



***Hexafluoropropylene***  
***(CAS No. 116-15-4)***

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**Hexafluoropropylene (CAS No. 116-15-4)****CONTENTS**

<b>EXECUTIVE SUMMARY</b>	1
<b>THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS</b>	2
<b>1. SUMMARY AND CONCLUSIONS</b>	3
<b>2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS</b>	5
2.1 Identity	5
2.2 EC classification and labelling	6
2.3 Physical and chemical properties	6
2.4 Conversion factors	7
2.5 Analytical methods	8
<b>3. PRODUCTION, STORAGE, TRANSPORT AND USE</b>	9
3.1 Production	9
3.1.1 <i>Manufacturers and quantity</i>	9
3.1.2 <i>Production processes</i>	9
3.2 Storage	9
3.3 Transport	10
3.4 Use	10
<b>4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION</b>	11
4.1 Emissions	11
4.1.1 <i>Natural sources</i>	11
4.1.2 <i>Emissions during production and use</i>	11
4.2 Environmental distribution	12
4.3 Environmental fate and biotransformation	12
4.3.1 <i>Atmospheric fate and impact</i>	12
4.3.2 <i>Aquatic fate</i>	16
4.3.3 <i>Terrestrial fate</i>	17
4.3.4 <i>Biodegradation</i>	17
4.3.5 <i>Bioaccumulation</i>	17
4.3.6 <i>Evaluation</i>	18
<b>5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE</b>	19
5.1 Environmental levels	19

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5.2 Human exposure levels and hygiene standards	19
5.2.1 <i>Non-occupational exposure</i>	19
5.2.2 <i>Occupational exposure</i>	19
5.2.3 <i>Hygiene standards</i>	19
5.2.4 <i>Public and environmental health standards</i>	20
5.3 Other standards	20
<b>6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT</b>	<b>21</b>
6.1 Micro-organisms	21
6.2 Aquatic organisms	21
6.3 Terrestrial organisms	21
6.4 Evaluation	22
<b>7. KINETICS AND METABOLISM</b>	<b>23</b>
7.1 <i>In vivo</i> studies	23
7.2 Metabolism <i>in vitro</i> and in cell-free systems	23
7.3 Summary	24
<b>8. EFFECTS ON EXPERIMENTAL ANIMALS AND <i>IN VITRO</i> TEST SYSTEMS</b>	<b>26</b>
8.1 Acute toxicity	26
8.1.1 <i>Inhalation</i>	26
8.1.2 <i>Metabolites</i>	32
8.1.3 <i>Other acute toxicity studies</i>	32
8.1.4 <i>Summary</i>	32
8.2 Skin, respiratory tract and eye irritation, sensitisation	33
8.3 Repeated dose toxicity	33
8.3.1 <i>Rats</i>	36
8.3.2 <i>Mice</i>	37
8.3.3 <i>Guinea pigs</i>	38
8.3.4 <i>Summary</i>	38
8.4 Genotoxicity	39
8.4.1 <i>Gene mutation in vitro</i>	42
8.4.2 <i>Chromosome aberration</i>	42
8.4.3 <i>DNA repair in vivo</i>	43
8.4.4 <i>Summary and evaluation</i>	43
8.5 Chronic toxicity and carcinogenicity	44
8.6 Reproductive toxicity	44
8.6.1 <i>Studies of potential relevance</i>	44
8.6.2 <i>Summary and evaluation</i>	44

<b>9. MECHANISTIC STUDIES</b>	46
9.1 Kidney toxicity	46
9.2 Summary and evaluation	46
<b>10. EFFECTS ON HUMANS</b>	47
<b>11. BIBLIOGRAPHY</b>	48
11.1 Databases consulted	48
11.2 References quoted	48
11.3 References not quoted	55
<b>APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES</b>	58
<b>APPENDIX B: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR</b>	59
<b>MEMBERS OF THE TASK FORCE</b>	60
<b>MEMBERS OF THE SCIENTIFIC COMMITTEE</b>	61

## 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 and ecotoxicity, and environmental fate and impact of hexafluoropropylene (HFP). A hazard/risk assessment is required under current OECD/EU schemes <sup>a,b</sup>. In the USA, HFP is included in the EPA (Environmental Protection Agency) Chemical Right-to-Know Initiative <sup>c</sup>.

HFP is a chemical intermediate used in the synthesis of fluoropolymers, fluoro-elastomers and also fluorinated oils and greases. It is a colourless gas that is only slightly soluble in water.

Any HFP released to the environment will be found mainly in the air, where it will be broken down by reaction with hydroxyl radicals to trifluoroacetic acid, hydrogen fluoride and carbon dioxide. HFP is unlikely to bioaccumulate. The environmental risk from exposure is low, since only a small amount is released into the environment. HFP does not deplete the stratospheric ozone layer. The global warming impact of HFP is insignificant, other than by contributing to carbon dioxide concentrations on atmospheric breakdown.

HFP has a low acute toxicity in laboratory animals. In repeated exposure studies, the kidney was the principal target organ, as manifest by an increase in relative kidney weight. In one study, there was also a decrease in relative spleen weight. Although no standard reproductive or developmental toxicity studies have been conducted, the reproductive system does not appear to be a target of HFP toxicity and it is not considered that there is a need for any further studies of these end-points. Genotoxicity studies have generally been negative, suggesting a low level of concern. However, recent findings with the structurally related tetrafluoroethylene of chronic toxicity, including certain tumours in life-time studies in mice and rats at high exposure levels, may indicate the possibility of carcinogenicity for HFP.

HFP is manufactured in closed systems and occupational exposure, limited to specific job classifications, is expected to be low. It is thus considered to be of low potential risk. Company internal occupational exposure limits range from 0.5 to 2 ppm (3 - 12 mg/m<sup>3</sup>). There is no known direct consumer exposure to HFP. Consumer exposure is negligible, arising only from low levels of residual monomer in end-use polymeric products.

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<sup>a</sup> OECD Existing Chemicals Programme [<http://www1.oecd.org/ehs/hazard.htm>]

<sup>b</sup> EU Existing Chemicals Work Area [<http://ecb.ei.jrc.it/existing-chemicals/>]

<sup>c</sup> US-EPA high production volume (HPV) challenge list [<http://www.epa.gov/oppt/chemrtk/>]

## **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 use) 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 and ecotoxicology, including environmental fate and impact, of hexafluoropropylene (CAS No. 116-15-4).

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

Hexafluoropropylene (HFP) is a colourless, odourless, non-flammable gas that is only slightly soluble in water. It is used as chemical intermediate primarily in the synthesis of fluoropolymers, fluoro-elastomers and fluorinated materials (e.g. perfluoropolyether functional fluids, oils and greases). Total production ranges from 10 to 20 metric kilotonnes (kt) per year in closed systems. HFP is normally utilised as a feedstock. However, it can be transported as a compressed, non-flammable gas in pressurised containers (1 - 15 t) or via pipelines to other processing and/or production facilities. There is no known direct consumer use. Consumer exposure through marketed polymeric products is anticipated to be negligible because the residual levels of HFP are expected to be low. Release to the environment from anticipated use is expected to be negligible.

By virtue of its physical form as a gas with a low affinity for water, soil and biota, any HFP released into the environment will partition almost entirely to the air compartment. Atmospheric breakdown, to trifluoroacetic acid, hydrogen fluoride and carbon dioxide, is by indirect photolysis (hydroxyl radicals) with a half-life of 3.5 days. HFP is unlikely to bioaccumulate, based on estimated partition coefficients. The environmental risk from exposure is low since only small amounts are released into the environment. HFP does not deplete the stratospheric ozone layer. The global warming impact of HFP itself is insignificant, compared with that of carbon dioxide. On atmospheric breakdown, it will not significantly contribute to carbon dioxide formation.

HFP is manufactured in closed systems and hence occupational exposure is expected to be low. None of the standard-setting authorities (e.g. American Conference of Governmental Industrial Hygienists and German MAK Commission) has set an occupational exposure limit value for HFP. Some manufacturers of HFP have set internal occupational exposure limits ranging from 0.5 ppm to 2 ppm (3 - 12 mg/m<sup>3</sup>) as an 8-hour time weighted average concentration.

HFP is low in acute toxicity. In repeated exposure studies in rodents, the kidney has been identified as the principal target organ; the mouse was more susceptible than the rat. A no-observed adverse effect level (NOAEL) of 10 ppm (60 mg/m<sup>3</sup>) has been identified in both rats and mice in well-conducted studies following exposure to HFP for 90 days. However, in a poorly reported study, rats exposed to HFP for 6 months showed an increase in relative kidney weight and a decrease in relative spleen weight.

The reproductive system does not appear to be a target of HFP toxicity, although no standard reproductive or developmental toxicity studies have been conducted. Given its low occupational exposure limit, which is based on systemic toxicity, and the fact that consumer exposure is anticipated to be negligible, it would seem unnecessary to conduct any further studies of these end-points.



Genotoxicity studies have generally been negative and suggest a low level of concern. However, recent findings with the structurally related tetrafluoroethylene of carcinogenicity (excess of liver haemangio-sarcomas, hepatocellular carcinomas and histiocytic sarcomas in the mouse, and renal tumours in the rat) in lifetime studies<sup>a</sup> may have toxicological significance for HFP. Repeated exposure studies following inhalation (route of concern since HFP is a gas under normal conditions) have identified the kidney as the target organ with the threshold for kidney effects around 200 ppm (1,230 mg/m<sup>3</sup>) in rats and 50 ppm in mice. Recent studies on the long-term effects of tetrafluoroethylene resulted in chronic toxicity (including cancer) under relatively high exposure conditions ( $\geq 156$  ppm; 960 mg/m<sup>3</sup>). The critical effect of HFP is nephrotoxicity. It is recommended that particular attention be given to the chemical similarity of HFP with tetrafluoroethylene, and a consideration of whether this relationship might indicate the possibility of carcinogenicity.

HFP is used as an intermediate and is produced in closed systems. Based on older occupational exposure monitoring records, the potential has existed in specific job classifications for exposures to occur above the recommended (internal) acceptable exposure limits. There may be site-specific occupational situations (specific job classifications) where current potential exposures need to be evaluated. There are no known direct consumer exposures to HFP. In all, HFP is considered to be of low potential risk and of low priority for further work.

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<sup>a</sup> Reviewed by ECETOC (2004)

## 2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

### 2.1 Identity

Name:	Hexafluoropropylene
IUPAC name:	1,1,2,3,3,3-Hexafluoro-1-propene
Synonyms:	FC-1216 Hexafluoropropene Hexafluoropropylene Perfluoropropene Perfluoro-1-propene Perfluoropropylene Propene, hexafluoro- 1-Propene, 1,1,2,3,3,3-hexafluoro- Propylene, hexafluoro-
Danish:	Hexafluorpropen
Dutch:	Perfluorpropeen, hexafluorpropeen
Finnish:	Heksafluoropropyleeni
French:	Perfluoropropène, hexafluoropropylène
German:	Hexafluorpropen, perfluorpropylen
Greek:	Εξαφλοροπροπένιο
Italian:	Esafluoropropene, perfluoropropene
Norwegian:	Hexafluorpropylen
Portuguese:	Hexafluoropropeno, perfluoropropeno
Spanish:	Hexafluoropropeno, perfluoropropeno
Swedish:	Hexafluorpropylen

CAS name: 1-Propene, hexafluoro-

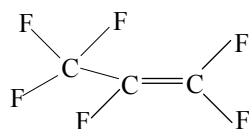
CAS registry number: 116-15-4

EC (EINECS) number: 204-127-4

Formula: C<sub>3</sub>F<sub>6</sub>

Molecular mass: 150.02

Chemical structure:



## 2.2 EC classification and labelling

The European Commission has classified and labelled hexafluoropropylene (HFP) in accordance with the Dangerous Substances Directive 67/548/EEC and its subsequent amendments (EC, 2002) as follows:

Number: 602-061-00-4

Classification: Xn, Harmful; Xi, Irritant

Labelling:	Symbol:	<b>X</b>	Harmful
	Risk phrases	R 20	Harmful by inhalation
		R 37	Irritating to respiratory system
	Safety phrases	S 2	Keep out of reach of children
		S 41	In case of fire and/or explosion do not breathe fumes

There seems to be no justification for this Xi classification and R 37-phrase.

