.0 bar]

[f] Atmospheric pressure not stated, presumably 1 atm (1,013 hPa)

[g] Reported as 0.018 g/100 g at 760 mm Hg (1,013 hPa)

[h] Reported as 0.018%

[i] Reported as 0.01649 wt% at 1 atm

[j] Reported as 165 ppm w/w

[k] Calculated

[l] Reported as 0.37582 atm.m^3/mol. Note that the solubility values listed above, which range from 165 to 405 mg/l at 25°C and 1 atm pressure (the later value being interpolated from the Veretennikov *et al* data), correspond to Henry's Law constants (H) ranging from 0.388 to 0.158 atm·m^3/mol, respectively, i.e. 39,320 to 16,020 Pa·m^3/mol, respectively. In particular, the Ausimont (2001) value for the solubility leads to H = 0.252 atm·m^3/mol = 25,540 Pa·m^3/mol (at 28°C). These calculations were performed using the formula H = (1 atm) / (solubility at 1 atm/molecular mass).

[m] These values are taken from Baratov and Kucher, 1965

2.4 Conversion factors

Conversion factors for VDF concentrations in air at standard conditions (25°C and 1,013 hPa) are:

- 1 mg/m^3 = 0.382 ppm
- 1 ppm = 2.617 mg/m^3

In this report, converted values are given in parentheses.

The generic formula, from which the conversion factors for vapour concentrations in air are derived, is given in Appendix B. According to the European standard conditions (20°C and 1,013 hPa) these would be 1 ppm = 2.662 mg/m^3 and 1 mg/m^3 = 0.376 ppm.

2.5 Analytical methods

Generally, VDF is determined and analysed in air by gas chromatography using an isothermal (100°C) column filled with Poropak type Q 80/100 (Bright and Matula, 1968) and equipped with a flame ionisation detector. The analytical limit of detection is 50 to 100 ppb (by volume) VDF in air (Solvay, 2004).

There are no standard methods for the analysis of VDF in water, sediment, soil, or biological media.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

VDF is produced by the high-temperature dehydrochlorination of 1-chloro-1,1-difluoroethane (HCFC-142b):

$$CClF_2CH_3 \rightarrow CF_2{=}CH_2 + HCl \quad \text{(Eq. 1)}$$

This pyrolysis process is conducted in a continuous closed reactor.

A total amount equivalent to 23 kt HCFC-142b (Section 3.4) is used in the production of VDF; this figure is assumed to be the global production of VDF.

3.2 Storage

VDF is stored in open air in steel containers (typical 50 - 100 m^3) fitted with a safety valve or vent; pumps are monitored by explosimeters. The containers are protected from direct sunlight and stored away from ignition and heat sources. Equipment and piping containing VDF is installed below ground level to avoid static build up and electrostatic discharges.

3.3 Transport

Manufacturers either polymerise VDF on-site or transport the substance in bulk quantities as liquefied gas under pressure (100 gallon gas cylinders or tube trailers).

3.4 Use

VDF is used in the manufacture of polyvinylidene fluoride (PVDF) and, with chlorotrifluoroethylene or hexafluoropropylene, in the manufacture of thermoplastic or elastomeric copolymers. Smaller quantities are used in the manufacture of terpolymers based on tetrafluoroethylene (TFE), hexafluoropropylene as well as in the production of 1,1,1-trifluoroethane (HFC-143a).

Consumption of PVDF increased from zero in 1960 to 6.2 kt in 1991 (Dohany, 1994). The amount of HCFC-142b (the precursor of VDF) used in 1999 for the production of fluorinated polymers and elastomers was 19, 14 and 2.8 kt for the USA, Western Europe and Japan, respectively (Will *et al,* 2001). The total amount used is equivalent to 23 kt of VDF.

SRI (2002) gives worldwide consumption figures as shown below (Table 2).

Table 2: Worldwide consumption of VDF

	kt polymer	kt VDF
PVDF homopolymer	14.2	14.2
Chlorotrifluoroethylene-VDF copolymer	0.45	~ 0 [a]
Tetrafluoroethylene-hexafluoropropylene-VDF terpolymer	~ 0	~ 0
Fluoroelastomers	15.0	9.5 [b]

[a] The SRI figure is assumed to refer to copolymers containing only a small percentage of VDF

[b] Based on the assumption that the average VDF content is equal to that of the most common formulations (e.g. Viton), with a VDF/HFP molar ratio of 4:1, corresponding to 63 wt-% VDF

The total VDF consumption for fluoropolymers and fluoroelastomers amounts to 23.7 kt/y. This figure is in agreement with the value of 23 kt/y derived from the consumption of HCFC-142b for the production of fluoropolymers and elastomers.

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Emissions

4.1.1 Natural sources

There is no known natural source of VDF.

4.1.2 Emissions during production and use

With regard to VDF emissions from modern production and polymerisation plants, any unconverted monomer is recovered and recycled, while all waste waters are stripped before discharge, to remove any dissolved VDF. VDF and other fluorinated organics present in vent gases are destroyed by high-temperature incineration or removed by adsorption on active carbon. The only emissions are therefore "fugitive" leakages, for example from pumps, valves or flanges.

Since VDF is employed in closed systems (sealed pipes and vessels) under high pressure, exposure is considered to be negligible. Emissions will therefore be incidental, occurring only in equipment failures and maintenance operations. Monitoring systems are capable of detecting levels of 0.1 ppm (0.3 mg/m^3).

Residual levels in polymers and polymer dispersions

VDF polymers contain less than 1 ppm unreacted monomer. The polymers are thermally, chemically, and ultraviolet-light resistant, and are used for pumps and valves and for lining tanks and pipes used in chemical or food processing equipment. When the polymer is used with compatible materials, the decomposition of the polymer is minimal, resulting in negligible VDF concentrations in food (when used in food processing equipment) or in the environment.

4.2 Environmental distribution

On account of its high volatility and vapour pressure, and its limited solubility in water, VDF is expected to partition preferentially to the atmospheric compartment of the environment. This conclusion is supported by a standard Mackay Level I (equilibrium) model calculation (Mackay *et al*, 1996), using the properties given in Table 1. Distribution was calculated to be: air 100.0%, water 0.03% and soil, sediment, suspended particles and biota (fish), each < 0.001% (Colombo, 2003).

A calculated water partition coefficient (K_{ow}) of 17.4 (log K_{ow} 1.24 in Table 1) indicates that VDF would not partition significantly to organic material in soil or water. The soil partition coefficient (K_{oc}) is calculated to be 34.7 (log K_{oc} 1.54 in Table 1). Hence the presence of organic matter would not increase significantly VDF concentrations in these compartments compared to those determined by its solubility and volatility.

Application of the equilibrium criterion (EQC) Level I partitioning model (Mackay *et al*, 1996) indicates that VDF partitions completely (100%) to air. Since discharge into water and soil occurs only rarely (e.g. after an accidental release) the EQC Level III model (Mackay *et al*, 1996) has been applied to evaluate the possible environmental distribution after such a release. Using the given half-lives for air and water (Section 4.3.1 and 4.3.2) and the EQC default emission of 1,000 kg/h only into the soil compartment, it is calculated that 100% of VDF partitions to the atmosphere (Colombo, 2003).

