

1, 1, 1, 3, 3-Pentafluoropropane
(HFC-245fa)

(CAS No. 460-73-1)

JACC Report No. 44

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European Centre for Ecotoxicology and Toxicology of Chemicals
4 Avenue E. Van Nieuwenhuysse (Bte 6), B-1160 Brussels, Belgium.

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1,1,1,3,3-Pentafluoropropane (HFC-245fa) (CAS No. 460-73-1)**CONTENTS**

EXECUTIVE SUMMARY	1
THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS	2
1. SUMMARY AND CONCLUSIONS	3
2. IDENTITY, PHYSICAL, AND CHEMICAL PROPERTIES, ANALYTICAL METHODS	5
2.1 Identity	5
2.2 EC classification and labelling	5
2.3 Physical and chemical properties	5
2.4 Conversion factors	6
2.5 Analytical methods	7
2.5.1 <i>In air</i>	7
2.5.2 <i>In water</i>	7
3. PRODUCTION, STORAGE, TRANSPORT AND USE	8
3.1 Production	8
3.2 Storage	8
3.3 Transport and handling	8
3.4 Use	8
4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION	9
4.1 Emissions	9
4.2 Environmental distribution	9
4.3 Environmental fate and biotransformation	10
4.3.1 <i>Atmospheric fate</i>	10
4.3.2 <i>Aquatic fate</i>	14
4.3.3 <i>Terrestrial fate</i>	14
4.3.4 <i>Biodegradation</i>	15
4.3.5 <i>Bioaccumulation</i>	15
5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE	16
5.1 Environmental levels	16
5.2 Human exposure levels and hygiene standards	16
6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT	17
6.1 Micro-organisms	17
6.2 Aquatic organisms	17
6.3 Terrestrial organisms	17
6.4 Ecosystems	17

7. KINETICS AND METABOLISM	18
7.1 Animal studies	18
7.2 Human studies	19
8. EFFECTS ON EXPERIMENTAL ANIMALS AND <i>IN VITRO</i> TEST SYSTEMS	20
8.1 Acute toxicity	20
8.1.1 <i>Dermal</i>	20
8.1.2 <i>Inhalation</i>	20
8.1.3 <i>Other studies</i>	20
8.2 Skin and eye irritation /allergic sensitisation	21
8.3 Repeated exposure	21
8.4 Genotoxicity	22
8.4.1 <i>In vitro</i>	22
8.4.2 <i>In vivo</i>	23
8.5 Chronic toxicity and carcinogenicity	24
8.6 Developmental and reproductive toxicity	24
8.6.1 <i>Reproductive effects</i>	24
8.6.2 <i>Embryotoxic and teratogenic effects</i>	24
9. EFFECTS ON HUMANS	25
10. BIBLIOGRAPHY	26
10.1 References quoted	26
10.2 References not quoted	31
APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES	32
APPENDIX B: NAMING AND NUMBERING SYSTEM FOR FLUORO COMPOUNDS	33
APPENDIX C: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR	36
MEMBERS OF THE TASK FORCE	37
MEMBERS OF THE SCIENTIFIC COMMITTEE	38

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 the toxicity and ecotoxicity data on 1,1,1,3,3-pentafluoropropane (HFC-245fa), including results of recent and unpublished toxicological studies conducted by Honeywell International.

HFC-245fa, a colourless liquid or gas, is a non-ozone depleting alternative for trichlorofluoromethane (CFC-11) and dichlorofluoroethane (HCFC-141b). In the atmosphere, HFC-245fa degrades over a lifetime of 7.2 years, to give mainly carbon dioxide and hydrogen fluoride. Its global warming potential is 950 compared to carbon dioxide for an integration time horizon of 100 years. This compares with a global warming potential for CFC-11 of 4,000 and for HCFC-141b of 600.

In experimental animals HFC-245fa possesses a low order of acute inhalation toxicity, although it may sensitise the heart at high exposure levels (44,000 ppm or greater; $\geq 241,000$ mg/m³). Long-term exposure to HFC-245fa vapour at high concentrations (50,000 ppm; 274,000 mg/m³) was tolerated with only minimal signs of toxicity. At that level HFC-245fa demonstrated no developmental effects.

In genetic testing, HFC-245fa was not mutagenic in bacteria (Ames test), but induced some chromosome aberrations in cultured human lymphocytes. No micronuclei were found in mice exposed (*in vivo*) to 100,000 ppm (548,000 mg/m³) of HFC-245fa. These data, complemented by data on analogous substances, suggest a low order of genotoxic and carcinogenic hazard on the part of HFC-245fa.

With respect to environmental organisms, HFC-245fa showed no significant toxicity to water fleas or trout at 80 to 90 mg/l (14,600-16,500 ppm), the highest levels tested. As expected for this class of chemicals, biodegradation and bioaccumulation of HFC-245fa were minimal.

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 of 1,1,1,3,3-pentafluoropropane (HFC-245fa) (CAS No. 460-73-1).

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

1,1,1,3,3-Pentafluoropropane (HFC-245fa), a colourless liquid or gas at room temperature, is a non-ozone depleting alternative for trichlorofluoromethane (CFC-11) in foam blowing and refrigeration systems, and for dichlorofluoroethane (HCFC-141b) in foam expansion applications.

Any HFC-245fa released to the environment is expected to partition almost exclusively into the ambient air. Atmospheric degradation yields CO₂, hydrogen fluoride and carbonyl fluoride; the carbonyl fluoride will rapidly hydrolyse to CO₂ and hydrogen fluoride. The ozone depleting potential of HFC-245fa is zero. Relative to CO₂ and for an integration time horizon of 100 years, its global warming potential is estimated to be 950. This compares with a global warming potential for CFC-11 and HCFC-141b of 4,000 and 600, respectively. The overall atmospheric lifetime for HFC-245fa is 7.2 years.

HFC-245fa has a low toxicity by inhalation. There were no deaths, or marked signs of toxicity in rats exposed for 4 hours to concentrations of 203,000 ppm (1,112,000 mg/m³).

In a study to evaluate its potential to cause cardiac sensitisation, dogs were injected with adrenaline while breathing an atmosphere containing up to 73,000 ppm (400,000 mg/m³) HFC-245fa. The one dog exposed to 73,000 ppm died from cardiac arrhythmia when injected with adrenaline. One of 4 dogs developed transient cardiac arrhythmia at 44,000 ppm (241,000 mg/m³), but there were no effects at 54,100 ppm (296,000 mg/m³) or 34,100 ppm (187,000 mg/m³). Thus, 44,000 ppm was considered to be the threshold for a response, and 34,100 ppm the no-observed effect level (NOEL).

Rats exposed to HFC-245fa vapour for up to 13 weeks at levels as high as 50,000 ppm (274,000 mg/m³) showed only minimal signs of toxicity. These consisted of an increase in urinary output, some alterations in clinical chemistry parameters (possibly related to the increased urine volume), and at 10,000 ppm (54,800 mg/m³) and 50,000 ppm (274,000 mg/m³), a mild inflammation of the myocardium (heart muscle). The no-observed adverse effect level (NOAEL) was 2,000 ppm (11,000 mg/m³).