## 2.3 Physical and chemical properties

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

**Table 1: Physical and chemical properties**

Parameter, units	Value, unit	Reference
Melting point	-156.2°C	ECB, 2000
	-156.5°C	Lide, 1999
Boiling point, at 1,013 hPa	-29.4°C	Lide, 1999; Gerhartz, 1999
	-29.6°C	Lewis, 1992
Relative density of liquid, D <sub>4</sub> <sup>20</sup> (density of water at 4°C is 1,000 kg/m <sup>3</sup> )	1.332	Du Pont, 2002
Viscosity, at 20°C	No data	
Refractive index n <sub>D</sub> at 20°C	No data	
Vapour pressure, at 20°C	6,890 hPa <sup>a</sup>	Solvay, 2002
	6,527 hPa <sup>b</sup>	Whipple, 1986
	6,427 hPa <sup>c</sup>	Kirk-Othmer, 1998 cited by OECD, 1998
	5,694 hPa <sup>d</sup>	Yaws, 1999

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

Parameter, units	Value, unit	Reference	
Vapour density at 20°C (air = 1)	5.2	Du Pont, 2002	
Threshold odour concentration, mg/m <sup>3</sup>	Not applicable (odourless)	ECB, 2000; HSDB, 2001	
Surface tension, at 20°C mN/m	No data		
Solubility in water, at 20°C	210 mg/l <sup>e</sup>	Nosov and Barlyaev, 1968	
	224 mg/l <sup>e</sup>	Horvath, 1982	
	98 mg/l <sup>e</sup>	Veretennikov <i>et al</i> , 1984	
	at 25°C	177 mg/l <sup>e</sup>	Nosov and Barlyaev, 1968
	193 mg/l <sup>e</sup>	Horvath, 1982	
at 28°C	82 mg/l <sup>e</sup>	Ausimont, 2001	
Partition coefficient, log K <sub>ow</sub> (octanol/water) at 25°C	2.12 <sup>f</sup>	US-EPA, 2003	
	1.99 <sup>g</sup>	Maaßen, 1996	
	1.981 <sup>g</sup>	Abraham <i>et al</i> , 2001	
Partition coefficient, log K <sub>oc</sub> (organic carbon/water) at 25°C	2.67 <sup>f</sup>	US-EPA, 2003	
Henry's Law constant, at 25°C Pa·m <sup>3</sup> /mol	1.47 x 10 <sup>5</sup> Pa·m <sup>3</sup> /mol <sup>h</sup>	Maaßen, 1996; Abraham <i>et al</i> , 2001	
	0.75 - 1.5 x 10 <sup>5</sup> Pa·m <sup>3</sup> /mol <sup>f,i</sup>		
Flash point, (closed cup)	Not applicable		
Explosion limits in air at 1,013 hPa	28.3 % (v/v) <sup>j</sup>	Yaws, 1999; ECB, 2000	
Flammability	Not flammable <sup>k</sup>	Du Pont, 2002; Solvay, 2002	
Auto-flammability, ignition temperature	No data		

<sup>a</sup> Reported as 6.89 bar at 20°C

<sup>b</sup> Reported as 4,896 torr at 20°C

<sup>c</sup> Calculated from an equation for vapour pressure as a function of temperature (from -29.4 to +85°C)

<sup>d</sup> Calculated from "Antoine-type" regression equation for vapour pressure as a function of temperature

<sup>e</sup> In equilibrium with gaseous HFP (at a partial pressure of 1,013 hPa, except for the Veretennikov *et al* reference, that does not state the pressure explicitly)

<sup>f</sup> Estimated

<sup>g</sup> Measured

<sup>h</sup> Calculated from the reported Ostwald solubility coefficient (0.0169)

<sup>i</sup> Calculated, assuming a solubility of 100 - 200 mg/l at an HFP partial pressure of 1,013 hPa

<sup>j</sup> Upper limit; temperature range not specified

<sup>k</sup> In air, but will burn in oxygen-enriched air if O<sub>2</sub> content > 24%; flammability limits in O<sub>2</sub>: 9 - 72%

## 2.4 Conversion factors

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

- 1 ppm = 6.132 mg/m<sup>3</sup>
- 1 mg/m<sup>3</sup> = 0.163 ppm

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 European standard conditions (20°C and 1,013 hPa) these would be: 1 ppm = 6.236 mg/m<sup>3</sup> and 1 mg/m<sup>3</sup> = 0.160 ppm.

### ***2.5 Analytical methods***

HFP is generally 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) equipped with a flame ionisation detector. The analytical limit of detection is 50 to 100 ppb by volume of HFP in air (Solvay, 2004).

There are no standard methods for the determination of HFP in sediment, water or soil.

### 3. PRODUCTION, STORAGE, TRANSPORT AND USE

#### 3.1 Production

##### 3.1.1 Manufacturers and quantity

Total production within the OECD countries was estimated in the range of 10 to 20 kt in 1999 (OECD, 2000a,b).

##### 3.1.2 Production processes

HFP (purity > 99.5%) is used and transported without the addition of stabilisers.

The most commonly used production process (Gerhartz, 1999) is pyrolysis of tetrafluoroethylene (TFE):



This reaction is carried out in a closed continuous reactor at 600 to 900°C. The yield can be improved at low partial pressure, achieved either by operating under reduced total pressure (down to 0.1 bar) or by injecting an inert diluent such as steam or CO<sub>2</sub>.

Significant quantities of by-products, including the highly toxic perfluoroisobutylene (PFIB), are formed during the pyrolysis of TFE. Such by-products are either incinerated directly or are collected and transported for incineration at a remote facility.

#### 3.2 Storage

HFP is stored in carbon-steel or stainless pressure resistant containers, in cool well-ventilated areas, away from sunlight, heat and ignition sources. HFP should not be stored below ground level, as the gas may accumulate.

Liquid HFP has unlimited storage life under pressure at room temperature in steel containers, even without stabilisers.

### 3.3 Transport

Limited quantities of HFP may be shipped under US-DOT (2001) regulations (using UN number 1858 hazard class 2.2) as a liquefied compressed gas in metal pressure resistant containers (cylinders, tubes, pressure drums and tanks) with a maximum filling degree of 1.11 kg/l and a minimum test pressure of 22 bar (2.2 MPa), subject to the International Maritime Dangerous Goods (IMDG, 2000), the International Carriage of Dangerous Goods by Rail (RID, 2003), the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR, 2003) and the Dangerous Goods Regulation of the International Air Transport Association (IATA, 2003).

Approximately 30% of the production volume is shipped by road or sea in 1 or 15-ton (1.02 - 15.2 t)<sup>a</sup> pressurised containers (OECD, 2000b).

### 3.4 Use

HFP is a reactive chemical and most (~ 90%) is used by the major producers (OECD, 2000b) as a co-monomer for the production of thermoplastics (in particular, the perfluorinated ethylene-propylene copolymer), of fluoro-elastomers based on HFP, vinylidene fluoride and in some cases other components such as TFE, and of perfluoropolyether functional fluids, oils and greases.

A relatively small fraction of HFP is used as a feedstock for producing the CFC alternative heptafluoropropane (HFC-227ea) and HFP oxide. It is also used as a monomer for perfluoropolyether and perfluorovinyl ether manufacture) and other specialty fluoro-chemicals.

There are no direct consumer uses of HFP. Polymeric products based on HFP as a co-monomer may contain low levels of unreacted HFP. Consumer exposure is anticipated to be negligible because the residual levels of HFP in end-use polymeric products will be low (cf. Section 5.2.4).

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<sup>a</sup> 1 metric tonne = 0.9842 ton

## 4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

### 4.1 Emissions

#### 4.1.1 Natural sources

There is no known natural source of HFP.

#### 4.1.2 Emissions during production and use

##### *Production releases*

HFP is used as an intermediate and is produced in closed systems. Furthermore, in most plants, by-products and vent gases are collected and sent directly to a thermal oxidation unit. Non-fugitive emissions are therefore negligible.

HFP is not reportable under the US Toxics Release Inventory (US-EPA, 2001).

In 1994, Du Pont estimated that total controlled non-fugitive releases from its facilities to the atmosphere amounted to approximately 100 tons (102 t) (~ 50% from production and 50% from use) (OECD, 2000b).

Ausimont has reported an estimated annual emission to the air of 50 kg as fugitive emissions. Hoechst has estimated fugitive emissions to air of < 200 kg/y from its manufacturing (Dyneon now operates the Hoechst facility). MDA Manufacturing has reported < 3 tons/y (3.05 t/y) released as airborne fugitive emissions (OECD, 2000b).

##### *Residual levels in polymers*

Release to the environment from anticipated use of fluoropolymers based on HFP as a co-monomer is expected to be negligible.

Small quantities of residual HFP (and other monomers and hydrogen fluoride) may be trapped and evolve slowly from fluoropolymer resins, as well as finished polymeric products based on HFP as a co-monomer. It has been confirmed that HFP can be found in finished products, but the conditions under which it is formed and in what quantities have not been investigated. If large quantities of fluoropolymer materials and products are stored in unventilated spaces, residual gases may accumulate at levels that could be hazardous. Sealed packages may also contain significant concentrations of residual gases (SPI, 1998).



## 4.2 Environmental distribution

On account of its high volatility and low water solubility, HFP is expected to partition preferentially into the atmospheric compartment of the environment. Although no data are available, this conclusion is supported by a Mackay Level I model calculation (Mackay *et al*, 1996). Using as input a Henry's Law constant of  $10^5 \text{ Pa}\cdot\text{m}^3/\text{mol}$  at  $25^\circ\text{C}$  and a  $\log K_{ow}$  of 2 (Table 1), the Level I model predicts equilibrium partitioning of 99.995% to air and 0.005% to water. The fractions estimated to be present in other compartments (air, soil, sediment, suspended sediment, biota [fish]) are all lower than 0.0005% (Franklin, 2003). This is as expected based on the relatively low values for  $\log K_{ow}$  and  $\log K_{oc}$  (Table 1) and a bioconcentration factor of 8.6, calculated using the EpiWin software (US-EPA, 2003).