Running the EQC Level III model with 1,000 kg VDF/h emissions solely into the water compartment, results in partitioning into air (~ 20%) and water (~ 80%). The same distribution results are obtained assuming more realistic emissions of 1 kg VDF/h to water. This indicates that if emission into water did occur, the compound would reach air (20%) immediately through volatilisation from the water compartment. Equilibrium between air and water would be achieved slowly, promoting volatilisation from water and elimination through advection. The total residence time of VDF in this last scenario is 300 to 400 hours (Colombo, 2003).

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric fate and impact

Atmospheric lifetime [a]

The degradation of VDF in the lower atmosphere will be initiated mainly by reaction with naturally occurring hydroxyl radicals (˙OH). The rate constant (k_{OH}) for this process was determined by Howard (1976) at low pressures, in the "fall-off" region (0.001 - 0.01 atm). Extrapolating Howard's values to atmospheric pressure gives $k_{OH} = 2.4 \times 10^{-12}$ cm^3/molecule·s at 296 K. Krejci (1995) found a similar value, $k_{OH} = 2.5 \times 10^{-12}$ cm^3/molecule·s, at the same temperature.

Assuming a mean tropospheric ˙OH concentration of 10^6 molecules/cm^3, the half-life of VDF is calculated to be approximately 3.3 days. (An atmospheric half-life of 2 days is used with

[a] Lifetime is the time necessary for 63% degradation; it is equal to the "half-life" divided by ln 2 (= 0.69)

persistent organic pollutants to give an indication of potential for long-range atmospheric transport). However, this is a global annual average value and, for such a short-lived species as VDF, the actual atmospheric persistence will vary greatly (with latitude and season of year, even time of day), mainly on account of variations in the local ˙OH concentration.

Becker *et al* (1974) determined the rate constant for reaction of VDF with ozone to be 8×10^{-20} cm^3/molecules at ambient temperature. Assuming the mean tropospheric O_3 concentration to be 7.5×10^{11} molecule·s/cm^3, the half-life of VDF with respect to reaction with O_3 is 134 days. This reaction will therefore make a negligible contribution to the atmospheric degradation of VDF.

The ultraviolet absorption of VDF falls off abruptly above 190 nm (Bélanger and Sandorfy, 1971; Sirkin and Pimentel, 1984) so that photolysis at wavelengths reaching the troposphere (> 290 nm) is not significant.

Ozone depleting potential

VDF contains neither chlorine nor bromine. Therefore, its ozone depleting potential is zero.

Global warming potential

No estimations of the global warming potential (GWP) of VDF have been made. However, by analogy with other fluorinated olefins having a half-life of only a few days (e.g. hexafluoropropylene) (Acerboni *et al*, 2001), the GWP of VDF is expected to be extremely low compared to CO_2. As the emissions of VDF are many orders of magnitude lower than those of CO_2, the absolute contribution of VDF to global warming will be negligible.

Tropospheric ozone formation

VDF emitted to the atmosphere will contribute to the formation of tropospheric ozone. Model calculations would be required to quantify this effect, which will also depend on the quantity emitted to the atmosphere. Since emissions of VDF are many orders of magnitude lower than those of the principal "volatile organic compounds" responsible for tropospheric ozone formation, VDF is expected to make a negligible contribution to photochemical smog.

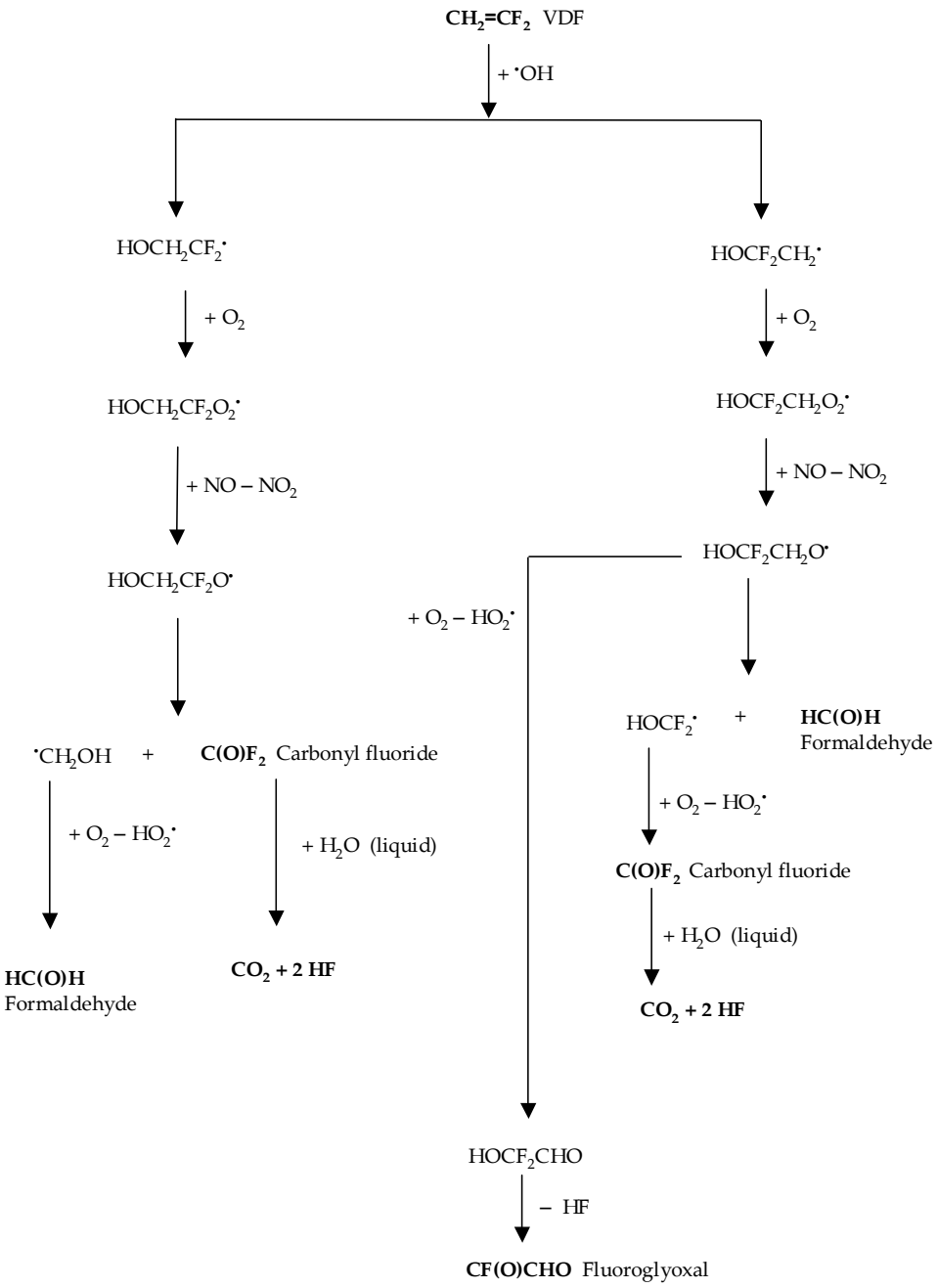
Degradation mechanism and products

A simplified breakdown scheme (Figure 1) is proposed on the basis of studies carried out on various fluorinated and chlorinated hydrocarbons (Atkinson *et al*, 1989; Cox *et al*, 1995; Lelieveld *et al*, 1999). The scheme is somewhat speculative, since little information is available in the literature on the mechanism and products of the atmospheric degradation of VDF specifically.