In developmental toxicity studies with rats, HFC-245fa was not teratogenic, causing no foetal effects at inhalation concentrations of up to 50,000 ppm (274,000 mg/m³), the highest level tested.

In genetic testing, HFC-245fa was not mutagenic in an Ames assay. In a human lymphocyte chromosome aberration assay, it was weakly positive without metabolic activation and inactive with metabolic activation. The substance was inactive in a mouse micronucleus assay, in which mice were exposed to 100,000 ppm (548,000 mg/m³) HFC-245fa.

HFC-245fa showed no significant signs of toxicity to *Daphnia magna* (48-hour $EC_{50} > 97.9$ mg/l) or trout (96-h $LC_{50} > 81.8$ mg/l). As is typical for hydrofluorocarbons, the 28-day biodegradation study with HFC-245fa showed only minimal degradation (2% by biochemical oxygen demand). The predicted bioconcentration factor is 2.2. As HFC-245fa is a gas, no algal testing was conducted.

Overall, results from the completed studies reviewed in this report demonstrate that HFC-245fa has a low order of toxicity.

The American Industrial Hygiene Association's Workplace Environmental Exposure Level Committee has established a permissible exposure limit for HFC-245fa of 300 ppm (1,600 mg/m³) as an 8-hour time-weighted average.

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

2.1 Identity

Name: 1,1,1,3,3-Pentafluoropropane

IUPAC name: 1,1,1,3,3-Pentafluoropropane

Synonyms: HFC-245fa
Pentafluoropropane
R-245fa

CAS name: 1,1,1,3,3-Pentafluoropropane

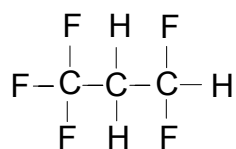
CAS registry number: 460-73-1

EC number: 419-170-6

Formula: $C_3H_2F_5$

Molecular mass: 134.05

Structure formula:



2.2 EC classification and labelling

1,1,1,3,3-Pentafluoropropane (HFC-245fa^a) is not classifiable as a dangerous substance according to the Dangerous Substances Directive 67/548/EEC and its subsequent amendments (EC, 2001).

2.3 Physical and chemical properties

HFC-245fa is a non-flammable, volatile, colourless liquid or gas at room temperature and normal atmospheric pressure. It has a faint ethereal odour and is slightly soluble in water. Physical and chemical properties are given in Table 1.

^a The naming and numbering system adopted for fluoro compounds is explained in Appendix B

Table 1: Physical and chemical properties

Property	Value, unit	Reference
Melting point	-160°C	Betteley, 1997
	< -160°C	Honeywell, 2001
Boiling point at 1,013 hPa	15.3°C	Betteley, 1997
	15°C	Honeywell, 2001
Relative liquid density D_4^{20} (density of water at 4°C is 1,000 kg/m ³)	1.32 ^a	Honeywell, 2001
Viscosity at 20°C	No data	
Refractive index nD at 20°C	No data	
Vapour pressure at 20°C	1,227 hPa ^c	Honeywell, 2001
Vapour density at 20°C (air = 1)	4.6	Honeywell, 2001
Threshold odour concentration	No data	
Surface tension at 20°C	68.5 mN/m	AlliedSignal, 1997
Solubility in water at 21°C	7.18 g/l ^d	AlliedSignal, 1997; Honeywell, 2001
Miscible with acetone, ethanol and petroleum solvents	Yes	Honeywell, 2001
Partition coefficient, log Kow (octanol/water) at 21.5°C	1.35 ^b	AlliedSignal, 1997; Honeywell, 2001
Partition coefficient, log Koc (organic carbon/water) at 20°C	No data	
Henry's Law constant at 21°C	2,290 Pa·m ³ /mol	Calculated ^e
Flash point (closed cup), flammability limits at 20 - 25°C	None	Honeywell, 2001
Explosion limits in air at 1,013 hPa, at ambient temperature	None	
Auto-flammability, ignition temperature	412° C	Honeywell, 2001

^a Reported as specific gravity^b Measured^c Reported as 17.8 psia (pounds/inch²) absolute pressure; 1 atm = 1,013.25 hPa = 14.7 psia^d In equilibrium with gaseous HFC-245fa at saturated vapour pressure^e Molecular mass x vapour pressure/solubility in water

Typically, commercial HFC-245fa has a purity of $\geq 99.8\%$ (AlliedSignal, 1997). Although no specific information is available, common impurities may include various other fluorocarbons, depending on the conditions of the production process (Section 3.1).

2.4 Conversion factors

Conversion factors for HFC-245fa concentrations in air at 25°C and 1,013 hPa are:

- 1 ppm = 5.479 mg/m³
- 1 mg/m³ = 0.183 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 C. According to European standard conditions (20°C and 1,013 hPa) these would be: 1 ppm = 5.573 mg/m³ and 1 mg/m³ = 0.179 ppm.

2.5 Analytical methods

2.5.1 In air

Rusch et al (1999) described a method for the analysis of HFC-245fa, based on gas chromatography (GC) equipped with capillary column and flame ionisation detector (FID), in which concentrations were determined by comparing the instrument response to a standard curve developed using known levels of HFC-245fa in standard Tedlar bags. The method has been used to determine HFC-245fa in air at levels of from 500 to 50,000 ppm (2,700 - 270,000 mg/m³); it is considered that the method should detect levels as low as 10 ppm (55 mg/m³).

2.5.2 In water

According to a method developed by Jenkins (1997a,b), water was placed in a sealed glass bottle held at 10°C and analysed using GC with FID. The area of the peak is compared to a standard curve developed using known concentrations of HFC-245fa, and the level of HFC-245fa in the test sample thus determined. The limit of detection (defined as the concentration required to produce a chromatogram peak twice the height of baseline noise) was estimated to be 0.1 mg/l. Under the conditions described, calibration was found to be linear over the nominal concentration range (2 to 20 mg/l).

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

A plant for the commercial production of HFC-245fa, by fluorination of pentachloropropane, has recently been completed. There is only one global producer and production capacity is confidential.

3.2 Storage

HFC-245fa is stored in containers that may be pressurised with nitrogen. Because of its low boiling point (15°C, Table 1), the containers are kept in a cool, well-ventilated area of low fire risk, avoiding exposure to high temperatures (> 50°C) and sources of ignition (such as sparks, hot spots, welding flames and lighted cigarettes) that might yield toxic and/or corrosive decomposition products. Contact with certain finely divided reactive metals, in combination with high temperature and/or pressure, may result in explosive or exothermic reactions (Honeywell, 2001).

At high temperatures (> 250°C), decomposition products include hydrogen fluoride (hydrofluoric acid, HF) and carbonyl fluoride (COF₂) (Honeywell, 2001).