## 4.3 Environmental fate and biotransformation

### 4.3.1 Atmospheric fate and impact

#### *Atmospheric persistence*

Direct photolysis of HFP is not a significant process in the lower atmosphere, due to its low ultraviolet absorption at wavelengths  $> 290 \text{ nm}$  (Orkin *et al*, 1997; Eden *et al*, 2003). According to a study by Eden *et al* (2003), the lifetime of HFP with respect to photolysis in the lower atmosphere is greater than 1 year. This implies that this removal process is negligible compared with degradation by reaction with the hydroxyl radical ( $\cdot\text{OH}$ ), and possibly the nitrate radical ( $\text{NO}_3\cdot$ ), as discussed below.

The tropospheric degradation of HFP will be initiated essentially by reaction with  $\cdot\text{OH}$ . Measurements of the ambient-temperature rate constant of this reaction all gave results close to  $2.3 \times 10^{-12} \text{ cm}^3/\text{molecule/s}$  (McIlroy and Tully, 1993; Dubey *et al*, 1996; Orkin *et al*, 1997; Mashino *et al*, 2000; Tokuhashi *et al*, 2000; Acerboni *et al*, 2001). Based on this value and a mean tropospheric  $\cdot\text{OH}$  concentration of  $10^6 \text{ molecule/cm}^3$ , a half-life of 3.5 days is calculated with respect to reaction with  $\cdot\text{OH}$  (An atmospheric half-life of 2 days is used with certain persistent organic pollutants to give an indication of potential for long-range atmospheric transport). Reaction of HFP with ozone ( $\text{O}_3$ ) or  $\text{NO}_3\cdot$  will make relatively minor contributions to its atmospheric degradation.

The rate constant for reaction of HFP with  $\text{O}_3$  at ambient temperature has been measured experimentally, by Mashino *et al* (2000) and Acerboni *et al* (2001), respectively, and reported to be  $< 3 \times 10^{-21}$  and  $0.62 \times 10^{-21} \text{ cm}^3/\text{molecule/s}$ . Adopting the latter value and a mean tropospheric  $\text{O}_3$  concentration of  $7 \times 10^{11} \text{ molecule/cm}^3$ , this leads to a half-life of over 50 years with respect to reaction with  $\text{O}_3$ .

For the reaction of HFP with  $\text{NO}_3^\cdot$ , only an upper limit to the rate constant of  $3 \times 10^{-15} \text{ cm}^3/\text{molecule/s}$  is available (Acerboni *et al*, 2001). Assuming a mean tropospheric  $\text{NO}_3^\cdot$  concentration of  $1.2 \times 10^8 \text{ molecule/cm}^3$ , this leads to a half-life greater than 22 days with respect to reaction with  $\text{NO}_3^\cdot$ .

Furthermore, a three-dimensional atmospheric chemical-transport modelling study gave an average global lifetime of 6 days (half-life 4.2 d) for HFP (Acerboni *et al*, 2001).

It should be noted that, because of its high reactivity, the atmospheric persistence of HFP will depend largely on the location (latitude, longitude) and season of the year of emission.

#### *Stratospheric ozone depletion*

HFP will not contribute to the destruction of stratospheric  $\text{O}_3$ , as it contains neither chlorine nor bromine, i.e. its  $\text{O}_3$  depleting potential is zero.

#### *Tropospheric ozone formation*

HFP emitted to the atmosphere will contribute to the formation of tropospheric  $\text{O}_3$ . Model calculations would be required to quantify this effect.

#### *Global warming*

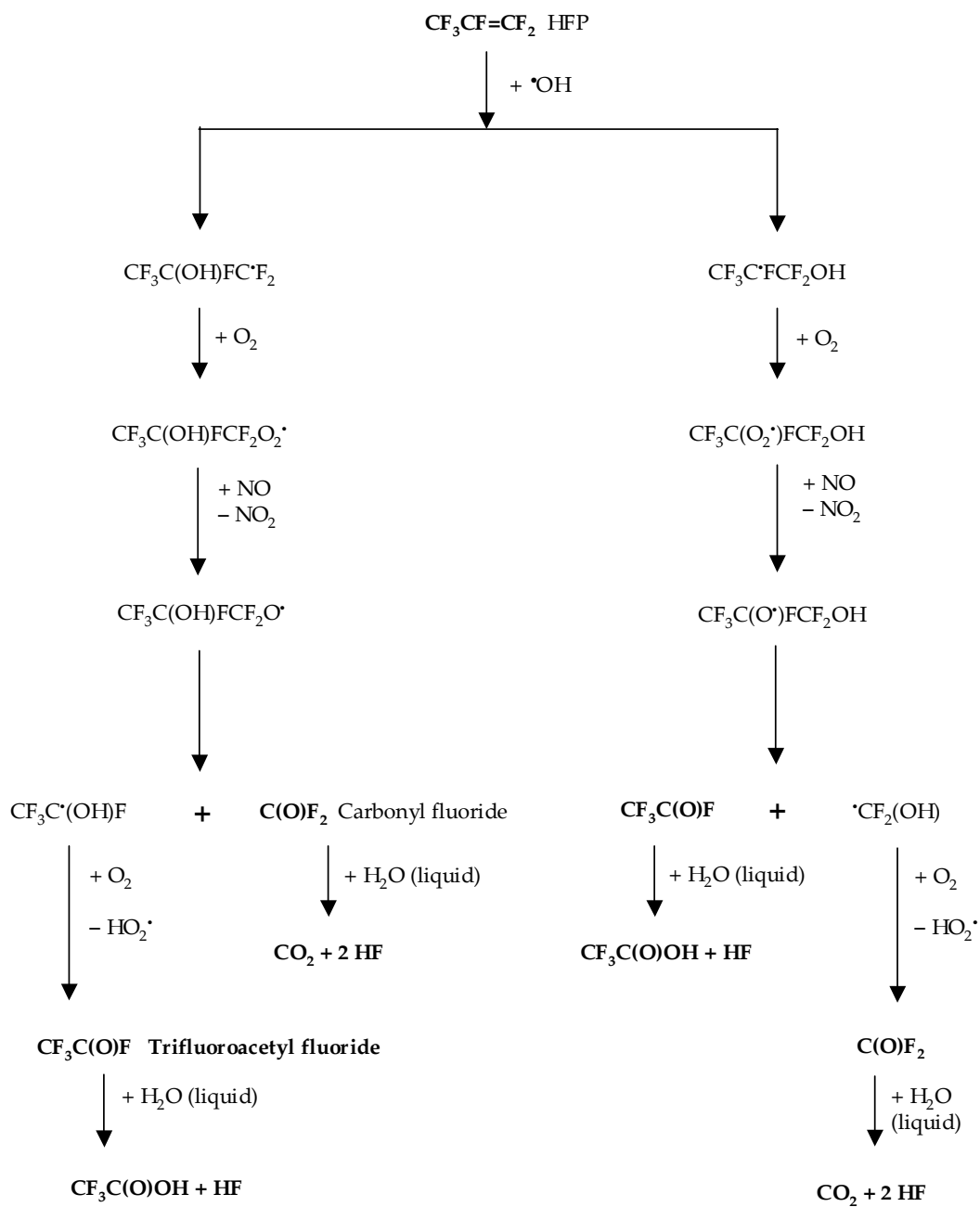
The global warming potential (GWP) of a greenhouse gas is the time-integrated radiative forcing resulting from emission to the atmosphere of a unit mass of a given substance, divided by the same quantity calculated for a reference substance. The radiative forcing is the additional earthward infrared radiation flux arising from the presence of the substance in the atmosphere. The GWP calculation is performed for a given "integration time horizon" (ITH). Depending on the reference substance, the ITH may be chosen to be finite (e.g. for  $\text{CO}_2$ ) or infinite (e.g. for CFC-11). Today, GWP values are almost invariably expressed relative to  $\text{CO}_2$ , for an ITH of 100 years.

Acerboni *et al* (2001) performed radiative transfer modelling studies to determine the GWP of HFP, on the basis of their  $\cdot\text{OH}$  rate constant and infrared absorption cross-section determination, and obtained values of 0.86, 0.25 and 0.079 (relative to  $\text{CO}_2 = 1$ ) for ITHs of 20, 100 and 500 years, respectively. Thus, the GWP of HFP is lower than that of  $\text{CO}_2$  for all three ITHs and the global warming impact of HFP will be insignificant, taking into account also the small amounts of HFP emitted as compared with  $\text{CO}_2$ .

*Degradation mechanism and products*

Laboratory studies on the  $\cdot\text{OH}$ -initiated degradation of HFP in the presence of air show that the main reaction products, namely trifluoroacetyl fluoride ( $\text{CF}_3\text{C}(\text{O})\text{F}$ ) and carbonyl fluoride ( $\text{C}(\text{O})\text{F}_2$ ), are formed in approximately equimolar proportions (Donahue *et al*, 1996; Mashino *et al*, 2000; Acerboni *et al*, 2001).

A proposed simplified atmospheric degradation scheme, based on the interpretation of Mashino *et al* (2000), is given in Figure 1.

**Figure 1: Tropospheric degradation mechanism for HFP**

<sup>a</sup> NO, NO<sub>2</sub>, free radicals

Theoretically, two different radicals can be formed by the addition of  $\cdot\text{OH}$  to the double bond of HFP. The regioselectivity is not known, but both radicals ultimately lead to the same primary molecular products, i.e.  $\text{CF}_3\text{C}(\text{O})\text{F}$  and  $\text{C}(\text{O})\text{F}_2$ . These will be taken up by cloud droplets and

rainwater within a few weeks (Cox *et al*, 1995) and hydrolysed to, respectively, trifluoroacetaldehyde ( $\text{CF}_3\text{C}(\text{O})\text{OH}$ ) and hydrogen fluoride (HF), and to  $\text{CO}_2$  and HF. The fluorinated acids formed will thus be removed from the atmosphere mainly by incorporation in precipitation, but some dry deposition to land and ocean surfaces may also occur.

The environmental occurrence and fate of trifluoroacetic acid (TFA), is discussed in the ECETOC report on 1,1,1,2-tetrafluoroethane (HFC-134a) (ECETOC, 2005). Clearly, the quantities of TFA found in the environment are much greater than can be explained by the degradation of synthetic fluorochemicals. Natural sources are likely to contribute.

#### 4.3.2 Aquatic fate

As a result of the high Henry's Law constant (Table 1), HFP will partition to air will be greatly in favour of the latter compartment; its water solubility is low and vapour pressure high. Under the natural conditions prevailing in soil and natural waters, at ambient temperature and pressure, and considering equilibrium between the environmental compartments (Section 4.2), HFP will partition completely to the atmosphere. Although HFP discharge into water and soil will occur only rarely (for example only after an accidental release of the compound into these environmental compartments), the equilibrium criterion (EQC) Level III model has been applied to evaluate the possible environmental distribution after such a release (Mackay *et al*, 1996).

Running the Level III model with HFP emissions into the water compartment, partitioning is 14% to air and 86% to water. Equilibrium between the two compartments is not achieved immediately, even if the overall residence time is in the order of hundreds of hours.

The volatilisation half-life from a model (EpiWin) river, characterised by 1 m depth, 1 m/s current velocity and 5 m/s wind speed (US-EPA, 2003), was calculated to be 1.25 hours; adapting the same model for a lake characterised by 1 m depth, 0.05 m/s current velocity and 0.5 m/s wind speed, gives a volatilisation half-life of 5 days. Adopting more realistic values for depth (5 and 20 metres for rivers and lakes, respectively) and wind velocity (5 m/s for both), together with the default current velocities, gives volatilisation half-lives of 18 hours for rivers and 142 days for lakes (Colombo, 2003).