As discussed above, a reaction with ˙OH is the only significant process able to initiate the breakdown of VDF. Since VDF is an unsymmetrical olefin, there is the potential for the addition of ˙OH at the double bond to either the hydrogen-substituted or the fluorine-substituted carbon, or to both. The orientation (or "regioselectivity") of this reaction is not known. There is nevertheless a considerable body of experimental and theoretical evidence showing that addition of ˙OH to the double bond of the unsymmetrical chlorinated ethylenes (CH_2=CHCl, CH_2=CCl_2 and CHCl=CCl_2) occurs predominantly at the less substituted carbon (Kirchner *et al*, 1990; Zhang *et al*, 1991; Sekušak *et al*, 1998; Zhu *et al*, 1999; Tichenor *et al*, 2001; Yamada *et al*, 2001; Baumgartner *et al*, 2002). This may not be the case for the corresponding fluorinated ethylenes, since Sekušak *et al* (1998) present theoretical calculations showing that in the case of CH_2=CHF, addition to both carbons occurs in comparable proportions. Pathways subsequent to ˙OH addition and according to both orientations are depicted in Figure 1.

According to the proposed reaction scheme, carbonyl fluoride (COF_2) and formaldehyde (HCHO) are predicted to be degradation products, irrespective of the regioselectivity of the addition of ˙OH to VDF. Formaldehyde occurs naturally in the atmosphere and its fate is not discussed further in this report. Carbonyl fluoride will not be photolysed or undergo chemical reaction in the gas phase of the atmosphere, but will be removed by uptake into cloud droplets and subsequent hydrolysis to CO_2 and HF, within a few weeks (Cox *et al*, 1995). According to Figure 1, if the initial addition of ˙OH to VDF occurs on the fluorine-substituted carbon, then fluoroglyoxal (CF(O)CHO) may be a degradation product. The possible origin and fate of this compound is discussed in more detail below.

Figure 1: Proposed tropospheric degradation mechanism for VDF



[a] NO, NO_2, free radicals

Fluoroglyoxal formation and fate

Studies on the ˙OH -initiated degradation of VDF have some relevance for determining the atmospheric degradation products of VDF. However, the studies were carried out under conditions that differ from those characteristics of the troposphere, namely a much lower total pressure (2.5 mbar), a lower absolute and relative O_2 fraction (0.510 mol%), and a higher VDF concentration (1.3 mol%). Results need to be interpreted in the light of these differences. To analyse the VDF degradation products, a molecular beam sample was fed directly from the reactor into the ion source of a mass spectrometer. Carbonyl fluoride was not identified as a reaction product. However, the electron energy used in the source of the mass spectrometer (16 eV) was apparently insufficient to ionise COF_2, which would explain why it was not reported. The author nevertheless considered that COF_2 would be a major atmospheric product, together with HCHO. The main degradation products observed corresponded to m/e ratios of 76 (possibly CF(O)CHO)), 29 (CHO) and 30 (HCHO). Fluoroglyoxal was a "main product", but it was not fully quantified. In particular, its abundance cannot be compared with that of COF_2, on account of the absence of the latter in the mass spectrum (Krejci, 1995).

The CF(O)CHO observed may result from reactions occurring subsequently to the addition of ˙OH to the fluorine-bearing carbon of VDF:

$$HOCF_2CH_2^{\cdot} + O_2 \rightarrow HOCF_2CH_2O_2^{\cdot} \quad \text{(Eq. 2)}$$

$$HOCF_2CH_2O_2^{\cdot} + RO_2^{\cdot} \rightarrow HOCF_2CH_2O^{\cdot} + RO^{\cdot} + O_2 \quad \text{(Eq. 3)}$$

$$HOCF_2CH_2O^{\cdot} + O_2 \rightarrow HOCF_2CHO + HO_2^{\cdot} \quad \text{(Eq. 4)}$$

$$HOCF_2CHO \rightarrow CF(O)CHO + HF \quad \text{(Eq. 5)}$$

The second reaction (Eq. 3) would likely be replaced, under atmospheric conditions, by:

$$HOCF_2CH_2O_2^{\cdot} + NO \rightarrow HOCF_2CH_2O^{\cdot} + NO_2 \quad \text{(Eq. 6)}$$

leading to the same alkoxy radical.

An alternative explanation for the formation of CF(O)CHO in the study by Krejci (1995), is that the low pressure used favoured fragmentation and rearrangement reactions of the "vibrationally excited" $HOCH_2CF_2^{\cdot}$ (initially formed by addition of ˙OH to the hydrogen-substituted carbon of VDF) rather than the stabilisation of these radicals through energy removal by collision with other molecules present, or reaction with O_2. The re-arrangement:

$$HOCH_2CF_2^{\cdot} \rightarrow HOCF_2CH_2^{\cdot} \quad \text{(Eq. 7)}$$

could be followed by the sequence of the first reactions (Eq. 2 - 5), leading to CF(O)CHO.

If this latter interpretation is correct, then CF(O)CHO may well not be formed in the case of atmospheric degradation, where higher pressures would favour the collisional deactivation of $HOCH_2CF_2^{\bullet}$ rather than its rearrangement.

In any case, CF(O)CHO (if formed) would not persist in the atmosphere. Likely removal processes are photolysis, hydrolysis and reaction with $^{\bullet}OH$. Data on these processes are lacking, but rough estimates of the rates of the latter two processes can be made by analogy with similar compounds.

If photolysis occurs, it is likely to lead to dissociation to 1-carbon fragments, the fluorine present being converted rapidly to HF by a sequence of reactions not detailed in this report. The rate of this process is unknown.

Hydrolysis may occur, following uptake of CF(O)CHO into cloud droplets. This would lead to glyoxylic acid:

$$CFOCHO + H_2O \rightarrow C(O)(OH)CHO + HF \quad \text{(Eq. 8)}$$

The lifetime of CF(O)CHO with respect to this process would be of the order of about a week to a few weeks, by analogy with other acid halides (Cox *et al*, 1995).

The lifetime of CF(O)CHO with respect to reaction with the $^{\bullet}OH$ would be expected to be of the order of 5 to 20 days, by analogy with the behaviour of other haloacetaldehydes (CCl_3CHO, CCl_2FCHO, $CClF_2CHO$ and CF_3CHO) (Rattigan *et al*, 1998).

In conclusion, VDF does not contribute to ozone depletion and the estimated contribution of VDF to radiative forcing (and hence global warming) is less than one millionth of the overall forcing due to all greenhouse gases present in the atmosphere. COF_2 resulting from the breakdown of VDF may make a greater, but still insignificant, contribution.

4.3.2 Aquatic and terrestrial fate

No experimental data are available on the degradation of VDF in water, sediment or soil. However, under the natural conditions prevailing in soil, natural waters, and at ambient temperature and pressure, VDF will partition completely to the atmospheric compartment before any significant degradation can take place.

The EpiWin model (US-EPA, 2003) has been applied to calculate the volatilisation half-life from a river and a lake, at first using default values (river and lake depth = 1 m) and then adopting more realistic representative values (river depth = 5 m and lake depth = 20 m). Table 3 below summarises the results of the two simulations.

Table 3: Volatilisation from water

	Wind velocity (m/s)	Current velocity (m/s)	Depth (m)	Half-life
Default values				
River	5	1	1	0.8 h
Lake	0.5	0.05	1	76 h
More realistic values				
River	5	1	5	12 h
Lake	5	0.05	20	93 d

While the EQC Level III results show that VDF remains predominantly in the aqueous phase as long as there is a continuous emission to water (Section 4.2), EpiWin modelling demonstrates that VDF volatilises fairly rapidly to the atmosphere once emission to water ceases.