3.3 Transport and handling

Under pressure with nitrogen, HFC-245fa can be shipped as a "liquefied gas, not otherwise specified (nitrogen, pentafluoropropane)" under US-DOT (UN No. 3163, Class 2.2) regulations (Honeywell, 2001). When shipped without nitrogen, the material is not regulated according to US-DOT.

In Germany, HFC-245fa is classified as a low hazard to water (Wassergefährdungsklasse, WGK 1) (Umweltbundesamt, 2003).

3.4 Use

The primary use of HFC-245fa is intended to be as a foam-blowing agent for closed cell foams. It will also be used in refrigeration and may have some application in solvent aerosols (Zipfel *et al*, 1998; Honeywell, 2001). These uses have been approved by the USA-EPA.

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Emissions

There is no known natural source of HFC-245fa.

4.2 Environmental distribution

The environmental partitioning of HFC-245fa has been assessed (Franklin, 2003) using the equilibrium criterion (EQC) Level I and Level III models (Mackay *et al*, 1996). The environmental partitioning of HFC-245fa has been assessed (Franklin, 2003) using the equilibrium criterion (EQC) Level I and Level III models (Mackay *et al*, 1996).

In the Level I model, a fixed quantity of a supposedly non-degradable chemical is introduced into a closed evaluative environment and equilibrium achieved between the various environmental compartments (air, water, soil, sediment). The Level III model simulates a situation in which a chemical is emitted at a constant rate into one or more of the compartments, in each of which it may degrade; the steady-state distribution between compartments is then calculated. Due to the resistance to mass transfer between compartments, the various phases are not in equilibrium and the steady-state partitioning depends on its "mode of entry", i.e. the compartment(s) into which the chemical is injected.

EQC modelling has been performed for HFC-245fa using the physical properties given in Table 1 and an atmospheric lifetime of 7.2 years (Section 4.3.1), corresponding to a half-life of 5.0 years. Degradation in other media was not taken into account. Table 2 gives the percentages of HFC-245fa calculated to be present in each compartment.

Table 2: Partitioning (%) into the environment (Franklin, 2003)

Compartment	EQC Level I	EQC Level III	
		Emission to air alone	Emission to water alone
Air	99.78	99.83	19.8
Water	0.21	0.15	80.0
Soil	0.004	0.014	0.003
Sediment	0.0001	0.0004	0.20

The Level III simulation, with emissions of HFC-245fa to air alone, leads to a distribution close to the Level I equilibrium situation as far as the air and water compartments are concerned.

However a much greater steady-state proportion of HFC-245fa is found in the water compartment when the emissions are to water alone. This is due to the resistances to inter-media transfer (in particular from water to air) introduced in the Level III model.

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric fate

Atmospheric lifetime^a

The atmospheric degradation of HFC-245fa occurs mainly in the troposphere, being initiated by reaction with naturally occurring hydroxyl radicals ($\bullet\text{OH}$). Values for the rate constant of this reaction have been reported by Nelson *et al* (1995) and Orkin *et al* (1996). From these two sets of data, DeMore *et al* (1997) recommended a rate constant of $6.1 \times 10^{-13} \exp(1,330/T) \text{ cm}^3 / \text{molecule} / \text{s}$ (where T = temperature in °K).

This latter value was used by IPCC (2001) in calculating their recommended overall atmospheric lifetime of 7.2 years. Slightly different values were published previously by Ko *et al* (1999) and Naik *et al* (2000).

Ozone depleting potential

As HFC-245fa contains neither chlorine nor bromine, its ozone depleting potential is zero.

Global warming potential

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 is calculated for a given "integration time horizon" (ITH). Depending on the reference substance, the ITH may be chosen to be finite (e.g. CO_2) or infinite (e.g. CFC-11). Almost invariably, GWP values are expressed relative to CO_2 , for an ITH of 100 years.

The estimated 100-year GWP for HFC-245fa, relative to 1.0 for CO_2 , is 950 (IPCC, 2001). Somewhat different values have been published by Ko *et al* (1999) and Naik *et al* (2000).

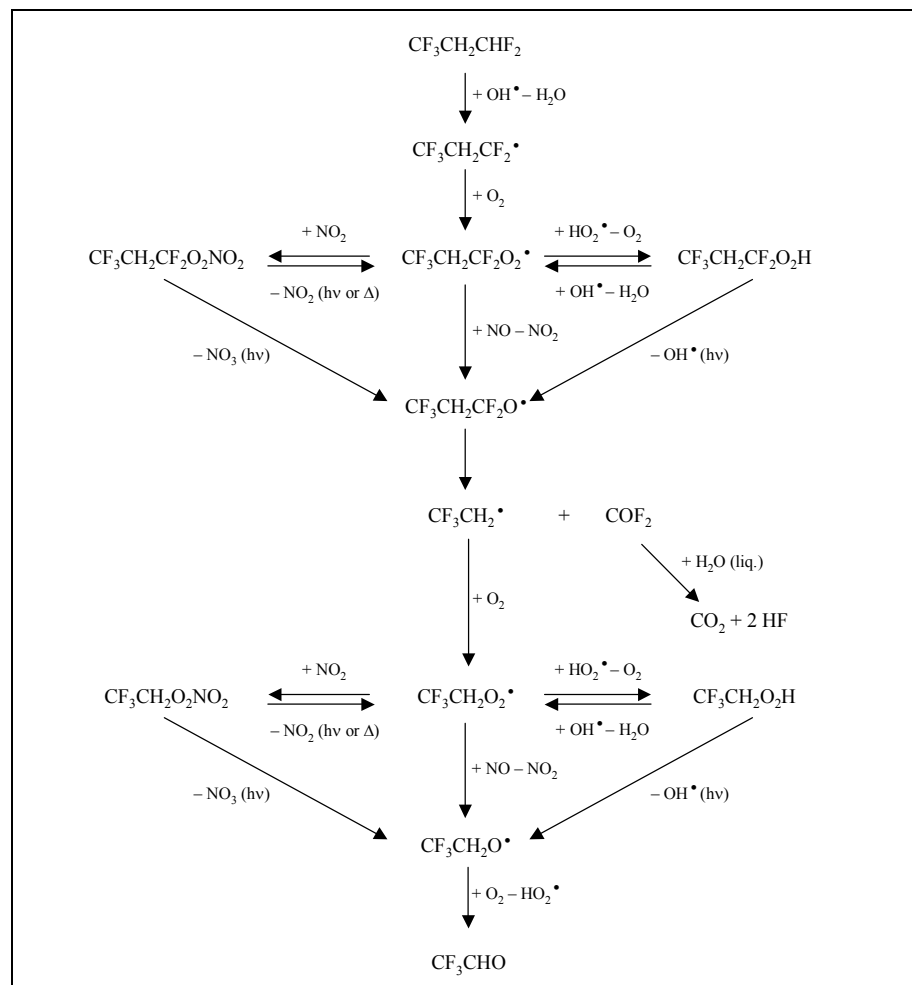
^a Lifetime is the time necessary for 63% degradation: it is equal to the "half-life" divided by $\ln 2$ (= 0.69)

Tropospheric ozone formation

By analogy with similar compounds (Niki, 1989; Hayman and Derwent, 1997), it can be concluded that HFC-245fa is too unreactive in the atmosphere to make any significant contribution to tropospheric ozone formation and related "photochemical smog" near the emission sources (particularly in urban areas). The US-EPA (1997) has excluded HFC-245fa as a volatile organic compound in its ozone control programme.