Hydrolysis is not expected to occur.

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

### 4.3.3 Terrestrial fate

Simulating emissions into the soil compartment, using the EQC default of 1,000 kg/h or a more realistic value of 1 kg/h, it is concluded that 100% of the HFP partitions to the atmosphere.

Due to the low log  $K_{oc}$  value of 2.65, HFP is expected to have moderate mobility in soil.

Volatilisation of HFP is expected from moist soil surfaces due to the high Henry's Law constant (Table 1) and from dry soil surfaces due to high vapour pressure (Table 1).

### 4.3.4 Biodegradation

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

In general, volatilisation processes from soil and water are expected to be faster than biodegradation. Application of the BioWin model (US-EPA, 2003) indicates that biodegradation rates are in the range of several months.

### 4.3.5 Bioaccumulation

Abraham *et al* (2001) reported an experimental BCF (Bioconcentration factor) value of 1.981 for HFP resulting from determinations of HFP-water and HFP-octanol partitioning.

The LogKow programme (US-EPA, 2003) was used to estimate the log  $K_{ow}$  of HFP. A log  $K_{ow}$  of 2.12 was used to estimate the BCF value. The regression equation used to estimate BCF was:

$$\log BCF = 0.77 \times \log Kow - 0.70 \dots\dots\dots (Eq. 2)$$

The BCF value was 8.6.

The US Hazardous Substances Database quotes a BCF value of 24. This value was calculated using another type of regression equation (Lyman *et al*, 1990):

$$\log BCF = 0.76 \log K_{ow} - 0.23 \dots\dots\dots (Eq. 3)$$

The log  $K_{ow}$  used is the same used for the above determination, i.e. log  $K_{ow} = 2.12$  (HSDB, 2001).

Kenaga and Goring (1980) estimated BCF values from experiments with different species of fish for 36 organic chemicals. The regression equation was:

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$$\log \text{BCF} = -0.973 + 0.767 \log K_{ow} \dots\dots\dots (\text{Eq. 4})$$

A BCF value of 3.5 was obtained using the experimental  $\log K_{ow}$  value of 1.981 (Abraham *et al*, 2001)

These results, based on estimation methods derived from observed correlations between the physical properties of different organic compounds, are reasonably close to each other. According to a recommended classification scheme (Franke *et al*, 1994), this indicates that HFP is not expected to bioconcentrate in aquatic organisms.

#### 4.3.6 Evaluation

HFP, a highly volatile substance sparingly soluble in water, partitions preferentially to the atmosphere on release to the environment. It degrades in the lower atmosphere, mainly by reaction with  $\cdot\text{OH}$ , with a half-life of a few days. It has no effect on stratospheric  $\text{O}_3$  and its contribution to global warming is negligible. In view of the low emissions of HFP, its contribution to tropospheric  $\text{O}_3$  formation is also likely to be insignificant. The atmospheric degradation of HFP leads to the formation of TFA, HF and  $\text{CO}_2$ . The fluorinated acids are removed from the atmosphere mainly by wet deposition to the earth's surface.

In the aquatic compartment HFP does not hydrolyse and does not adsorb to sediment or to suspended organic matter. On the basis of the estimated BCF value, HFP will not bioconcentrate in fish. Moreover the low  $\log K_{ow}$  indicates that no bioaccumulation should occur in wildlife.

In the soil compartment, HFP is expected to have moderate mobility due to the low  $\log K_{oc}$  value. On account of its high volatility, any HFP present in soil will readily evaporate into atmosphere. Although no experimental data are available, no biodegradation is expected under either abiotic or biotic conditions.

## 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

### 5.1 Environmental levels

No data are available.

### 5.2 Human exposure levels and hygiene standards

#### 5.2.1 Non-occupational exposure

There are no reports dealing with non-occupational exposure to HFP.

There are no consumer uses of HFP as such. Polymeric products based on HFP as a co-monomer are expected to contain only very low levels of unreacted HFP. As a consequence, consumer exposure is expected to be negligible although the actual levels have not been evaluated.

#### 5.2.2 Occupational exposure

No data are available.

#### 5.2.3 Hygiene standards

None of the standard-setting authorities (e.g. American Conference of Governmental Industrial Hygienists and German MAK Commission) has proposed an occupational exposure limit value (OEL) for HFP (ACGIH, 2002; DFG, 2003).

Some companies have set internal OELs. For example, AtoFina has set an OEL of 2 ppm (12 mg/m<sup>3</sup>) (8-h TWA) based on a NOAEL (no-observed adverse effect level) of 10 ppm (60 mg/m<sup>3</sup>) in the rat (Elf Atochem, 1998). Solvay has set an OEL of 1 ppm (6 mg/m<sup>3</sup>) (8-h TWA) (Solvay, 2002).

Du Pont established an acceptable exposure limit (AEL) of 0.5 ppm (3 mg/m<sup>3</sup>) (8- and 12-h TWA) based on a no-observed effect level of 50 ppm (307 mg/m<sup>3</sup>) determined in a 2-week rat inhalation study (Du Pont, 2000).



### 5.2.4 Public and environmental health standards

HFP is included, with a specific migration of 0.01 mg/kg foodstuff, in the European 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

The American Industrial Hygiene Association (AIHA, 1996) has established Emergency Response Planning Guideline (ERPG) values for HFP as the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without:

- Experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odour (ERPG-1: 200 ppm) (1,230 mg/m<sup>3</sup>);
- experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action (ERPG-2: 1,000 ppm) (6,130 mg/m<sup>3</sup>);
- experiencing or developing life-threatening health effects (ERPG-3: 10,000 ppm) (61,300 mg/m<sup>3</sup>).

Du Pont (1987) set emergency exposure limits (EELs) for situations such as a major spill or the accidental release of a chemical, and specified brief durations and concentrations from which escape is feasible without causing impairment of, or irreversible effects on, health. The EEL for short exposures (up to 60 min) to HFP was 6,000 ppm·min (36,800 mg/m<sup>3</sup>·min) with a ceiling of 1,000 ppm HFP (6,130 mg/m<sup>3</sup>). It should be noted that EELs are only applicable to emergency situations that are expected to occur rarely in the lifetime of an individual.

## 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

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

### 6.1 Micro-organisms

No data are available.

Some information can be obtained from the Ames test performed on *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 (Section 8.4.1). A screening test, conducted to select the concentrations to be used in the Ames test, revealed clear cytotoxicity at a concentration of 5% HFP (50,000 ppm; 307,000 mg/m<sup>3</sup>). Slight toxicity was observed at 0.5% (5,000 ppm) and 1% (10,000 ppm) (30,700 and 30,700 mg/m<sup>3</sup>, respectively) (Russell and Krahn, 1980; CoR 1d).

### 6.2 Aquatic organisms

The ecotoxicity of HFP was estimated using the ECOSAR programme (US-EPA, 2001; CoR 2f) and a log K<sub>ow</sub> of 2.12 (Table 1), and following the method of (Boethling *et al*, 1994) (Table 2).

**Table 2: Predicted acute toxicity to aquatic organisms**

Organism	Duration (h)	Effect	Concentration (mg/l) at 25°C
Fish	96	LC <sub>50</sub>	86
Daphnia	48	EC <sub>50</sub>	93
Green algae	96	EC <sub>50</sub>	58

### 6.3 Terrestrial organisms

A value of 848 mg/kgbw was predicted for the 14-day LC<sub>50</sub> for earthworms using the ECOSAR model (US-EPA, 2001; CoR 2f).

## **6.4 Evaluation**

When evaluating the results from the Ames test, it should be noted that in such a test the microorganisms are in contact with HFP in the exposure chamber; in the environment, HFP would volatilise immediately into the atmosphere (Section 4.3.3).

The results obtained from the application of the ECOSAR model, indicate acute ecotoxicity values slightly below 100 mg/l. This, in association with the non-biodegradability of the compound and the fact that all the results obtained are near the lower end of the range of solubility values of the compound (82 mg/l at 28°C, Table 1), might indicate a slight concern for the environment. On the other hand, HFP is expected to disappear from the water compartment (due to the high Henry's Law constant of  $5.41 \times 10^5 \text{ Pa}\cdot\text{m}^3/\text{mol}$ , Table 1) and an increase of concentrations over time is not expected. Thus it is concluded that HFP would be unlikely to cause negative effects on the aquatic ecosystem.

It is further concluded that HFP is of no concern for the terrestrial environment, in view of the estimated  $\text{LC}_{50}$  for earthworms and taking into account its environmental behaviour (Section 4.3.3).

## 7. KINETICS AND METABOLISM

### 7.1 *In vivo studies*

No quantitative absorption, distribution, metabolism and excretion studies are available for HFP in either laboratory animals or humans; some qualitative data are available in rats and rabbits. There is no information concerning the fate of HFP in humans.

HFP is a gas at room temperature and exposure is expected to occur by inhalation. Exposure via other routes is considered to be negligible.

Dilley *et al* (1974) exposed male Sprague-Dawley rats to 2,600 ppm HFP (15,940 mg/m<sup>3</sup>) for 30 minutes. Urine samples were collected for 2 weeks post-exposure and analysed for fluoride ion. Fluoride excretion was increased on the first day and between days 4 to 6 and 13 to 14. The authors suggested that the cyclical excretion of fluoride ion might have been due to storage in a compartment with a slow turnover rate or due to enterohepatic recirculation. Kidney damage was also noted in this study.

Ding *et al* (1980) exposed rabbits to 1,000 ppm for an unspecified period. The alveolar absorption rate was reported to be 12.46%, with 88.35% of the absorbed dose degraded to non-volatile products. HFP was not detectable in urine; the highest concentrations were found in kidney, bone and lung.

Koob and Dekant (1990) exposed female Wistar rats initially to 800 ppm HFP (4,910 mg/m<sup>3</sup>). The atmosphere was not maintained and after 1 hour HFP was no longer detectable in the exposure chamber. Urine was collected for up to 24 hours post exposure. Approximately 10% of the dose was excreted in the first 6 hours after exposure and a further 1% between 6 and 24 hours. A single metabolite was detected in urine, which was identified as N-acetyl-S-(1,1,2,3,3,3-hexafluoropropyl) cysteine (N-acetyl-HFPC). In a second experiment, rats were fitted with biliary cannulae and exposed to HFP as above. Bile and urine were collected for 8 hours and analysed for HFP metabolites. Two glutathione conjugates were identified in bile, S-(1,2,3,3,3-pentafluoropropenyl) glutathione (PFPG) and S-(1,1,2,3,3,3-hexafluoropropyl) glutathione (HFPG) in the ratio 50:1. The only metabolite identified in the urine from the cannulated rats was N-acetyl-HFPC, which comprised 8% of the administered dose.

### 7.2 *Metabolism in vitro and in cell-free systems*

*In vitro* metabolic data are available from three studies using rat tissues; there are no data in human tissues.