4.3.3 Biodegradation

No experimental data are available on the biodegradation of VDF in water, sediment or soil.

Application of the BioWin model (US-EPA, 2003) indicates that biodegradation rates are in the range of several months. Direct emissions to the soil compartment are unlikely and will occur only following accidental release. In any case, volatilisation processes from the soil and water compartments are expected to occur faster than biodegradation.

4.3.4 Bioaccumulation

VDF has a calculated log K_{ow} of 1.24 (Table 1), indicating that possible bioaccumulation in the food chain is not significant. Moreover, the limited solubility of VDF, as well as its almost total distribution to air and its short half-life in that compartment, makes significant contact with the organisms in the food chain negligible. (This is supported by the BCF programme results in the EpiWin model [BCF: 1.8]). It is therefore concluded that bioaccumulation of VDF in the food chain is of low concern.

4.3.5 Summary and evaluation

Environmental release of VDF through various waste streams (e.g. stack emissions from waste incinerators) results largely in emission into the air compartment. The degradation of VDF in the lower atmosphere is initiated mainly by reaction with OH radicals; the estimated mean half-life is 3.3 days. VDF does not deplete the stratospheric ozone. It makes a negligible contribution to global warming, since its GWP is believed to be comparable to that of CO_2, while its emissions are many orders of magnitude lower. In view of the low emissions, the contribution of VDF to the formation of ground-level ozone is not expected to be significant. The tropospheric degradation of VDF is thought to lead mainly to the formation of HCHO and COF_2. The former is a naturally occurring atmospheric trace gas and the latter is removed from the atmosphere, on a time-scale of a few weeks or less, by uptake into cloud water and hydrolysis to HF and CO_2. Fluoroglyoxal may also be a degradation product of VDF. If formed, it is likely to be photolysed rapidly to 1-carbon fragments, its fluorine content being washed out of the atmosphere as HF.

The low K_{oc} of 34.7 (log K_{oc} 1.54 in Table 1) indicates that VDF has a moderate mobility when released into soil; most of any VDF present will evaporate into the atmosphere. Insufficient data are available to assess the importance of biodegradation in the soil elimination process.

In the aquatic compartment, most of the VDF will be eliminated by slow volatilisation. No data are available to calculate the biodegradation rate of VDF in water. Based on its high volatility and low water solubility, the half-lives in rivers and lakes are calculated to be in the range of several hours and a few months respectively. Even if the residence time for VDF in water was longer, aquatic bioconcentration and adsorption to sediment would not be expected to be important fate processes.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

VDF is a gas, has a low calculated log K_{ow} of 1.24 (Table 1) and is thus considered to have no significant bioaccumulation potential. Records indicate that releases to the environment will be minimal during the manufacturing and processing of VDF under standard operating conditions. No indirect human exposure is expected.

5.2 Human exposure levels and hygiene standards

5.2.1 Non-occupational exposure

Based on the physico-chemical properties and anticipated use of VDF, no consumer exposure is expected. There are no direct consumer uses of fluoroalkenes. In addition, final products for which VDF is used will contain no more than 1 ppm unreacted VDF. Thus, no consumer exposure is anticipated.

5.2.2 Occupational exposure

Potential exposure to VDF is limited to its production and polymerisation.

In a survey of a European VDF production plant in 1992 and 1993, a mean workplace VDF concentration of 0.9 ppm (2.4 mg/m^3) was determined; during 0.7% of the working time the level in the work atmosphere was 22.7 ppm (59.4 mg/m^3) (Solvay, 1995 cited by OECD, 2001). In the mid-1980s, two plants in the USA were monitored for exposures to VDF during the polymerisation process. In one, there were no exposures above 1.2 ppm VDF (3.1 mg/m^3) as a time-weighted average (TWA). In the second, depending on the function of the person involved, personal sampling concentrations were < 0.1 ppm to 40 ppm VDF (< 0.3 - 100 mg/m^3). All measurements above 10 ppm (26 mg/m^3) were from incidental exposures (other than normal working conditions and maintenance) and of short duration. For example, a 40 ppm (personal sampling) value was obtained during non-routine maintenance (when an emergency repair of a malfunctioning pump required a vapour line to be bled) resulting in a short-term elevated exposure of the worker (US-EPA, 1999). Since then, process controls and structural production conditions have been improved, and the possibility of worker exposure to VDF has decreased further.

No monitoring data are available for VDF manufacturing and processing in other countries.

5.2.3 Hygiene standards

The American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold limit value (TLV) [a] of 500 ppm VDF (1,300 mg/m^3) (TWA), based on the following considerations. The target organ of VDF toxicity in animals is the liver and the hepatotoxicity has been shown to require metabolism of VDF to a reactive epoxide (Conolly *et al*, 1979; CoR 2e). This is consistent with the concept that toxic effects of haloethylenes result from metabolism to reactive epoxides. The maximum rate of metabolism of VDF is 100 times lower than the metabolic rate of the closely related chloroethylene, vinylidene chloride, which has a TLV of 5 ppm (TWA) (ACGIH, 2002).

5.2.4 Public and environmental health standards

VDF is included, with a specific migration limit of 5 mg/kg, on the positive list of monomers and other starting substances for plastics materials and articles intended to come into contact with foodstuffs (EC, 2002).

5.3 Other standards

None are available.

[a] Threshold limit value expressed as a time-weighted average; the concentration of a substance to which most workers can be exposed without adverse effects.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Due to the specific physico-chemical properties of VDF, no aquatic or terrestrial toxicity testing has been carried out. Specific containment techniques would have to be used to obtain and maintain adequate concentrations in such test systems, and these would cause artefacts (e.g. O_2 depletion and increases in CO_2 concentration) not representative of the natural environment.

In the absence of experimental data, a modelling approach has been used to assess the effects of VDF on aquatic and terrestrial organisms.

6.1 Micro-organisms

No data are available.

6.2 Aquatic organisms

EcoSar software (US-EPA, 2003; CoR 2f) was used to predict the aquatic toxicity of VDF to green algae, daphnids and fish. A log K_{ow} of 1.24 (Table 1) was used for the calculations. EcoSar predictions are based on actual toxicity data for classes of compounds with similar modes of action, i.e. narcosis in the case of fluorocarbons (Boethling *et al*, 1994) (Table 4).

Table 4: Predicted acute toxicity to aquatic organisms

Species	Duration (h)	Effect/ parameter	Concentration (mg/l)
		Growth inhibition	
Green alga	96	EC_{50}	150
		Immobility	
Daphnia	48	EC_{50}	250
		Lethality	
Fish	96	LC_{50}	246

The predicted EC_{50} and LC_{50} values are of the same order of magnitude as the solubility of VDF at a pressure of 1 atmosphere (Table 1). As mentioned previously, this underlines the difficulty of conducting ecotoxicity tests under realistic conditions, since at these VDF concentrations oxygen would be excluded from the test system.

6.3 Terrestrial organisms

A value of 675 mg/kgbw was predicted for the 14-day LC_{50} in earthworms, using the EcoSar programme (US-EPA, 2003; CoR 2f).