Degradation mechanism and products

A reaction scheme for the degradation of HFC-245fa in the troposphere is proposed in Figure 1 and 2. This scheme is based on the general mechanisms developed by Atkinson *et al* (1989), those elucidated for a large number of HCFCs and HFCs since the late 1980s (Cox *et al*, 1995; Lelieveld *et al*, 1999), on specific studies on HFC-245fa itself (Chen *et al*, 1997) and on other compounds containing the structural moiety CF_3CH_2 - (Nielsen *et al*, 1994, Barry *et al*, 1997).

Figure 1: Tropospheric degradation mechanism for HFC-245fa (Part 1^a)

^a NO_2 , NO and NO_3 , free radicals

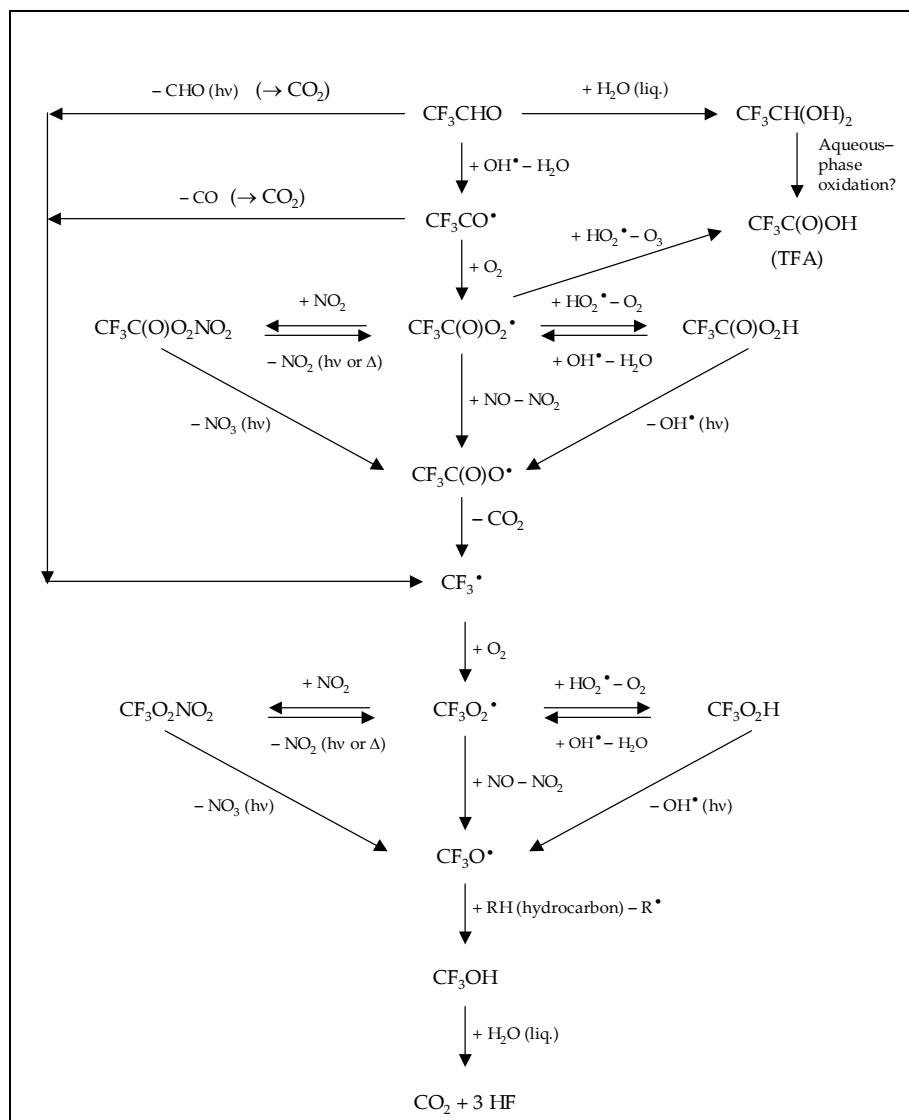
According to the scheme presented in Figure 1 and 2, the principal ultimate degradation products of HFC-245fa are CO_2 and HF , with COF_2 , CF_3CHO (trifluoroacetaldehyde, fluoral) and CF_3OH (trifluoromethanol) as the main non-radical intermediates.

The peroxy nitrates ($\text{CF}_3\text{CH}_2\text{CF}_2\text{O}_2\text{NO}_2$, $\text{CF}_3\text{CH}_2\text{O}_2\text{NO}_2$ and $\text{CF}_3\text{O}_2\text{NO}_2$) and hydroperoxides ($\text{CF}_3\text{CH}_2\text{CF}_2\text{O}_2\text{H}$, $\text{CF}_3\text{CH}_2\text{O}_2\text{H}$ and $\text{CF}_3\text{O}_2\text{H}$) are believed to be rather short-lived intermediates, undergoing photolysis, thermal decomposition or reaction with $\text{OH}^\bullet$, leading to the regeneration of peroxy radicals ($\text{RO}_2^\bullet$) or the formation of alkoxy radicals ($\text{RO}^\bullet$) (Cox *et al*, 1995; Lelieveld *et al*, 1999).

The COF_2 and CF_3OH formed as intermediates will be taken up by cloud droplets, on a timescale of days to weeks, and hydrolysed to CO_2 and HF (Cox *et al*, 1995; Huey *et al*, 1995; Lovejoy *et al*, 1995).

Figure 2 focuses on the fate of the intermediate CF_3CHO .

Figure 2: Tropospheric degradation mechanism for HFC-245fa (Part 2^a)



^a NO_2 , NO and NO_3 , free radicals; R, alkyl group

Photolysis is likely to be the major pathway for CF_3CHO , leading to the $\text{CF}_3\bullet$ radical and hence to CO_2 and HF (via CF_3OH), since the calculated lifetime of this process is only about 4 hours, by analogy with chloral (CCl_3CHO) (Rattigan *et al*, 1998). The authors assumed a unit quantum efficiency, as observed for the analogous CCl_3CHO (Talukdar *et al*, 2001). Reaction of CF_3CHO with $\bullet\text{OH}$ will be considerably slower than photolysis, since the lifetime for this process is estimated to be 24 days (Scollard *et al*, 1993). Furthermore, uptake of CF_3CHO into cloud droplets

will also be slower than photolysis, occurring with a lifetime of around 10 to 20 days, a typical range for highly soluble species formed in the free troposphere (Giorgi and Chameides, 1986).