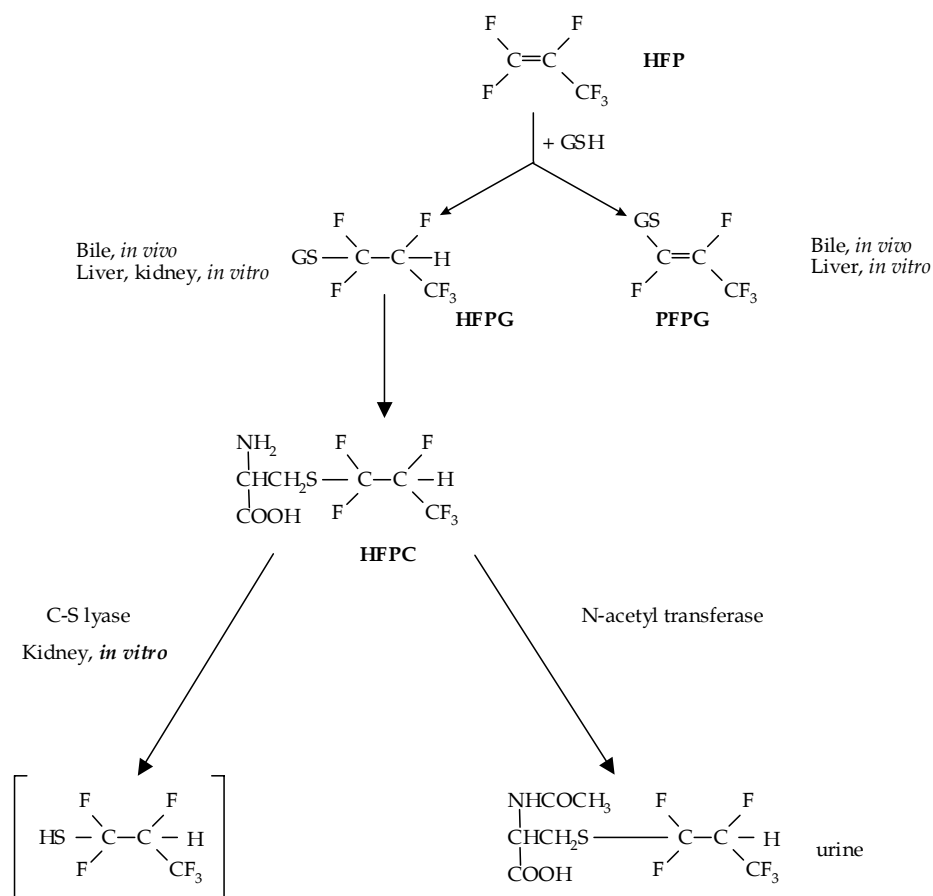
Conjugation of HFP with glutathione has been demonstrated in rat liver and kidney fractions (Koob and Dekant, 1990). The reaction is catalysed by both microsomal and cytosolic glutathione S-transferases. Two products are formed, one by the displacement of a fluorine atom, the other by addition of glutathione to the double bond of HFP. In liver microsomes both the fluorine displacement product PFPG (240 nmol/min/mg) and the addition product HFPG (36 nmol/min/mg) are formed. In liver cytosol fractions only HFPG (136 nmol/min/mg) was produced. Glutathione conjugation could not be detected in kidney microsomes, and in kidney cytosol only HFPG (46 nmol/min/mg) was formed. Total metabolism (PFPG + HFPG) was 9-fold greater in the liver than the kidney. No oxidative metabolism of HFP could be demonstrated in these studies.

The cysteine conjugates derived from PFPG and HFPG (PFPC and HFPC) were both shown to be substrates for rat kidney  $\beta$ -lyase (Green and Odum, 1985). The activity of this enzyme was 8-fold greater with HFPC than with PFPC.

Dilley *et al* (1974) reported that HFP was metabolised *in vitro* by washed red blood cells. The rates observed were 10-fold greater than those in other tissues examined (not specified) suggesting that extrahepatic metabolism may be important. The reaction, which was favoured by an alkaline media and was sensitive to sulphhydryl inhibitors, appeared to involve haemoglobin.

### 7.3 Summary

The limited information available suggests that HFP is metabolised in the rat (*in vivo* and *in vitro*) by conjugation with glutathione (Figure 2). Two conjugates are formed, the first (PFPG) by displacement of a fluorine atom, the second (HFPG) by addition of glutathione without loss of fluorine. In the liver, PFPG appears to be the major product, both *in vitro* and *in vivo*; it is excreted in the bile. HFPG was the only metabolite formed in the kidney *in vitro*. The only metabolite identified in rat urine following exposure to HFP was N-acetyl-HFPC. The cysteine conjugates of HFP (PFPC and HFPC) are substrates for renal cysteine conjugate  $\beta$ -lyase.

**Figure 2: Metabolism of HFP in the rat<sup>a</sup>**

<sup>a</sup> HFPC, S-(1,1,2,3,3,3-hexafluoropropyl) cysteine; HFPG, S-(1,1,2,3,3,3-hexafluoropropyl) glutathione; PFPG, S-(1,2,3,3,3-pentafluoropropenyl) glutathione; [ ] postulated

## **8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS**

### ***8.1 Acute toxicity***

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

#### **8.1.1 Inhalation**

A number of acute inhalation toxicity studies were reported, mostly in rats but also in mice, rabbits and guinea pigs (Table 3). The LC<sub>50</sub> values for each reported exposure period are relatively consistent and show no particular sex- or species-related sensitivity.

**Table 3: Acute inhalation toxicity (whole-body exposure)**

Species Strain, number and sex/group	Concentration (ppm)	Time (h)	LC <sub>50</sub>		Remark, result	Reference	CoR
			(ppm)	(mg/m <sup>3</sup> )			
<b>Rat</b>							
Sprague-Dawley, 10 M	140, 320, 690, 1,090,	4	3,060	(18,800)	Post-exposure period 28 days. Mortality 0 deaths ≤ 1,980 ppm, then 1, 2, 8, 4, 4, 6 at 2,220, 2,520, 2,600, 2,870, 3,020, 3,400 and 3,440 ppm, respectively. Death within 2 - 12 d. ↓ bw at ≥ 320 ppm, discomfort, depression ≥ 2,520 ppm; nephrosis ≥ 320 ppm. NOAEL = 140 ppm	Clayton <i>et al.</i> , 1960	1d
	1,520, 1,980, 2,220,						
	2,520, 2,600, 2,870,						
	3,020, 3,400, 3,440						
F344, 10 M	380, 470, 660, 1,200	4	> 1,200	(> 7,360)	Focus on kidney only. Killed on d 1 - 5 following exposure. No deaths; ↑ F ion urine excretion, urine LDH excretion, serum creatinine and BUN at all doses; cellular necrosis of proximal renal tubules within 24 h at each concentration; regeneration from d 3 post exposure	Potter , 1981	2e
F, species, strain and sex NS <sup>a</sup>	NS	4	(1,830)	11,200	Clonic spasms, lung oedema, alteration of the renal tubule epithelium. Renal necrosis in some rats, concentration NS	Smirnova, 1971	3a
	NS	4	2,800	(17,170)	Mortality within 1 d for highest concentrations, within 8 - 10 d for lower concentrations	Paulet and Desbrousses, 1966	3a
F, NS	NS	2	(4,470)	27,400	Depression, clonic spasms, lung oedema, alteration of the epithelium of renal tubule, necrosis in some rats were observed, concentration NS	Smirnova, 1971	3a

<sup>a</sup> Not stated



**Table 3: Acute inhalation toxicity (whole-body exposure) (cont'd)**

Species Strain, number and sex/group	Concentration (ppm)	Time (h)	LC <sub>50</sub>		Remark, result	Reference	CoR
			(ppm)	(mg/m <sup>3</sup> )			
<b>Rat (cont'd)</b>							
Wistar, NS	NS	2	4,000	(24,530)	Mortality with in 1 d at highest concentration, within 8 - 10 d at lower concentrations	Paulet and Desbrousses, 1966	3a
Wistar, 2 M, 2 F	50, 250, 500, 5,000, 50,000 <sup>a</sup>	2	NS	NS	Post exposure observation for 9 d. Histology not examined. Mortality 0% ≤ 250 ppm, 25% at 500 ppm, 100% ≥ 5,000 ppm, death within 1 - 46 h after exposure. Torpor, loss of coordination, difficult breathing ≥ 5,000 ppm and above. Lung oedema ≥ 500 ppm. No symptoms ≤ 250 ppm.	Salvaneschi, 1971	3b
NS	3,260, 7,335, 9,780, 13,447 <sup>a,b</sup>	2	NS	NS	Each concentration considered as absolute lethal concentration. Histology: pulmonary oedema, dystrophic changes in liver and kidney, including necrosis of convoluted tubules	Danishvskii and Kochanov, 1961	3a
F, NS	NS	1	(9,230)	56,600	Clonic spasms, lung oedema, alteration of the epithelium of renal tubule. Necrosis in some rats, concentration NS	Smirnova, 1971	3a
Sprague-Dawley, 10 M/ metabolism 5 M/ serial histology	2,600	0.5	NS	NS	↑ in F ion urinary excretion the day after exposure. Marked necrosis of the proximal tubules, almost complete regeneration after 7 d	Dilley <i>et al.</i> , 1974	2e

**Table 3: Acute inhalation toxicity (whole-body exposure) (cont'd)**

Species Strain, number and sex/group	Concentration (ppm)	Time (h)	LC <sub>50</sub>		Remark, result	Reference	CoR
			(ppm)	(mg/m <sup>3</sup> )			
<b>Rat (cont'd)</b>							
Wistar, NS	NS	0.5	15,750	(96,600)	Mortality within 1 d at highest concentration, within 8 - 10 d at lower concentrations	Paulet and Desbrousses, 1966	3a
Wistar, 2 M, 2 F	50, 250, 500, 5,000, 50,000	5	NS	NS	Observation for only 9 d post exposure. Histology not examined. Mortality 0% ≤ 250, and 100% ≥ 500 ppm. Torpor, loss of co-ordination, difficult breathing ≥ 5,000 ppm. Lung oedema at ≥ 500 ppm. No symptoms ≤ 250 ppm	Salvaneschi, 1971	3b
2, NS	600, 735, 880, 1,250, 1,760	6	735	(4,510)	Mortality 0, 1, 0, 2, 2 deaths at 600, 735, 880, 1,250 and 1,760 ppm, respectively. Nephrosis ≥ 600 ppm, lung oedema ≥ 1,250 ppm	Limperos, 1956; Clayton <i>et al.</i> , 1960	3a
NS	440, 880	6			Lethal at 880 ppm, survival at 440 ppm. Lung oedema and kidney injury at both concentrations	Limperos and Zapp, 1952; Clayton <i>et al.</i> , 1960	3a
Wistar, NS	NS	6	2,350	(14,410)	Mortality within 1 d at highest concentration, within 8 - 10 d at lower concentrations	Paulet and Desbrousses, 1966	3a
Wistar, NS	NS	8	2,400	(14,720)	Mortality within 1 d at highest concentration, within 8 - 10 d for lower concentrations. Minimum lethal concentration 2,000 ppm	Paulet and Desbrousses, 1966	3a