6.4 Summary and evaluation

The predicted LC_{50} and EC_{50} values for the aquatic environment are in general greater than 100 mg/l, even if below the solubility value (442 mg/l at 20°C). As VDF is expected to disappear rapidly from the soil and water phase, it is concluded that VDF will not be of concern for the aquatic environment.

With reference to soil, the LC_{50} 14-day value is higher than the solubility of the compound, and this, combined with rapid volatilisation (faster than that estimated for water), indicates that there is no risk for the terrestrial environment.

7. KINETICS AND METABOLISM

7.1 Body distribution

Medinski *et al* (1990; CoR 2e) calculated kinetic parameters for VDF in rats. Steady-state blood levels of VDF in rats were 15 ng/ml at 30 ppm (80 mg/m^3) and 2,400 ng/ml at 16,000 ppm (42,000 mg/m^3); t_{max} was 15 minutes for all concentrations tested. After exposure, blood levels decreased to 10% of C_{max} in 1 hour. VDF tissue-air partition coefficients were 0.07, 0.18, 0.8, 1.0 and 0.29 for water, blood, liver, fat and muscle, respectively.

Kinetic values measured and calculated for mice appeared to be lower than those found for rats (Bechtold *et al*, 1988; CoR 2e).

7.2 In vitro metabolism

VDF was found to inactivate P450 enzyme and haem only to 17% in primed and unprimed rat hepatic microsomes when exposed to 60 µM for 30 minutes. Only a minimal amount of fluoride was released (Baker *et al*, 1987; CoR 2e).

7.3 In vivo metabolism

When rats were exposed to 2,200 ppm VDF (5,800 mg/m^3) for 30 minutes, there was an increased urinary excretion of fluoride for 7 days post exposure; there was no increase in creatinine excretion or urinary volume. In the kidneys, there was hyperaemia in the medulla and a pale whitish band in the cortex, but no histopathological changes (Dilley *et al*, 1974; CoR 2e).

After an 8-hour exposure to 500 ppm VDF (1,300 mg/m^3), rats exhaled acetone, which was considered to be an indication that VDF was partly metabolised to fluoroacetate via hepatic cytochrome P450 (Filser and Bolt, 1980; CoR 2e).

Metabolism seems to be saturated at 100 ppm VDF (260 mg/m^3). The V_{max} was calculated to be 1.1 µM/h/kgbw (Filser *et al*, 1978) and it was suggested that an epoxide intermediate was formed with subsequent rearrangement to halogenated acetaldehyde or acyl halide and formation of fluoroacetic acid; the latter could interfere with the citric acid cycle (Filser and Bolt, 1980; CoR 2e). Zwart (1985; CoR 1d) observed saturation of VDF metabolism in rats at 400 ppm (1,000 mg/m^3).

Stöckle *et al* (1979; CoR 2e) found a metabolic rate for VDF similar to that observed by Filser *et al* (1978) in rats and observed that exposure to 2,000 ppm VDF (5,200 mg/m^3) for 14 weeks

induced minimal depletion of adenosine triphosphate in rat hepatocytes. Bolt *et al* (1979; CoR 2e) reported that interaction with P450 with slowly metabolised compounds such as VDF might lead to the inhibition of the metabolism of drugs and other xenobiotics (e.g. inhibition of *p*-hydroxylation of aniline and demethylation of aminopyrine).

8. EFFECTS ON EXPERIMENTAL ANIMALS

8.1 Acute toxicity

8.1.1 Oral and dermal toxicity

No specific oral or dermal acute toxicity data are available on VDF (gas at room temperature).

8.1.2 Inhalation

Several acute inhalation toxicity tests have been conducted with VDF; these studies are comparable to LC_{50} studies (Table 5).

In a series of acute inhalation studies, the lethal concentration for rats and mice after a 1-hour exposure was greater than 200,000 ppm VDF. Animals were observed for 7 days post exposure; mice showed some minor behavioural changes (Latven, 1974). In another study, rats were exposed to levels up to 800,000 ppm VDF (enriched with 200,000 ppm O_2) for up to 19 hours. There was no mortality and no pathological changes; minor CNS effects were noted (Lester and Greenwood, 1950). Other reports mentioned mortality of mice at 128,000 ppm after a 4-hour exposure, but results were difficult to interpret because of variable exposure periods and the possibility of an inadequate oxygen supply (Carpenter *et al*, 1949).

In an acute hepatotoxicity test, Holtzman rats were exposed to concentrations of 0, 500, 15,000 or 25,000 ppm VDF (0, 1,300, 39,000 or 65,000 mg/m^3) for 4 to 6 hours. No mortality was observed. Only animals pre-treated with polychlorinated biphenyls showed increased liver weights, increased serum sorbital dehydrogenase activity and hepatocellular damage at 500 ppm VDF and above (≥ 1,300 mg/m^3) (Conolly *et al*, 1979; CoR 2e).

Table 5: Acute inhalation toxicity

Species / Strain, number, sex	Concentration tested (ppm)	Concentration tested (mg/m^3)	Exposure time (h)	LC_{50} (ppm)	LC_{50} (mg/m^3)	Observation period (d)	Symptom	Reference	CoR
Mouse									
CF1, 5 M	4,000, 8,000, 20,000, 40,000, 100,000, 200,000	(10,000, 21,000, 50,000, 100,000, 260,000, 520,000)	1	> 200,000	> 260,000	7	Excessive grooming in highest dose animals	Latven, 1974	2c
Rat									
Not stated, 6 F, 6 M	Not stated		4	128,000	335,000		Not reported	Carpenter *et al*, 1949	3b
Wistar, 5 F, 5 M	Not stated		1	> 200,000	> 260,000	7	None observed	Latven, 1974	2c
Not stated	100,000, 200,000, 300,000, 400,000, 500,000, 800,000 [a]	(260,000, 520,000, 790,000, 1,000,000, 1,300,000, 2,100,000)	0.5 - 19	> 800,000	> 2,100,000		Unsteady gait at 800,000 ppm	Lester and Greenberg, 1950	3a

[a] O_2-enriched air

8.1.3 Cardiac sensitisation

Dogs and cats primed with adrenalin and exposed to 250,000 to 500,000 ppm VDF in air (650,000 - 1,300,000 mg/m^3) for 5 to 15 minutes showed no signs of cardiac sensitisation (Burgison, 1955; CoR 2e).

8.1.4 Summary

Several acute inhalation studies were carried out in rats and mice with up to 800,000 ppm VDF for 1 to 19 hours. Observed or calculated LC_{50} values were from 128,000 to above 800,000 ppm (335,000 - > 2,100,000 mg/m^3). Although none of the studies were conducted according to currently prescribed standard protocols, the available data indicate that VDF has a low acute toxicity.

Another acute hepatotoxicity study supports the conclusion of low acute toxicity.

VDF does not sensitise the heart.

8.2 Skin, respiratory tract and eye irritation, sensitisation

8.2.1 Skin, eye and respiratory tract irritation

As VDF is a gas at ambient temperature, no specific cutaneous or ocular irritancy studies have been conducted. Results of other toxicity studies indicate that VDF is not significantly irritant to skin, eyes or respiratory tract. Accidental releases of liquefied VDF may cause frostbite if contact with skin occurs.

8.3 Repeated dose toxicity

The available toxicity studies on repeated exposure to VDF are summarised in Table 6.