Some trifluoroacetic acid (TFA) might conceivably be formed from HFC-245fa, but data required for making a quantitative estimate of the yield of TFA are lacking. Speculatively, TFA might be produced by the gas-phase reaction $\text{CF}_3\text{C}(\text{O})\text{O}_2 + \text{HO}_2 \rightarrow \text{CF}_3\text{COOH} + \text{O}_3$ or by aqueous-phase oxidation of fluoral hydrate, $\text{CF}_3\text{CH}(\text{OH})_2$, in cloud droplets. However, even if these processes were to occur, they would be likely to be of minor importance, since they would proceed only after the reaction of CF_3CHO with OH or the uptake of CF_3CHO into cloud water, both of which are considerably slower than photolysis (leading to a one-carbon product).

4.3.2 Aquatic fate

The hydrolysis of HFC-245fa (1,047.1 µg/ml nominal or about 1 g/l analysed) was determined at 50°C in water buffered at three different pHs, following a standard EC protocol. The results are summarised in Table 3.

Table 3: Hydrolysis (% removal) at 50°C and different pH (Betteley, 1997)

Time	pH value		
	4	7	9
2.4 h	10.6	2.9	6.2
5 d	16.3	20.4	24.2

The author concluded that at greater than 5% (erroneously stated as 50%) and greater than 10%, hydrolysis at 50°C occurred in 2.4 hours and 5 days respectively, equivalent to abiotic half-lives of 1 day and 1 year, respectively, at 25°C (Betteley, 1997; CoR 1a). (Measurements were conducted at 50°C and extrapolated to 25°C as hydrolysis would have been too slow to measure at 25°C).

Any HFC-245fa that might be present in aqueous waste streams discharged directly into rivers or lakes would be expected to have a half-life with respect to volatilisation of days or at most a few weeks, by analogy with similar compounds.

4.3.3 Terrestrial fate

No data are available.

4.3.4 Biodegradation

In a closed bottle assay with activated sludge, the percentage of transformation of HFC-245fa (initial concentration 5.93 mg/l) was only 2% as judged by biochemical oxygen demand or 8% by GC after 28 days (Katsuura, 1997; CoR 1a). Thus HFC-245fa is considered to be not readily biodegradable. There is no indication that the viability of the sludge was determined after the test.

4.3.5 Bioaccumulation

No measured data are available.

Based on the $\log K_{ow}$ of 1.35 (Table 1), BcfWin software (US-EPA, 2003) predicts a bioconcentration factor of 2.2 for HFC-245fa. This is as expected for a material with a high vapour pressure and low K_{ow} (Thompson, 2003).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 *Environmental levels*

HFC-245fa has only recently been put into commercial production. To date there are no reports of it being found in the environment.

5.2 *Human exposure levels and hygiene standards*

At present only limited information is available on human exposure to HFC-245fa vapours in the workplace. Typical values (based on personal sampling with adsorption tubes) are in the range of 10 to 100 ppm during foam blowing (Honeywell, 2001; CoR 1b).

The American Industrial Hygiene Association has recommended a workplace environmental exposure level guide (WEEL) of 300 ppm (8-hour time-weighted average) (AIHA, 1996). This was based on a 13-week inhalation toxicity study in rats, where myocarditis was seen at 10,000 ppm while 2,000 ppm represented either a NOAEL or possibly a threshold (Rusch *et al*, 1999; CoR 1a) (Section 8.3).

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 *Micro-organisms*

No data are available.

6.2 *Aquatic organisms*

HFC-245fa was tested in the water flea *Daphnia magna* under static conditions following OECD Guideline 202 (Directive 92/69/EEC Part C2) (OECD, 1984). Because of the volatility of the test compound (nominal concentration 100 mg/l), the vessel was completely filled, leaving no headspace. The actual concentration of the test solution was analysed by GC (Section 2.5.2) at 0 and 48 hours. No immobility was seen after 2 days at 97.9 mg/l, the highest concentration tested. The 48-hour EC₅₀ was greater than 97.9 mg/l (Jenkins, 1997a; CoR 1a).

HFC-245fa was tested in rainbow trout (*Oncorhynchus mykiss*) under semi-static conditions following OECD Guideline 203 (Directive 92/69/EEC Part C1) (OECD, 1992). Because of the volatility of the test compound (nominal concentration 100 mg/l), the vessel was completely filled leaving no headspace. The actual concentration of the test solution was monitored by means of GC analysis (Section 2.5.2) at 0 and 72 hours in fresh media, and again at 24 and 96 hours in expired media. After 96 hours, there was no mortality at 81.8 mg/l, the highest level tested. Therefore, the 96-hour LC₅₀ was greater than 81.8 mg/l (Jenkins, 1997b; CoR 1a).

No algal testing was carried out with HFC-245fa, as such a test is not a viable study with gaseous substances.

6.3 *Terrestrial organisms*

No data are available.

6.4 *Ecosystems*

No data are available.