**Table 3: Acute inhalation toxicity (whole-body exposure) (cont'd)**

Species Strain, number and sex/group	Concentration tested (ppm)	Time (h)	LC <sub>50</sub>		Remark, result	Reference	CoR
			(ppm)	(mg/m <sup>3</sup> )			
Mouse							
10, NS	1,000, 1,500, 1,515, 1,990, 2,000, 2,600, 3,020	4	2,000	(12,260)	Deaths: 0, 4, 1, 9, 6, 9 and 8 out of 10 from 1,000 - 3,020 ppm. Death within 1 - 9 d. Depression, nephrosis, laboured breathing in all concentrations	Clayton <i>et al</i> , 1960	1d
Swiss, NS	NS	4	750	(4,600)	Mortality within 1 d at highest concentration, within 8 - 10 d for lower concentrations	Paulet and Desbrousses, 1966	3a
Swiss, NS	NS (whole body)	2	1,200	(7,360)	Mortality within 1 d at highest concentration, within 8 - 10 d at lower concentrations	Paulet and Desbrousses, 1966	3a
F, NS	NS	2	(1,520)	9,300	NS	Smirnova, 1971	3a
ddN strain, 3 M	NS	1	4,200	(25, 750)	Observation for 7 d post exposure. Tremor, loss of co-ordination and dyspnoea observed at high concentrations	Yoshida, Y, 1977	3ab
Swiss, NS	NS	0.5	3,000	(18,400)	Mortality within 1 d at highest concentration, within 8 - 10 d at lower concentrations	Paulet and Desbrousses, 1966	3a
Swiss, NS	NS	6	680	(4,170)	Mortality within 1 d at highest concentration, within 8 - 10 d at lower concentrations	Paulet and Desbrousses, 1966	3a
Swiss, NS	NS	8	600	(3,680)	Mortality within 1 d at highest concentration, within 8 - 10 d at lower concentrations. Minimum lethal concentration 400 ppm (2,450 mg/m <sup>3</sup> )	Paulet and Desbrousses, 1966	3a

**Table 3: Acute inhalation toxicity (whole-body exposure) (cont'd)**

Species Strain, number and sex/group	Concentration (ppm)	Time (h)	LC <sub>50</sub>		Remark, result	Reference	CoR
			(ppm)	(mg/m <sup>3</sup> )			
<b>Guinea pig</b>							
NS, 4 - 10, NS	1,000, 1,500, 2,000, 2,600, 3,020, 3,440	4	2,600	(15,940)	2/4 deaths at 1,500 and 2,000 ppm, 4/10 at 2,600, 7/10 at 3,020 ppm and 8/10 at 3,440 ppm. Death within 1 - 15 d. Nephrosis at all exposure levels.	Clayton <i>et al</i> , 1960	1d
					Depression, laboured breathing at $\geq 2,600$ ppm		
<b>Rabbit</b>							
NS, 2 - 6, NS	1,000, 1,500, 2,000, 2,600, 3,020, 3,440	4	2,600	(15,940)	1/2 died at 2,000, and 4/6, 3/6 and 5/6 at 2,600, 3,020 and 3,440 ppm, respectively. Death within 3 - 21 d. Nephrosis at all concentrations	Clayton <i>et al</i> , 1960	1d
NS	1,000, 2,000, 5,000	1	NS	NS	Assessment by function test and histology. Dose related nephrotoxicity. Functional and histological alteration $\geq 2,000$ ppm	Ding <i>et al</i> , 1985	4a,d

<sup>a</sup> Nominal concentrations<sup>b</sup> 4 samples with different degree of purity

Four-hour LC<sub>50</sub> values ranged from 1,830 to 3,060 ppm (11,200 to 18,800 mg/m<sup>3</sup>) in rats, from 750 to 2,000 ppm (4,600 - 12,260 mg/m<sup>3</sup>) in mice, and were approximately 2,600 ppm (15,940 mg/m<sup>3</sup>) in rabbits and guinea pigs. As indicated by Clayton *et al* (1960), the possibility that the lowest values reported are partly due to traces of the highly toxic PFIB in the HFP sample tested cannot be excluded.

Mortality occurred at and above 2,000 ppm (12,260 mg/m<sup>3</sup>) within 1 to 2 days, and within 8 to 12 days at lower exposure levels. The clinical symptoms most often reported were discomfort, depression, loss of coordination, clonic spasms and laboured respiration. Mice seem more susceptible to exposure showing clinical signs at lower concentrations (1,000 ppm; 6,130 mg/m<sup>3</sup>).

Kidney damage, evidenced by functional and/or histological alterations, occurred in all species tested. In the mouse, rabbit and guinea pig, these alterations were seen following exposure to 1,000 ppm for 4 hours. In the rat, where lower concentrations were tested, necrosis of renal tubules was observed at concentrations of 320 ppm (1,960 mg/m<sup>3</sup>) and above for 4 hours (Clayton *et al*, 1960). During the 28-day post-exposure period, regenerating epithelium of renal tubules (reflecting recovery process) was observed in surviving animals exposed at up to 690 ppm (4,230 mg/m<sup>3</sup>), but not at higher exposure levels. Histological examination revealed pulmonary congestion and oedema from about 500 ppm (3,070 mg/m<sup>3</sup>), especially in mice.

The overall NOAEL following 4-hour exposure in rats was 140 ppm (860 mg/m<sup>3</sup>). The kidney was the target organ.

### **8.1.2 Metabolites**

Indications of possible acute toxicity of HFP metabolites are discussed in Chapter 9.

### **8.1.3 Other acute toxicity studies**

Two dogs exposed to high concentrations of HFP (500,000 or 750,000 ppm; 3,070,000 or 4,600,000 mg/m<sup>3</sup>) in oxygen-rich air for an unspecified duration showed signs of respiratory irritation and tremors; no anaesthetic effect was demonstrated (Lu *et al*, 1953; CoR 4).

### **8.1.4 Summary**

The acute inhalation data on HFP are relatively consistent and do not demonstrate any particular sex- or species-related effect. In the rat, the most reliable 4-hour LC<sub>0</sub> value was estimated to be around 1,900 ppm (11,650 mg/m<sup>3</sup>) and the LC<sub>50</sub> 3,000 ppm (18,400 mg/m<sup>3</sup>). Mortality occurred

in 1 or 2 days at high concentrations ( $\geq 2,000$  ppm;  $12,260$  mg/m<sup>3</sup>), and within 8 to 12 days at lower exposure levels. The primary toxic effect is kidney damage (proximal tubule necrosis) observed in the rat without any clinical sign of toxicity at concentrations as low as 320 ppm ( $1,960$  mg/m<sup>3</sup>) for a 4-hour exposure period. Signs of central nervous system (CNS) depression, pulmonary congestion and oedema were reported at higher concentrations. The overall NOAEL was 140 ppm ( $860$  mg/m<sup>3</sup>).

HFP does not present any significant anaesthetic potential at up to 750,000 ppm ( $4,600,000$  mg/m<sup>3</sup>) in dogs.

### ***8.2 Skin, respiratory tract and eye irritation, sensitisation***

No data are available on skin and eye irritation or sensitisation potential.

Effects on the respiratory tract (delayed respiratory troubles with pulmonary congestion and oedema) were observed at high exposure levels (most often lethal or sublethal range concentrations) in the acute toxicity animal studies. This might in part be due to traces of PFIB (present in the HFP sample tested).

### ***8.3 Repeated dose toxicity***

Results and details of repeated dose toxicity studies on HFP are presented in Table 4 below, followed by a discussion in Section 8.3.1 to 8.3.4.

**Table 4: Repeated inhalation toxicity**

Species strain, number and sex/group	Concentration		Exposure regime, duration	Result	Reference	CoR
	(ppm)	mg/m <sup>3</sup>				
<b>Rat</b>						
16, NS <sup>a</sup>	0, 103, 183	(0, 630, 1,120)	34 x 4 h	At 183 ppm ↑ relative kidney weight, ↑ relative adrenal cortical weight, ↓ ascorbic acid level	Smirnova, 1971	3a
22, NS	0, 4.6, 73	(0, 28, 45)	5 h/d, 6 months	Both concentrations ↑ relative kidney weight, ↓ relative spleen weight. At 73 ppm ↑ alkaline phosphatase activity and ↓ cholinesterase activity. LOAEL 4.6 ppm, based on changes in relative organ weights	Smirnova, 1971	3a
Sprague-Dawley, 10 M	0, 213.5, 324	(0, 1,310, 1,990)	4 h/d, 5 d/wk, 2 wk (14 d recovery)	No changes in urinary fluoride and no exposure-related effects	Brown, 1976	2a
CD, 10 M	0, 10, 50, 200	(0, 61, 307, 1,230)	6 h/d, 5 d/wk, 2 wk (14 d recovery)	At 200 ppm mild nephrosis after exposure which was not present after 14 d recovery	Kinney <i>et al</i> , 1985	1b
CD, 20 M, 20 F	0, 10, 50, 150	(0, 61, 307, 920)	6 h/d, 5 d/wk, 90 d (28 d recovery)	No effects on body or organ weight and no exposure-related pathological findings. Evidence of metabolism of HFP (↑ urinary F <sup>-</sup> ) in M and hypematraemia, ↑ urinary volume and ↓ urinary osmolarity in both M and F exposed to 50 and 150 ppm. Statistically significant low mean lymphocyte count in males exposed to 150 ppm. NOAEL 10 ppm	Stadler, 1989	1b

<sup>a</sup> Not stated

**Table 4: Repeated inhalation toxicity (cont'd)**

Species strain, number and sex/group	Concentration		Exposure regime, duration	Result	Reference	CoR
	(ppm)	mg/m <sup>3</sup>				
<b>Mouse</b>						
10, NS	0, 4.6, 73	(0, 28, 45)	5 h/d, 5.5 months	↓ growth rate at 73 ppm. Relative non-conditioned avoidance responses at 73 ppm (13.9%) lower than controls (58.4%) (maximum possible 100%). No pathological effects	Smirnova, 1971	3a
ICR, 10 M	0, 5, 20, 75	(0, 31, 123, 460)	6 h/d, 5 d/wk, 2 wk (14 d recovery)	At 75 ppm showed ↑ mean relative kidney weight and regeneration of renal cortical tubule. No effects after 14-day recovery. NOAEL 20 ppm	Kelly, 1988.	1b
ICR, 25 M, 25 F	0, 10, 50, 150	(0, 61, 307, 920)	6 h/d, 5 d/wk, 90 d (28 d recovery)	M and F exposed to 50 or 150 ppm showed regeneration of the inner cortical tubules, cytomegaly and necrosis of the tubular epithelium. Effects present 28 d after exposure. NOAEL 10 ppm	Stadler, 1989	1b
<b>Guinea pig</b>						
7, NS	0, 4.6, 73	(0, 28, 45)	5 h/d, 6 months	Fluorine levels in bones of both exposed groups higher than controls. ↓ growth rate at 73 ppm. NOAEL 4.6 ppm, based on reduced growth rate	Smirnova, 1971	3a



### 8.3.1 Rats

Rats (strain and sex not specified) were exposed (34 x 4 h) by inhalation to concentrations of 0, 103 or 183 ppm HFP. Details of the experimental procedures were not reported. There were no effects on mortality, haematology, serum alkaline phosphatase activity or on blood residual nitrogen levels. Rats exposed to 183 ppm HFP showed functional changes in adrenal cortical activity (increased relative weight and reduced ascorbic acid level), an increased eosinophil count, a statistically insignificant reduction in cholesterol levels and a statistically significant increase in relative kidney weights. The NOAEL was 103 ppm (Smirnova, 1971).