Table 6: Repeated inhalation toxicity

Species (strain, number and sex/group)	Concentration (ppm)	Concentration (mg/m^3)	Exposure regime	Result	Reference	CoR
Rat						
ChR-CD albino, 10 M	0, 25,000	(0, 65,000)	6 h/d, 5d/wk, 2 wk	↑ urinary fluoride excretion, isolated ↑ RBC count, respiratory structural changes (tracheitis and/or mucosal hyperplasia)	Du Pont, 1977	1d
Sprague-Dawley, weanling and young adult, 180/type/sex	0 , 250, 1,000, 7,000	(0, 650, 3,000, 18,000)	6 h/d, 5d/wk, 13 wk	No effects on fertility. Transient effect on vomeronasal organ at 7,000 ppm	Reuzel *et al*, 1986	1b
Fisher 344, 10 M, 10 F	0, 500, 1,500, 5,000, 15,000, 50,000	(0, 1,300, 3,900, 13,000, 39,000, 130,000)	6 h/d, 5d/wk, 13 wk	Dose-unrelated changes in haematology of males. Changes in clinical chemistry parameters (↓ SGPT, ↑ SGOT, ↑ SDH, ↑ creatinine, ↑ BUN) and (relative and/or absolute organ weights (↑ liver, ↑ kidney, ↑ thymus, ↓ brain, ↓ heart, ↓ testis). Changes were neither dose- nor sex-related. 1 animal of the high dose with serous rhinitis and erosion of the nasal epithelium. NOEL < 500 ppm	Manus, 1984a	1b
Sprague-Dawley, 30 M, 30 F	0, 1,000, 7,000, 40,000	(0, 3,000, 18,000, 100,000)	6 h/d, 5d/wk, 13 wk	Changes in body weight, haematology, clinical chemistry, urinalysis and organ weights. These occurred at different concentrations, were not dose-related and were sometimes transient. Impaired spermatogenesis in mid- and high-dose groups. Treatment-related lymphoid depletion in the spleen of mid- and high-dose males and females. Vacuolar degeneration of the vomeronasal organ in all treated groups. Mineralisation of the kidneys in males of the high-dose group. NOEL < 1,000 ppm	Appelman, 1985	2b

Table 6: Repeated inhalation toxicity (cont'd)

Species (strain, number and sex/group)	Concentration (ppm)	Concentration (mg/m^3)	Exposure regime	Result	Reference	CoR
Mouse						
CD1, 5 M, 5 F	0, 1,000, 5,000, 15,000, 40,000	(0, 3,000, 13,000, 39,000, 100,000)	6 h/d, 5 d/wk, 2 wk	NOEL = 40,000 ppm	Newton, 1988	1b
CD1, 10 M, 10 F	0, 1,000, 7,000, 40,000	(0, 3,000, 18,000, 100,000)	6 h/d, 5 d/wk, 13 wk	Treatment-related transient ↑ locomotor activity. ↑ sensitivity to touch in high-dose males and mid- and high-dose females. Dose-related rough hair coat in males after 8 weeks. ↑ corpuscular Hb in high-dose males at end of study. NOEL = 7,000 ppm.	Newton, 1989	1b
BCF, 10 M, 10 F	0, 500, 1,500, 5,000, 15,000, 50,000	(0, 1,300, 3,900, 13,000, 39,000, 130,000)	6 h/d, 5 d/wk, 13 wk	Weight changes in females. Dose-unrelated liver weight changes. Mild regenerative changes in kidneys in very low incidences in all treated males and high-dose females. NOEL < 500 ppm	Manus, 1984b	1b

8.3.1 Rat

Male albino rats (10/group) were exposed to 0 or 25,000 ppm VDF in a 2-week inhalation study. Five rats/group were assessed for urinalysis, haematology, clinical chemistry and histopathology at the end of the exposure period; the remaining 5/group were re-assessed 14 days post exposure. There was a slight increase in urinary fluoride excretion at the end of the exposure period but not at 14 days post exposure. A slight increase in RBC count observed at the end of the exposure period was still present at the end of the post exposure period. (As this finding was isolated, without associated changes in haemoglobin (Hb), haematocrit (Hct) or mean cell volume values, its biological significance is unclear). There were no changes in clinical chemistry. Various degrees of tracheitis and/or mucosal hyperplasia were seen in some exposed animals at the end of the exposure period, but these effects were absent in recovered animals (Du Pont, 1977).

Weanling and young adult Sprague-Dawley rats were exposed by inhalation to 0, 250, 1,000 or 7,000 ppm VDF for 13 weeks. This study was combined with a fertility/reproduction study (Koeter, 1986). An interim sacrifice and evaluation was made at 4 weeks. Satellite groups were subjected to a recovery period of 10 weeks post exposure. No treatment-related changes were observed regarding body weight, haematology, urinalysis, mortality, oestrus cycle, and organ weights. Gross pathology revealed no changes on histopathology; no treatment-related effects were noted on sperm concentration, number of sperm cells with deformed heads/tails or on numbers of isolated heads/tails in weanlings or young adults. There was a slight degeneration of the vomeronasal organ in animals exposed to 7,000 ppm at 4 weeks in weanlings and young adults, and at 13 weeks only in weanlings; no such effect was observed after the 10-week recovery period (Reuzel *et al*, 1986; Beems, 1988).

As part of the study, a simple fertility study was also carried out, in which male and female rats exposed to VDF for 13 weeks were mated with untreated partners. No effects of potential reproductive significance were observed (Koeter *et al*, 1986).

Fisher 344 rats were exposed by inhalation to 0, 500, 1500, 5,000, 15,000 or 50,000 ppm VDF for 90 days. Transient body weight changes were observed which had subsided at the end of the study; unexplained body weight changes were also seen in the controls. RBC counts, Hb and Hct levels decreased in males at 1,500 and 50,000 ppm; no such changes were observed in females. Some changes in clinical chemistry and organ weights were observed. However, these were not dose or sex related. Histopathological examination revealed only one animal with well-defined rhinitis and erosion of the epithelium of the nasal cavity (50,000 ppm). The NOEL was < 500 ppm, and although observable effects were noted at all exposure levels, dose-related effects were only apparent at the highest concentration (Manus *et al*, 1984a).

In an inhalation study with Sprague-Dawley rats, animals were exposed to 0, 1,000, 7,000 or 40,000 ppm VDF for 13 weeks. Interim sacrifices and observations were made at 2 and 4 weeks. Changes were observed in body weight (transient), and in haematological parameters (from mid-dose males and in high-dose females), clinical chemistry (mid- and high-dose males, high-dose females), urinalysis (high-dose males, mid- and high-dose females) and organ weights (heart, lungs, spleen). The latter occurred at different concentrations, were not dose-related and were sometimes transient. Microscopic examination of testis and epididymis showed treatment-related changes in mid- and high-dose groups throughout the study; these were characteristic of impaired spermatogenesis. The spleen showed treatment-related changes characterised by lymphocyte depletion of the marginal zone (mid- and high-dose males and females, low-dose females) at week 2. All treated animals showed vacuolar degeneration of the vomeronasal organ. Mineralisation of the kidneys was increased in high-dose males after week 4. The NOEL was < 1,000 ppm (Appelman *et al*, 1985).

8.3.2 Mouse

No mortality was observed in CD1 mice exposed by inhalation to 0, 1,000, 5,000, 15,000 or 40,000 ppm VDF for 2 weeks. There were no treatment-related effects on body weight or organ weights and no pathological changes. The NOEL was 40,000 ppm VDF (Newton, 1988).