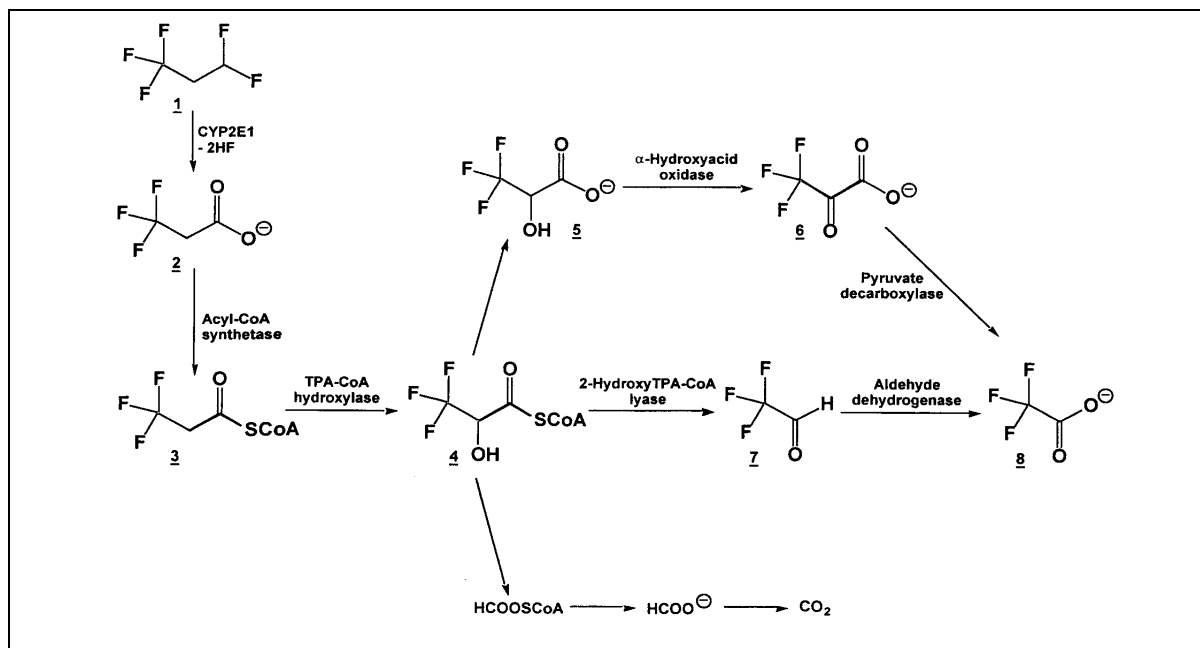
7. KINETICS AND METABOLISM

7.1 Animal studies

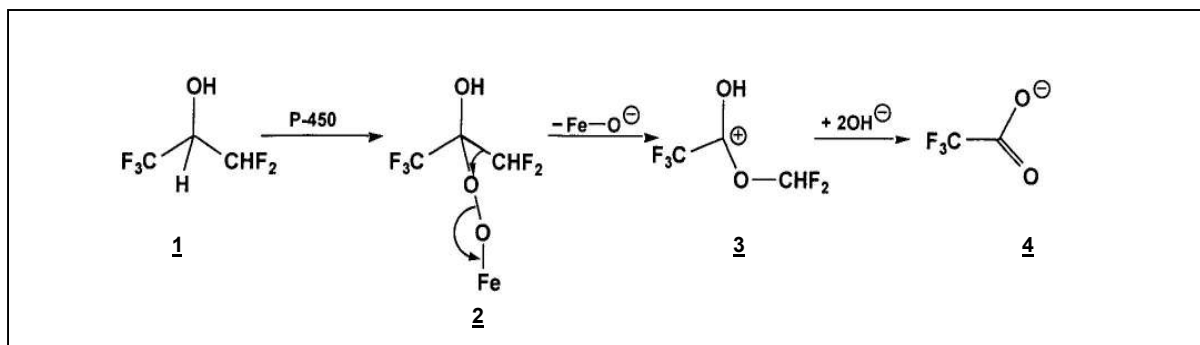
Male and female Sprague-Dawley rats (5/sex/group) were exposed by inhalation to 0, 2,000, 10,000 or 50,000 ppm HFC-245fa (0, 11,000, 54,800, 274,000 mg/m³) for 6 hours. Urine was collected at 6-hour intervals for 72 hours, and excreted metabolites identified by ¹⁹F-NMR spectroscopy and quantified by GC coupled with a mass spectrometer (GC-MS). TFA and inorganic fluorides were identified as major, and 3,3,3-trifluoropropanoic acid and 1,1,1,3,3-pentafluoropropan-2-ol as minor urinary metabolites, respectively. The metabolic pathway leading to the formation of TFA has not been identified. However, trifluoropropanoic acid does not appear to be the precursor, as no TFA was found in studies with 3,3,3-trifluoropropanoic acid. This implies that the TFA is formed directly from HFC-245fa and not as a consequence of decarboxylation of the C-3 acid. The rate of formation of TFA and 3,3,3-trifluoropropanoic acid in rat liver microsomes was 99.2 ± 20.5 pmol/mg protein/min and 17.5 ± 4.0 pmol/mg protein/min, respectively. In human liver microsomes, rates of TFA formation and 3,3,3-trifluoropropanoic acid formation ranged from 0 to 30.4 pmol/mg protein/min and 0.7 to 7.6 pmol/mg protein/min. These results indicated that 1,1,1,3,3-pentafluoropropane was metabolised at low rates *in vivo* and *in vitro* (Bayer *et al*, 2002; CoR 1a).

The authors concluded that the toxicity of HFC-245fa might be associated with the formation of the 3,3,3-trifluoropropanoic acid, which is highly toxic in the rat. They further concluded that the lower rates of 3,3,3-trifluoropropanoic acid formation in human liver microsomes as compared with the rat, indicated that humans would form less 3,3,3-trifluoropropanoic acid than rats and thus might be at a lower risk for potential adverse effects after exposure to HFC-245fa (Figure 3 and 4).

Metabolism of HFC-245fa occurs at a lower rate in humans compared with rats, and thus more is likely to be eliminated unchanged in the exhaled air. As a consequence, the level of both the toxic metabolite, 3,3,3-trifluoropropanoic acid, and the less toxic metabolite, TFA, would be expected to be lower in humans.

Figure 3: Metabolic pathways^a (Bayer et al, 2002)

^a Compounds: HFC-245fa (1), 3,3,3-trifluoropropanoic acid (2), 3,3,3-trifluoropropanoyl-CoA (3), 2-hydroxy-3,3,3-trifluoropropanoyl-CoA (4), 2-hydroxy-3,3,3-trifluoropropanoic acid (5), 3,3,3-trifluoropyruvic acid (6), trifluoroacetaldehyde (7) and TFA (8)

Figure 4: Metabolic pathways^a (Bayer et al, 2002)

^a Compounds: 1,1,1,3,3-pentafluoro-2-propanol (1), ferryl peroxide intermediate (2), carbocationic intermediate (3) and TFA (4)

7.2 Human studies

There are no data relating to the absorption, distribution, metabolic transformation, or elimination of HFC-245fa in humans.

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

8.1 Acute toxicity

8.1.1 Dermal

Hydrofluorocarbons are only slightly adsorbed through the skin.

No reaction was seen following application of 2 ml HFC-245fa (2.64 mg/kgbw) covered with an occlusive dressing placed on the backs of 5 male and 5 female New Zealand rabbits for 24 hours. It is probable that the test substance evaporated well before the end of the 24-hour period even though an occlusive dressing was used (Rusch *et al*, 1999; CoR 1a).

8.1.2 Inhalation

A series of 4-hour exposures was conducted with groups of 5 male and 5 female Sprague-Dawley rats at levels of 0, 116,000, 143,000 or 203,000 ppm HFC-245fa (0, 636,000, 783,000, 1,112,000 mg/m³). Some exposure-related clinical signs of central nervous system depression (such as irregular respiration, restless behaviour, intermittent muscular contractions, abnormal posture and reduced response to external stimuli) were seen. However, there was no mortality, or effects on body weight or other clinical parameters (Rusch, *et al*, 1999; CoR 1a).

Five male and 5 female CD-1 mice were exposed, snout only, to 0 or 101,300 ppm HFC-245fa (0 or 555,000 mg/m³) for 4 hours. No mortality, effects on body weight or clinical signs of toxicity were seen (Rusch *et al*, 1999; CoR 1a).

8.1.3 Other studies

A limited study was conducted in which groups of 2 dogs were exposed (snout-only, 6 h/d, 5 d/wk) to levels of 0, 1,000, or 10,000 ppm HFC-245fa (0, 5,480, 54,800 mg/m³) for 2 weeks. On the day following the final exposure, each dog was evaluated in a cardiac sensitisation study involving exposure to 35,000 ppm HFC-245fa (192,000 mg/m³) and a challenge injection of adrenaline. There were no adverse responses or histopathological changes in the heart (Kenny, 1998; CoR 1a).