Rats (strain and sex unspecified) were exposed by inhalation to 0, 4.6 or 73 ppm HFP for 6 months. No details of the experimental procedures were reported. There were no effects on erythrocyte and leukocyte counts, haemoglobin or blood non-protein nitrogen levels. In rats exposed to 73 ppm HFP, there was an increase in relative neutrophil level, an increase in alkaline phosphatase activity and a decrease in cholinesterase activity. Relative kidney weights were increased and relative spleen weights decreased in both exposed groups. In addition, there were indications of hyperfunction of the adrenal cortex. No pathological effects were observed. The lowest-observed effect level (LOAEL) was 4.6 ppm, based on changes in relative organ weights. No NOAEL was obtained (Smirnova, 1971).

Male Sprague-Dawley rats were exposed by inhalation to 0, 213.5 or 324 ppm HFP for 2 weeks. Urine was collected overnight from each group prior to the last exposure and analysed for total fluoride. Following exposure, 5 rats/group were killed for pathological examination; the remaining rats were allowed to recover for an additional 14 days and then examined pathologically. No changes in urinary fluoride levels and no exposure-related effects were seen in the exposed groups (Brown, 1976).

Male CD rats were exposed by inhalation to 0, 10, 50 or 200 ppm HFP for 2 weeks. At the end of the exposure period, blood and urine samples were collected for clinical analysis and 5 rats/group killed for pathological examination. Following the exposure period, the remaining rats were retained without exposure for an additional 14 days and subsequently killed for pathological examination. No significant effects were seen in rats exposed to 10 or 50 ppm HFP. Male rats exposed to 200 ppm HFP showed mild nephrosis which was characterised by diffuse degeneration of the inner cortical tubules. The lesion was not present after the 14-day recovery period. The NOAEL was 50 ppm HFP, based on kidney toxicity (Kinney *et al*, 1985).

CD rats were exposed by inhalation to 0, 10, 50 or 150 ppm HFP for 90 days, followed by a recovery period of 28 days (10 rats/sex/group). Body weights were recorded weekly; water and food consumption were monitored throughout the study. Ophthalmological examination was performed prior to the start and at the end of the exposure phase. Clinical chemistry was

evaluated prior to exposure, on days 45 and 90 (approximately), and at the end of the recovery period. The pathology of 10 rats/sex/group was examined on day 90 (approximately). All surviving rats were examined pathologically at the end of the recovery period. There were no significant effects on body weight gain or food consumption. Males exposed to 150 ppm HFP showed increased water consumption. There were no exposure-related effects on mortality or ophthalmology. A statistically significant low mean lymphocyte count occurred in male rats exposed to 150 ppm HFP. Males exposed to 50 and 150 ppm showed a statistically significant increase in urinary fluoride. These groups also showed hypernatraemia, increased urinary volume and reduced osmolarity, as did the females exposed to the same concentrations. There were no effects on organ weights and no pathological findings in rats that were considered to be related to HFP. The NOAEL for rats was 10 ppm, based on clinical chemistry findings (Stadler, 1989).

### 8.3.2 Mice

Mice (strain and sex unspecified) were exposed by inhalation to 0, 4.6 or 73 ppm HFP for 5.5 months. No details of the experimental procedures were reported. The growth rate of mice exposed to 73 ppm HFP was slower than controls. Also, the relative number of conditioned avoidance responses in this group was lower (13.9% of the maximum possible) than in controls (58.4%). No pathological effects were observed (Smirnova, 1971).

Male ICR mice were exposed by inhalation to 0, 5, 20 or 75 ppm HFP for 2 weeks. At the end of the exposure period, blood samples were collected for haematological analysis and 5 mice/group killed for pathological examination. The remaining mice were allowed to recover for an additional 14 days and subsequently subjected to haematological and pathological examination. No significant effects were seen in mice exposed to 5 or 20 ppm HFP. Mice exposed to 75 ppm HFP showed an increase in mean relative kidney weight and regeneration of the renal cortical tubules at the end of the exposure period. Evidence of renal toxicity had essentially disappeared after the 2-week recovery period. There were no other exposure-related adverse findings. The NOAEL was 20 ppm (Kelly, 1988).

ICR mice were exposed by inhalation to 0, 10, 50 or 150 ppm HFP for 90 days, followed by a recovery period of 28 days (10 mice/sex/group). Body weights were recorded weekly and water and food consumption monitored throughout the study. Ophthalmological examinations were performed before and after the exposure period. Clinical chemistry was evaluated prior to exposure, on days 45 and 90 (approximately) and at the end of the recovery period. Pathological examination of 10 mice/sex/group was conducted on day 45 and on day 90 (approximately). All surviving mice were subjected to a pathological examination at the end of the recovery period. There were no significant effects on body weight gain or food consumption; females exposed to 150 ppm HFP showed increased water consumption. No exposure-related effects were seen on

mortality or ophthalmology and no haematological findings in mice. There was a statistically significant increase in the incidence of blue-ish colouration of the abdomen in males exposed to 50 and 150 ppm HFP. The relationship of this observation, if any, to exposure was not established. There were no effects on body or organ weights in males exposed to HFP, and no effects on body weights in females. At the end of the exposure period, mean relative heart weights were lower than controls in females exposed to 150 ppm HFP and mean relative kidney weights were lower than controls in all exposed groups of females. Mice exposed to 50 or 150 ppm HFP showed microscopic lesions of the kidney (regeneration of the inner cortical tubules, cytomegaly of the tubular epithelium and tubular epithelial necrosis) at 45 and 90 days. Cytomegaly and nephropathy were present in the males at the end of the recovery period. The NOAEL in this study was judged to be 10 ppm, based on kidney toxicity (Stadler, 1989).

### 8.3.3 Guinea pigs

Guinea pigs (strain and sex unspecified) were exposed by inhalation to 0, 4.6 or 73 ppm HFP for 6 months. No details of the experimental procedures were reported. The growth rate of guinea pigs exposed to 73 ppm HFP was slower than controls. The fluorine level in the bones was  $0.540 \pm 0.060$  mg/g at 4.6 ppm and  $0.966 \pm 0.111$  mg/g at 73 ppm, both higher than in the controls ( $0.285 \pm 0.040$  mg/g) (Smirnova, 1971).

### 8.3.4 Summary

In all, nine repeat-dose inhalation studies on HFP have been reported; five in the rat, three in the mouse and one in the guinea pig.

In a well-conducted 90-day study in the rat, the kidney was the principle target organ for the toxicity of HFP, toxicity being characterised as exposure-related changes in urine chemistry, increased organ weights and mild nephrosis at the higher dose levels studied. HFP nephrotoxicity was shown to be reversible within 14 days at the exposure levels studied. The NOAEL for HFP in the rat was 10 ppm ( $61 \text{ mg/m}^3$ ).

In a well-conducted 90-day study in the mouse, the kidney was also the principle target organ for the toxicity of HFP. Mice were more susceptible than rats to the nephrotoxic effects of HFP, irreversible tubular regeneration and necrosis being observed following exposure to 50 ppm and above ( $\geq 307 \text{ mg/m}^3$ ). The NOAEL for HFP in the mouse was 10 ppm ( $61 \text{ mg/m}^3$ ).

While the NOAELs for HFP in both the rat and the mouse were 10 ppm ( $61 \text{ mg/m}^3$ ) in well-conducted studies, adverse effects (increased kidney and adrenal cortical weights) were seen in

the rat after exposure to lower concentrations (4.6 ppm; 28 mg/m<sup>3</sup>) for 6 months in a poorly reported study.

#### **8.4 Genotoxicity**

HFP has been assessed for mutagenic activity in genetic toxicity assays for the two primary endpoints, i.e. gene mutation in *Salmonella typhimurium* strains (Ames test) and Chinese hamster ovary (CHO) cells at the hypoxanthine phosphoribosyl transferase (HPRT) locus, and for chromosome aberration in CHO cells *in vitro* in the mouse micronucleus test and rat dominant lethal test (Table 5). Additionally, two mouse micronucleus tests, a rat dominant lethal test and a DNA repair assay (to assess *in vivo* unscheduled DNA synthesis in rat hepatocytes) have been conducted (Table 6). These studies are discussed below in Section 8.4.1 to 8.4.4.

**Table 5: Genotoxicity tests in vitro**

Endpoint/organism	Strain/target	Exposure regime, duration	Concentration(%)	Result	Metabolic activation	Reference	CoR
<b>Gene mutation</b>							
<i>Salmonella typhimurium</i>	TA1535, TA1537, TA98, TA100	2 d	0, 0.075, 0.1, 0.25, 0.5, 1.0, 2.5, 5.0	-ve	+/- S9 <sup>a</sup>	Russell and Krahn 1980	1d
CHO cells	HPRT locus	18 h	0, 0.05, 0.15, 0.20, 0.30, 0.35	-ve	-S9	Kinney <i>et al.</i> , 1985	1a,c
		5 h	0, 0.1, 0.5, 1.0, 1.5	-ve	+S9		
CHO cells	HPRT locus	18 h	0, 0.05, 0.15, 0.16, 0.22, 0.23, 0.28, 0.31, 0.32	-ve	-S9	Kinney <i>et al.</i> , 1988	1a,c
		5 h	0, 0.11, 0.22, 0.25, 0.46, 0.47, 0.81, 0.83, 1.09, 1.26	-ve	+S9		
CHO cells	HPRT locus		0, 0.05, 0.15, 0.20, 0.30, 0.35	-ve	-S9	Stahl, 1988	1a
			0, 0.10, 0.25, 0.50, 1.00, 1.50	-ve	+S9		
<b>Chromosome aberration</b>							
CHO cells (structural chromosome aberrations)		5 h	0, 0.01, 0.02, 0.10, 0.17, 0.29, 0.37, 0.43, 0.59	+ve	-S9, at the highest four dose levels	Rickard <i>et al.</i> , 1986	1a,c
		2 h	0, 0.09, 0.17, 0.33, 0.46, 0.55, 0.67, 0.85, 1.40	+ve	+S9, at the highest four dose levels		

<sup>a</sup> 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 6: Genotoxicity tests in vivo**

Endpoint/ organism, sex	Strain, target	Exposure regime, duration	Concentration (ppm)	Concentration (mg/m <sup>3</sup> )	Result	Remark	Reference	CoR
<i>In vivo/ex vivo</i>								
<b>Micronucleus</b>								
Mouse, M and F	CrI:CD-1, bone marrow	6 h (inhalation)	0, 100, 310, 1,200	(0, 613, 1,900, 7,360)	+ve	In M at 1,200 ppm. Bone marrow sampled at 24, 48, and 72 h after exposure	Vlachos, 1986	1a,c
Mouse, M and F	CD-1, bone marrow	6 h (inhalation)	0, 300, 600, 800, 1,200	(0, 1,840, 3,680, 4,910, 7,360)	-ve		Hoechst, 1993 cited by ECB, 2000	4c
<b>Dominant lethal mutations</b>								
Rat, M	Charles River CD	6 h/d, 5 d (F mated with exposed M, killed 12 d after the mating wk)	0, 25, 100, 400	(0, 153, 613, 2,450)	-ve	No ↑ resorptions. Animals had normal mating indices and pregnancy rates	Bio/dynamics, 1987	1a
<i>In vivo</i>								
<b>DNA repair (unscheduled DNA synthesis)</b>								
Rat, M	Alpk:APISD, hepatocytes	6 h (inhalation)	0, 1,000, 1,500	(0, 6,130, 9,200)	-ve		Fox, 1997	1a

### 8.4.1 Gene mutation *in vitro*

#### *Bacteria*

HFP was not mutagenic in the *Salmonella typhimurium* gene mutation assay (Ames test) when tested at targeted atmospheric concentrations of up to 5.0% (50,000 ppm) in strains TA1535, TA100, TA98 and TA1537 in the presence and absence of metabolic activation (Russell and Krahn, 1980).