CD1 mice were exposed by inhalation to VDF concentrations of 0, 1,000, 7,000 or 40,000 ppm for 13 weeks. A treatment-, but not dose-related, increase in locomotor activity was noted in both sexes and was prominent in mid-study, declining thereafter. There was increased sensitivity to touch in the high-dose males during the last week of exposure and in mid- and high-dose females in the last 2 weeks of exposure. Dose-related rough hair was observed in males after 8 weeks and an increase in mean corpuscular Hb in the high-dose males. There were no treatment-related effects on body weight, food consumption or organ weights and no treatment-related macroscopic or microscopic pathological changes. Since the (subjective) clinical symptoms were not related to pathological changes, the NOAEL was 7,000 ppm (Newton, 1989).

Manus *et al* (1984b) exposed BCF mice by inhalation to 0, 500, 1,500, 5,000, 15,000 or 50,000 ppm VDF for 90 days. There was some mortality and transient body weight loss during the study; this was suspected to be related to a failing watering system. Body weight changes were seen in females. Liver weight changes occurred (1,500 ppm males and 15,000 ppm females), but were not dose related. Histopathology revealed only a low incidence of mild renal changes indicative of regeneration in all treated males and in high-dose females; this was not dose related. The NOEL in this study was < 500 ppm.

8.3.3 Summary

Mice and rats were exposed by inhalation to up to 50,000 ppm VDF for up to 13 weeks. In one mouse study, increased mean corpuscular Hb concentration was observed at 40,000 ppm at the end of the 13 weeks. The NOAEL was 7,000 ppm. In another 13-week mouse study, mild renal regenerative changes were observed in males at all doses and in females at the high dose (50,000 ppm). The NOAEL was < 500 ppm.

In one rat study (13 weeks), a reversible degeneration of the vomeronasal organ was observed at 7,000 ppm, the highest dose tested. The NOAEL was 1,000 ppm. In an earlier study (13 weeks, up to 50,000 ppm) haematological clinical chemistry and organ weight changes were noted, but no clear dose or sex relationship was established. Histopathology revealed only one animal with rhinitis and nasal epithelial erosion. The NOAEL was < 500 ppm.

In another 13-week rat study (up to 40,000 ppm), there were transient changes in haematology, clinical chemistry and organ weights; these were not related to dose. In the 7,000 and 40,000 ppm males, histological signs of impaired spermatogenesis were seen. Increased mineralisation of the kidneys in the 40,000 ppm males and vomeronasal degeneration in all treated groups were also observed at the end of the study. The NOAEL was < 1,000 ppm.

8.4 Genetic toxicology

Several *in vitro* and *in vivo* genotoxicity tests have been carried out with VDF. The results are presented in Tables 7 and 8.

Table 7: Mutagenicity in vitro

Endpoint/ Species, strain or target	Metabolic activation	Concentration		Result	Reference	CoR
		(%)	(mg/m^3)			
Reverse mutation						
Salmonella typhimurium, TA1535, TA100, TA1537, TA98	+/– S9 [a]	Up to 50%	(1,300,000)	TA1535, slightly +ve from 10% onwards with metabolic activation only	Russell, 1979	1b
S. typhymurium, TA100	+/– S9	20 - 50	(500,000 - 1,300,000)	Non-significant increase at 50% in presence of metabolic activation	Bartsch, 1979	3b
Mutant frequency						
CHO cells HGPRT locus	+/– S9	0, 20, 40, 60, 80, 100	(0, 500,000, 1,000,000, 1,600,000, 2,100,000, 2,600,000)	–ve	Rickard, 1986	1b
Chromosome aberration						
CHO cells	+/– S9	0, 25, 50, 75, 100	(650,000, 1,300,000, 2,000,000)	–ve	Rickard, 1986	1a

[a] Supernatant of centrifuged 9,000 x g liver homogenate, containing the microsome and cytosol fractions, derived from rats previously treated with Aroclor to induce microsomal enzyme activity

Table 8: Genotoxicity in vivo

Species	Endpoint	Concentration		Result	Reference	CoR
		(%)	(mg/m^3)			
Mouse	Micronucleus erythrocytes bone marrow	0, 0.5, 1.5, 4	(0, 13,000, 39,000, 105,000)	–ve	Hodson-Walker, 1988	1b
Drosophila melanogaster	Sex-linked recessive lethal mutations	0, 4.95, 22.8, 43	(0, 129,500, 597,000, 1,130,000)	–ve	Sernau, 1989	1b

8.4.1 Gene mutations

In vitro

In an Ames test, in which *S. typhimurium* strains TA1535, TA100, TA1537 and TA98 were exposed (with and without S9 activation) to up to 500,000 ppm VDF in the gas phase, only strain TA 1535 reverted significantly at 100,000 ppm and above, and only in presence of the activation system (number of revertant colonies increased maximally 2.6 times compared to controls) (Russell, 1979).

Bartsch *et al* (1979) exposed *S. typhimurium* TA 100 for 24 hours to 200,000 to 500,000 ppm VDF in the gas phase; a marginal non-significant increase in revertant colonies was noted at 50%, only in the presence of the S9 activation system.

In some earlier *in vitro* tests, including an *E. coli* test (Landry and Fuerst, 1968), an Ames test (Jagannath, 1977) and a BALB/3T3 cell transformation test (Matheson, 1978), mutagenic effects were observed. Since the exposure concentrations were not described or were unknown, and in some cases inadequate details of the studies were included, the results are not considered to be as reliable as the more recent studies mentioned above.

In a hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) test, Chinese hamster ovary (CHO) cells were exposed to 0, 200,000 400,000 600,000 800,000 or 1,000,000 ppm VDF in the gas phase for 19 and 5 hours (with and without S9 activation system). No mutant frequency increase was observed (Rickard and Vlachos, 1986).

In vivo

In a sex-linked recessive lethal test, male fruit flies (*Drosophila melanogaster*) were exposed for 24 hours to 0, 49,500, 228,000 or 430,000 ppm VDF. After exposure, males were mated with non-exposed females. As there was no significant difference in lethality of the progeny between controls and exposed males, VDF was not considered to be mutagenic to the X-chromosome of *D. melanogaster* (Sernau, 1989).

8.4.2 Chromosomal aberrations

In vitro

To investigate the occurrence of chromosomal aberrations, CHO cells were exposed to 0, 250,000, 500,000, 750,000 or 1000,000 ppm VDF in the gas phase for 5 or 2 hours (with and

without S9 activation). No chromosomal aberrations were observed in the presence or absence of the activation system. VDF had no toxic effects on the cells (as measured by replication delay in subcultures) (Rickard and Vlachos, 1986).

In vivo

Male and female mice were exposed to 0, 5,000, 15,000 or 40,000 ppm VDF for 6 hours. Bone marrow was collected (24, 48 and 72 hours after initiation of exposure) for microscopic evaluation of incidence of micronuclei in erythrocytes. VDF was not found to be toxic to bone marrow or to influence the incidence of micronuclei (Hodson-Walker *et al*, 1988).

8.4.3 Summary

From the available genotoxicity data, it can be concluded that VDF does not significantly interfere with the genome of organisms. The marginal but positive finding in *S. typhimurium* TA1535 at ≥ 100,000 ppm VDF (260,000 mg/m^3) in the presence of an activation system cannot be explained. It may indicate that some metabolite of VDF (epoxide suggested by Filser and Bolt, 1980; Section 7.3) may interfere directly or indirectly with the genomic integrity of some selected protocaryotic organisms.