The potential of HFC-245fa to sensitise the heart to adrenaline was investigated in a group of 6 beagle dogs. Each dog was exposed to HFC-245fa for 5 minutes, and then given an injection of adrenaline and observed for an additional 5 minutes during which exposure was continued. Exposure to 73,000 ppm (400,000 mg/m³) caused a fatal ventricular fibrillation, while at 44,000 ppm (241,000 mg/m³), 1 of 4 dogs developed an arrhythmia. Neither response was

observed in the 4 dogs exposed to 34,100 ppm (187,000 mg/m³) or in the 3 exposed to 54,000 ppm (296,000 mg/m³). Based on these results, the threshold for development of cardiac arrhythmia in the presence of injected adrenaline was assumed to be 44,000 ppm, with a NOEL of 34,100 ppm (Rusch, *et al*, 1999; CoR 1a).

8.2 Skin and eye irritation/allergic sensitisation

HFC-245fa is a gas at room temperature and thus no specific test data are available on these endpoints.

However, no signs of eye or nasal irritation were noted in the acute inhalation studies in rats and mice (Section 8.1.2). No signs of skin irritation were seen in rabbits following dermal application for 24 hours in a study of acute dermal toxicity (Section 8.1.1) (Rusch *et al*, 1999).

8.3 Repeated exposure

A series of three inhalation toxicity studies, all involving daily exposures up to 50,000 ppm HFC-245fa (274,000 mg/m³) was conducted in the rat.

The first study, which served as a pilot for the other two, involved 14 consecutive snout-only exposures (6 h/d) of groups of 5 male and 5 female Sprague-Dawley rats to levels of 0, 5,000, 15,000 or 50,000 ppm HFC-245fa (0, 27,000, 82,000, 274,000 mg/m³). There were no treatment-related effects on body weight, clinical observations, survival, or histological parameters. Frequently, blood urea nitrogen (BUN), glutamic pyruvic transaminase (GPT), and glutamic oxaloacetic transaminase (GOT) levels were found to be elevated compared to controls, while cholesterol levels tended to be lower (Rusch, *et al*, 1999; CoR 1a). Most of these changes at 15,000 and 50,000 ppm, but only some at 5,000 ppm, were statistically significant. No clear exposure related pattern was seen, with some effects at 15,000 ppm being similar or greater than those at 50,000 ppm.

In the second study, groups 5 male and 5 female Sprague-Dawley rats were exposed (whole body, 6 h/d) to 0, 500, 2,000, 10,000 or 50,000 ppm HFC-245fa (0, 2,700, 11,000, 54,800, 274,000 mg/m³) for 28 consecutive days and killed at the end of the exposure period. Additional groups of 5 males and 5 females were exposed to air and to 50,000 ppm, held for 2 weeks and then killed. Again, there were no treatment-related effects on body weight, survival or histological parameters. Urine volumes were increased and increases were seen in BUN and activities of alkaline phosphatase (AP), GPT, GOT, and creatinine phosphokinase (CPK), primarily in rats exposed at 10,000 and 50,000 ppm HFC-245fa. There were no treatment-related changes in urinary fluoride levels (Rusch, *et al*, 1999; CoR 1a).

In the final study, groups of 10 male and 10 female Sprague-Dawley rats were exposed (whole-body, 6 h/d, 5 d/wk) to 0, 500, 2,000, 10,000 or 50,000 ppm HFC-245fa (0, 2,700, 11,000, 54,800, 274,000 mg/m³) for 13 weeks. There were no treatment-related effects on survival, clinical observations, body weight gain or food consumption. Urinary fluoride levels were elevated and increases were seen in AP, GOT and GPT (CPK) activities. Histopathological examination did not show any effects on the kidney, liver or lungs. An increased incidence of mild myocarditis was observed in all animals exposed to 50,000 ppm and in the majority exposed to 10,000 ppm. At 2,000 ppm, 1 female showed a trace of diffuse myocarditis (Grade 1 of 5). This observation was not statistically significant and it was concluded by the authors that this single Grade 1 observation might be unrelated to treatment, or at most, represent a threshold for this effect (Table 4) (Rusch *et al*, 1999; CoR 1a).

Table 4: Histopathological heart findings in the 13-week inhalation study in rats (Rusch *et al*, 1999)

Exposure concentration (ppm):	Males					Females				
	0	500	2,000	10,000	50,000	0	500	2,000	10,000	50,000
Total number examined	10	10	10	10	10	10	10	10	10	10
- No abnormalities	8	8	6	0	0	10	9	7	1	0
- Myocarditis focal	2	2	4	2	1	0	1	2	0	0
- Myocarditis diffuse ^a	0	0	0	8 ^b	9 ^b	0	0	1	9 ^c	10 ^b
Grade 1	0	0	0	0	0	0	0	1	8	5
Grade 2	0	0	0	7	6	0	0	0	1	4
Grade 3	0	0	0	1	3	0	0	0	0	1

^a Grade 1 = trace; 2 = minimal; 3 = mild (4 = moderate; 5 = severe)

^b p < 0.01 with Fisher's exact test

^c p < 0.05 with Fisher's exact test

As HFC-245fa is a gas at room temperature, no specific data are available from specific study of oral or dermal toxicity.

8.4 Genotoxicity

8.4.1 *In vitro*

HFC-245fa was not active in either of two Ames vapour phase studies employing airborne concentrations up to 40 or 100% v/v (400,000 or 1,000,000 ppm; 2,190,000 or 5,480,000 mg/m³). The studies were conducted using 5 strains of *Salmonella typhimurium* (TA98, TA100, TA1538, initial study only, TA1535 and TA1537) and *Escherichia coli* (WP2 *uvrA*) with and without S9 metabolic activation (Rusch, *et al*, 1999; CoR 1a).

The mutagenic potential of HFC-245fa was also evaluated using an *in vitro* cytogenetic study with cultured human lymphocytes (Table 5). In this assay, weak evidence of clastogenic activity was seen in the absence of S9 with 24-hour exposures to levels of 30 and 40%, but not with 24-hour exposures at 10 or 20%, or with 6-hour exposures to any concentration. No evidence of clastogenic activity was seen in cultures with S9. In all cases where evidence for clastogenicity was seen, there was also a reduction in mean mytotic index suggestive of cytotoxicity (Rusch *et al*, 1999; CoR 1a).

Table 5: Cytogenetic test with cultured human lymphocytes (Rusch *et al*, 1999)

	Without S9					With S9		
Exposure time (h):	24					3		
Concentration (%)	0	10	20	30	40	0	50	70
Mean mytotic index	13.0	17.1	13.6	9.7	14.8	16	17.3	15.4
Mean % cells with aberrations ^a	5.0	7.0	7.5	12 ^a	2.5	3.0	2.5	5.0
Mean % cells with aberrations other than gaps	3.0	2.5	2.0	4.5	0.5	1.5	1.0	2.5
Exposure time (h):	6							
Concentration (%)	0	40	50	70				
Mean mytotic index	15.2	13.3	12.6	13.2				
Mean % cells with aberrations ^a	3.0	3.0	2.0	4.5				
Mean % cells with aberrations other than gaps	1.5	1.0	1.0	2.0				
Exposure time (h):	24					Chlor-ambucil		
Concentration (%)	0	20	30	40				
Mean mytotic index	14.6	14.0	7.2	4.6		15.8		
Mean % cells with aberrations ^a	3.0	6.0	14.0 ^b	13.5 ^b		23.5 ^b		
Mean % cells with aberrations other than gaps	1.5	3.5	7.0 ^c	9.0 ^b		17.5 ^b		

^a Two replicates

^b $p \geq 0.001$

^c $p \geq 0.01$

8.4.2 *In vivo*

The potential for a 4-hour exposure to 100,000 ppm HFC-245fa (548,000 mg/m³) to cause chromosomal or other damage leading to the formation of micronuclei, was evaluated in polychromatic erythrocytes from mice. There was no evidence of induced chromosomal or other damage leading to micronucleus formation in polychromatic erythrocytes of treated mice evaluated 24 and 48 hours after exposure (Rusch, *et al*, 1999; CoR 1a).