Based on the reported HFP nephrotoxicity, two cysteine conjugates were tested at dose levels up to 1,000 µg/plate in strains TA1535, TA100, TA98, TA1538 and TA1537. These conjugates were also without mutagenic activity in the presence and absence of kidney S9 (Green and Odum, 1985).

#### *Mammalian cells*

HFP has been tested with the HPRT locus in cultured Chinese hamster ovary cells (CHO/HPRT) for induction of gene mutations at in the presence and absence of metabolic activation. In one study, 3 trials were performed without activation (18 hours) at nominal HFP vapour concentrations of up to 0.35% (corresponding to measured concentrations of 0.02 - 0.31%). Only results from two trials were used since one activated trial was eliminated because of culture contamination. In 3 trials with metabolic activation (5 hours), nominal HFP concentrations were up to 1.5% (measured concentrations 0.01 - 1.7%). In all, HFP did not induce mutations with and without metabolic activation (Kinney *et al*, 1985).

Stahl (1988) re-evaluated HFP in the CHO/HPRT assay without metabolic activation, at nominal concentrations of up to 0.35% (corresponding to measured concentrations in one trial of 0, 0.05, 0.16, 0.23, 0.28 or 0.32 and 0, 0.05, 0.15, 0.22, 0.23 or 0.31% in the second trial). With activation, nominal concentrations were 0, 0.10, 0.25, 0.50, 1.00 or 1.50% (corresponding to measured concentrations in one trial of 0, 0.11, 0.22, 0.46, 0.83 or 1.26%, and 0, 0.06, 0.25, 0.47, 0.81 or 1.09% in the second trial). HFP was not mutagenic with or without metabolic activation.

### 8.4.2 Chromosome aberration

#### *Mammalian cells in vitro*

The ability of HFP to induce structural chromosome aberrations was evaluated in CHO cells exposed to variable concentrations of HFP for 2 hours with metabolic activation or for 5 hours without activation (Rickard *et al*, 1986). Non-activated cultures were treated with HFP

concentrations of up to 0.59%; with activation 0, 0.09, 0.17, 0.33, 0.46, 0.55, 0.67, 0.85 or 1.40% HFP. Significant increases were observed in the number of chromosome aberrations/cell, percentage normal cells, and percentage cells with more than one aberration relative to negative controls in the non-activated cultures at the highest four dose levels. Positive dose-related trends were observed for all three measurements with and without metabolic activation.

#### *Mammalian cells in vivo/ex vivo*

Male and female Crl:CD-1 mice were exposed by whole-body inhalation exposure to 0, 100, 310, or 1,200 ppm HFP for 6 hours. Bone marrow smears were prepared 24, 48, and 72 hours following exposure. Evidence for bone marrow toxicity was seen as a decreased polychromatic/normochromatic erythrocyte ratio at all concentrations in males and at 1,200 ppm in females. In females, there was no statistically significant increase in micronucleated polychromatic erythrocytes at any dose level. In males, a slight statistically significant increase in micronuclei was seen with the 1,200 ppm group, but only after pooling the data across all sampling times (Vlachos, 1986).

Subsequent to the marginal positive results obtained in males in the mouse micronucleus test, HFP was assessed in the dominant lethal assay. Male Charles River CD rats (10 animals/group) were exposed by inhalation to 0, 25, 100 or 400 ppm HFP for 5 consecutive days. Each male was mated with 2 untreated females a week for 8 weeks. The females were killed 12 days after the mating week and the presence of early resorption sites (dominant lethals) determined. The animals had normal mating indices and pregnancy rates, and there were no increases in resorptions (Bio/dynamics, 1987).

#### **8.4.3 DNA repair *in vivo***

Male Alpk:APfSD rats were exposed to 0, 1,000, or 1,500 ppm HFP for 6 hours. HFP did not induce unscheduled DNA synthesis in the hepatocytes of these animals (Fox, 1997).

#### **8.4.4 Summary and evaluation**

The genotoxic potential of HFP has been assessed in a number of studies for gene mutation and chromosome aberrations. HFP did not induce gene mutations in bacteria or in mammalian cells *in vitro*. It exhibited weak clastogenic activity in CHO cells *in vitro* and in males in the mouse micronucleus test, but only at 1,200 ppm and when data from all sampling times (24, 48 and 72 hours) were pooled and analysed. HFP was not mutagenic in the rat dominant lethal test (a germ-cell chromosome aberration assay). HFP was negative in an *in vivo* assay for UDS (unscheduled



DNA synthesis) in rat hepatocytes. The cysteine conjugates were also without mutagenic activity in the Ames test; the glutathione conjugates were not considered (Section 7.3).

It is concluded that the mutagenicity endpoint is of low concern for HFP.

### ***8.5 Chronic toxicity and carcinogenicity***

No data are available.

### ***8.6 Reproductive toxicity***

No specific reproductive and developmental toxicity studies have been conducted on HFP.

#### **8.6.1 Studies of potential relevance**

No adverse effects of HFP on the male reproductive system were seen in a rat dominant study (Section 8.4.2).

CD rats (20/sex/group) were exposed (6 h/d, 5 d/wk) by inhalation to 0, 10, 50 or 150 ppm HFP (0, 61, 307, 920 mg/m<sup>3</sup>) for 90 days. Following exposure, 10 rats/sex/group were retained without exposure for an additional 28 days. No exposure-related effects were reported on testicular weight in males or ovarian weight in females, or on the pathology of these organs in the group exposed for 90 days or in the recovery group (Stadler, 1989).

ICR mice (25/sex/group) were exposed (6 h/d, 5 d/wk) by inhalation to atmospheric concentrations of 0, 10, 50 or 150 ppm HFP (0, 61, 307, 920 mg/m<sup>3</sup>) for 90 days. Following exposure, 10 mice/sex/group were retained without exposure for an additional 28 days. No exposure-related effects were reported on testicular weight in males or ovarian weight in females, or on the pathology of these organs in the group exposed for 90 days or in the recovery group (Stadler, 1989).

#### **8.6.2 Summary and evaluation**

No standard reproductive or developmental studies have been conducted on HFP.

Repeat-dose inhalation studies with HFP in rats and mice have shown no evidence of effects on male or female reproductive organs. HFP did not affect male reproductive performance at

exposure up to 400 ppm (2,450 mg/m<sup>3</sup>). On the basis of the data available, the potential for effects on the overall functioning of the reproductive system cannot be fully evaluated.

## 9. MECHANISTIC STUDIES

### 9.1 *Kidney toxicity*

Exposure of laboratory animals to HFP has identified the kidney as the target organ (Green and Odum, 1985; Koob and Dekant, 1990). These studies suggest a mode of action to explain the kidney toxicity.

Koob and Dekant (1990) found that HFP is metabolised by glutathione conjugation in the rat to two glutathione conjugates PFPG and HFPG (Section 7). PFPG was identified in the bile, but not in urine as its mercapturate, suggesting that this conjugate may not be re-absorbed from the gastro-intestinal tract. HFPG, as its mercapturate (N-acetyl cysteine conjugate) was identified in urine as a major metabolite. The precursor to the mercapturate, i.e. the cysteine conjugate, S-(1,1,2,3,3,3-hexafluoropropyl)cysteine, has been shown to be a substrate for rat kidney  $\beta$ -lyase forming a reactive thiol, pyruvate and ammonia. The action of  $\beta$ -lyase on this conjugate has also been shown to produce reactive and toxic species that inhibit ion transport in kidney slices *in vitro*. The same reactive species were not mutagenic in bacteria (Green and Odum, 1985).

### 9.2 *Summary and evaluation*

There is evidence to suggest that HFP is nephrotoxic by the renal  $\beta$ -lyase pathway, as a result of glutathione conjugation and activation of the resulting cysteine conjugate. In this respect, the mode of action of HFP is analogous to that of its structural analogue TFE (Green and Odum, 1985).

Although it is probable that the same metabolic pathways operate in animals and humans, there is no information on the fate of HFP in humans, and hence the potential of HFP to cause kidney toxicity in humans is unknown. The possibility of a genotoxic, rather than cytotoxic, mechanism through a glutathione conjugate cannot be excluded (Section 7.3 and 8.4.4).

## **10. EFFECTS ON HUMANS**

No data are available.

No reports of human exposure to HFP have been cited in the literature or were otherwise available to the Task Force.

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## APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES

*Adapted from Klimisch et al (1997)*

Code of Reliability (CoR)	Category of reliability
<b>1</b>	<b>Reliable without restriction</b>
1a	GLP guideline study (OECD, EC, EPA, FDA, <i>etc.</i> )
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, <i>etc.</i> )
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
<b>2</b>	<b>Reliable with restrictions</b>
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
<b>3</b>	<b>Not reliable</b>
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
<b>4</b>	<b>Not assignable</b>
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.

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

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

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

$$1 \text{ mg/m}^3 = 24.0556/\text{Mw} \text{ ppm} \dots\dots\dots (\text{Eq. B.3})$$

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

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

$$1 \text{ mg/m}^3 = 24.4661/\text{Mw} \text{ ppm} \dots\dots\dots (\text{Eq. B.5})$$

$$1 \text{ ppm} = \text{Mw}/24.4661 \text{ mg/m}^3 \dots\dots\dots (\text{Eq. B.6})$$



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## ECETOC PUBLISHED REPORTS

### *Monographs*

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No. 4	Hepatocarcinogenesis in Laboratory Rodents: Relevance for Man (Published October 1982)
No. 5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology) (Published December 1983)
No. 6	Acute Toxicity Tests, LD <sub>50</sub> (LC <sub>50</sub> ) Determinations and Alternatives (Published May 1985)
No. 7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies (Published December 1985)
No. 8	Structure-Activity Relationships in Toxicology and Ecotoxicology: An Assessment (Summary) (Published June 1986)
No. 9	Assessment of Mutagenicity of Industrial and Plant Protection Chemicals (Published June 1987)
No. 10	Identification of Immunotoxic Effects of Chemicals and Assessment of their Relevance to Man (Published August 1987)
No. 11	Eye Irritation Testing (Published June 1988)
No. 12	Alternative Approaches for the Assessment of Reproductive Toxicity (with emphasis on embryotoxicity/teratogenicity) (Published November 1989)
No. 13	DNA and Protein Adducts: Evaluation of their Use in Exposure Monitoring and Risk Assessment (Published October 1989)
No. 14	Skin Sensitisation Testing (Published March 1990)
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| No. 4  | The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man (updated by TR No. 17) (Published June 1982)   |
| No. 5  | Toxicity of Ethylene Oxide and its Relevance to Man (Published September 1982)   |
| No. 6  | Formaldehyde Toxicology: An Up-Dating of ECETOC Technical Reports 1 and 2 (Published September 1982)   |
| No. 7  | Experimental Assessment of the Phototransformation of Chemicals in the Atmosphere (Published September 1983)   |
| No. 8  | Biodegradation Testing: An Assessment of the Present Status (Published November 1983)  |
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