8.5 Chronic toxicity and carcinogenicity

Sprague-Dawley rats were exposed (6 h/d, 5d/wk) by inhalation (whole-body) to 0, 150, 600, 2,500 or 10,000 ppm VDF (0, 390, 1,600, 6,500 or 26,000 mg/m^3) for 104 weeks. Control groups consisted of 140 animals/sex and treated groups of 80 animal/sex (including 20 animals/sex/group as satellites). Interim kill of 20 animals/sex/group was conducted at 12 months. There was no treatment-related mortality or clinical changes and no treatment-related effects on ophthalmologic examination. There were no clear and consistent treatment-related effects on body weight gain (food consumption tended to be lower in treated animals than in controls), haematology or urinalysis. Absolute organ weights after 12 months were similar in all groups. Relative organ weights (brain, heart, epididymis) of the 150 ppm males were decreased at study termination. Macroscopic and microscopic examination revealed no treatment-related effects. Some differences in the incidence of minor nasal changes were considered to be of negligible toxicological concern. Evaluation of the observed neoplasms revealed no treatment-related changes in benign or malignant tumour incidence, total number of tumours, or total number of tumour-bearing animals (Arts *et al*, 1991; CoR1a).

Newton (1991; CoR 1b) exposed (6 h/d, 5 d/wk) CD-1 mice (82/sex/group) by whole-body inhalation to 0, 600, 2,500 or 10,000 ppm VDF (0, 1,600, 6,500 or 26,000 mg/m^3) for 18 months. No treatment-related effects were observed on survival, clinical symptoms, ophthalmology, body weight gain, food consumption, haematology, or in macroscopic or microscopic pathology. There was no difference in the incidence of observed benign and malignant neoplasms in exposed animals as compared with controls. Overall the findings were not considered to be of any toxicological or oncological significance with respect to VDF.

Sprague-Dawley rats were fed 0, 4.12 or 8.25 mg VDF dissolved in olive oil by oral gavage (4 - 5 d/wk) for 52 weeks. Animals were allowed to die naturally and lipomas and liposarcomas observed at necropsy. The number of lipomas was increased in the high-dose group as compared to controls; no lipomas were seen in the low-dose group. The number of liposarcomas appeared to be dose-related (Maltoni and Tovoli, 1979; CoR 3a). The study protocol deviated significantly from current guidelines, in terms of number of animals, exposure period, route of administration and statistical evaluation and was not reported in detail; this impedes interpretation of results. Moreover, liposarcomas were found in fat tissue of different embryonic origin but were considered as one type of tumour.

8.5.1 Evaluation

In a 1-year gavage study in rats, lipomas and liposarcomas were observed in treated animals after their natural death. The results are difficult to interpret, as the study was not carried out according to current protocols, and the observations were inadequately reported.

Two subsequent lifetime inhalation studies in rats (2 years) and mice (18 months) showed no significant treatment-related adverse non-carcinogenic or carcinogenic effects at the highest dose tested (10,000 ppm; 26,000 mg/m^3).

It is therefore considered unlikely that VDF has significant long-term toxic or carcinogenic properties.

8.6 Reproductive toxicity

As previously mentioned in Section 8.3.1, studies on male rat fertility have been documented.

In the study by Appelman *et al* (1985; CoR 2b) microscopic examination of the testis and epididymis revealed treatment-related changes in the mid- and high-dose groups. Observations were characteristic of impaired spermatogenesis. However, these findings were not reproduced in

a subsequent study by Reuzel *et al* (1986; Beems, 1988; CoR 1b) where males were exposed to VDF for 13 weeks and then specifically evaluated for effects. Organ weights evaluated at weeks 5 and 13 included coagulating glands, epididymis, prostate, seminal vesicles, testes, uterus and testes of animals in the 10 week recovery group. Microscopic evaluation included sperm morphology at week 14, histological examination of testis and epididymis (all animals), ovaries and uterus (control and high dose). Gross and microscopic pathology revealed no treatment-related effects on sperm concentration, on number of sperm cells with deformed heads/tails, or on numbers of isolated heads/tails in weanlings or young adults. A NOEL of 7,000 ppm (18,000 mg/m^3) was established.

Koeter *et al* (1986; CoR 1b) exposed male and female rats for 15 weeks prior to mating and 2 weeks during mating to 0, 250, 1,000 or 7,000 ppm VDF (0, 650, 2,600, 18,000 mg/m^3). After mating, females were exposed until day 15 of gestation to the same doses. No effects were observed on mortality, parental body weight, fertility indices, reproductive performance, male reproductive organ weights, or on histopathology. There were no treatment-related effects on ovary weights, or litter data. The NOEL was 7,000 ppm or greater.

In a teratology study, pregnant rats were exposed to 0, 2,000 or 10,000 ppm VDF (0, 520, 2,600 mg/m^3) during gestation (days 6 - 15). Mothers were sacrificed on day 20 of pregnancy. No effects were observed on maternal body weight, food consumption, or on number of implantation sites, corpora lutea, live and dead foetuses, or resorption sites. No treatment-related effects were seen on foetal soft tissues of head, thoracic and visceral organs, or on skeletal structures. The NOEL for teratogenicity was 10,000 ppm or greater (Mecler *et al*, 1978; CoR 2e).

8.6.1 Evaluation

The potential effect of VDF inhalation on male and female rat fertility, and reproduction has been examined.

In a 13-week inhalation study, an effect was observed in the testes of male rats, which indicated impaired spermatogenesis. However a subsequent 13-week study, with emphasis on male fertility, did not confirm this earlier finding.

In the rat, a combined male/female inhalation and reproduction study revealed no effect on these parameters at the highest dose tested (7,000 ppm; 18,000 mg/m^3).

A teratology study in the rat indicated no embryotoxic, foetotoxic or teratogenic effect at the highest dose tested (10,000 ppm; 2,600 mg/m^3).

9. EFFECTS ON HUMANS

No data are available.

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APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

Code of Reliability (CoR)	Category of reliability
1	**Reliable without restriction**
1a	GLP guideline study (OECD, EC, EPA, FDA, *etc.*)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, *etc*.)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	**Reliable with restrictions**
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	**Not reliable**
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	**Not assignable**
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated
4e	Documentation insufficient for assessment

APPENDIX B: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR

Conversion factors for vapour concentrations in air can be calculated from the molar volume of an ideal gas at 0°C: 22.4136 litre.

$1\ mg/m^3 = 22.4136/Mw \times 1{,}013.25/P \times (273+T)/273\ ppm$ .....(Eq. B.1)
$1\ ppm = Mw/22.4136 \times P/1{,}013.25 \times 273/(273+T)\ mg/m^3$ .....(Eq. B.2)

where Mw = molecular weight, T = temperature (°C) and P = pressure (hPa).

For European standard conditions, 20°C and 1,013.25 hPa (=1 atm = 760 mm Hg), the formulae become:

$1\ mg/m^3 = 24.0556/Mw\ ppm$ .....(Eq. B.3)
$1\ ppm = Mw/24.0556\ mg/m^3$.....(Eq. B.4)

In the USA and other countries 25°C is used, and the formulae are:

$1\ mg/m^3 = 24.4661/Mw\ ppm$ .....(Eq. B.5)
$1\ ppm = Mw/24.4661\ mg/m^3$.....(Eq. B.6)

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