8.5 Chronic toxicity and carcinogenicity

No data were found for studies with exposure phases of longer than 13 weeks.

There are no data available on carcinogenicity. However, the absence of mutagenic activity in the Ames and mouse micronucleus assays and the minimal activity seen in the chromosome aberration assay reduce concern regarding the potential carcinogenicity of HFC-245fa. Furthermore, other similar chemicals such as chlorotetrafluoroethane (Malley *et al*, 1998; CoR 1a) and tetrafluoroethane (Collins, *et al*, 1995; CoR 1a) were not carcinogenic in lifetime inhalation studies in rats.

8.6 Developmental and reproductive toxicity

8.6.1 Reproductive effects

No data are available.

A 2-generation reproduction toxicity study is planned for completion in 2004.

8.6.2 Embryotoxic and teratogenic effects

Five groups of 25 time-mated pregnant Crl:CDBR rats were exposed (whole-body, 6 h/d) to levels of 0, 500, 2,000, 10,000 or 50,000 ppm HFC-245fa (0, 2,700, 11,000, 54,800, 274,000 mg/m³) from days 6 to 15 of gestation. A slight reduction in pup weight was seen at 50,000, but not at 10,000 ppm. Dam body weights were also significantly reduced at 50,000 ppm, but not in the lower level exposure groups. There were no developmental effects at any level tested (Rusch *et al*, 1999; CoR 1a).

9. EFFECTS ON HUMANS

Commercial production of HFC-245fa has only recently been initiated, limiting the opportunity for health effects screening.

To date no reported adverse health effects have been ascribed to HFC-245fa.

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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, <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
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: NAMING AND NUMBERING SYSTEM FOR FLUOROCARBON COMPOUNDS

The naming and numbering system currently used by industry was officially adopted as Standard 34 of the American Society of Heating, Refrigeration, and Air-conditioning Engineers (ASHRAE) on June 3, 1957 (Du Pont, 1999).

B.1 Prefixes

These prefixes are generally applicable:

- FC = Fluorocarbon
- CFC = Chlorofluorocarbon
- HFC = Hydrofluorocarbon
- PFC = Perfluorocarbon (also Perfluorocompound, Persistent Fluorinated Compound)
- HFOC = Hydrofluoroether
- HCFC = Hydrochlorofluorocarbon
- FOC = Fluoroether

B.2 Numbering code

The first digit from the right is the number of fluorine atoms in the molecule. The second digit from the right is one more than the number of hydrogen atoms in the molecule. The third digit from the right is one less than the number of carbon atoms in the molecule (omit if zero).

The number of chlorine atoms in the compound is calculated by subtracting the sum of fluorine and hydrogen atoms from the total atoms which can be connected to the carbon atoms. If some of the chlorine has been replaced by bromine, then the number is followed by a "B", then the number of chlorine atoms so replaced.

The fourth digit from the right indicates the number of double bonds in the molecule, for example:

- PFC-116 = 6 Fs, 0 Hs, 2 Cs and 0 Cls $\rightarrow$ C₂F₆
- HFC-23 = 3 Fs, 1 H, 1 C, and 0 Cls $\rightarrow$ CF₃H
- PFC-1216 = 6 Fs, 0 Hs, 3 Cs, 0 Cls with 1 double bond $\rightarrow$ C₃F₆ $\rightarrow$ CF₂=CF-CF₃

For cyclic molecules, the letter C is used before the identifying number, for example:

- PFC-C318 = 8 Fs, 0 Hs, 4 Cs and 0 Cls with cyclic structure $\rightarrow$ c-C₄F₈

For isomeric compounds, each has the same number designation, but the various isomers are indicated by a lowercase letter following the number; the letters are assigned based on the symmetry of the molecule. The most symmetrical structure has no letter, followed by the next most symmetrical isomer designated "a", and so on. The symmetry is determined by summing the atomic weights of all atoms attached to each carbon, and comparing the two numbers. The smaller their difference, the more symmetrical the molecule. For example $C_2H_2F_4$ can have two structural isomers:

- CF_2H-CF_2H , more symmetrical, HFC-134
- CF_3-CF_2H , less symmetrical, HFC-134a

B.3 Extension to 3-carbon molecules

For C3s, the isomer designation is slightly different, and uses a two-letter code. The codes below are used to determine the substituents on the central carbon, which determines the first letter of the code. The second letter in the code designates the various isomers based on symmetry, with the most symmetrical structure designated "a", and so forth.

B.4 Letter central carbon

- a = CCl_2
- b = $CClF$
- c = CF_2
- d = $CClH$
- e = CHF
- f = CH_2

For example:

HFC-236fa = $C_3F_6H_2$ → Central carbon designated "f" → CH_2 → "a" designation → $CF_3CH_2CF_3$

B.5 C4 and larger molecules

For 4-carbon atom and larger molecules, string together the letter designations from the above and following lists to indicate the current isomer. Always start either at the molecule's more fluorinated end or at the end needing the least number of suffix letters to assign the structure. If a digit is larger than 9, it is offset by a dash.

- j = CCl_3
- k = CCl_2F

- l = CClF_2
- m = CF_3
- n = CHCl_2
- o = CH_2Cl
- p = CHF_2
- q = CH_2F
- r = CHClF
- s = CH_3
- t = C
- x = CCl
- y = CF
- z = CH

Example: HFC-43-10mee = 10 Fs, 2 Hs, 5 Cs, no Cls $\rightarrow \text{C}_5\text{H}_2\text{F}_{10}$

m indicates $\text{CF}_3 \dots \text{CF}_3$

e indicates CHF, so CF_3CHF

e indicates CHF, so CF_3CHFCHF

HFC-43-10mee $\rightarrow \text{CF}_3\text{CHFCHFCHFCF}_2\text{CF}_3$

The assignment of a string of letters, to denote structural groups, is stopped when the structure is unambiguous (i.e. one does not need to call the compound HFC-43-10mee**cm**, since once one reaches "mee", one knows that 5 fluorine atoms still need to be attached to the remaining two carbons, so the rest of the molecule must be $-\text{CF}_2\text{CF}_3$).

APPENDIX C: 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.

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

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

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

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

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

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

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

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

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^b Retired

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