ECETOC

Joint Assessment of Commodity Chemicals No. 24

Pentafluoroethane (HFC 125)

CAS No. 354-33-6

May 1994

European Centre for Ecotoxicology
and Toxicology of Chemicals

Avenue E. Van Nieuwenhuyse 4, (Bte. 6)
B - 1160 Brussels, Belgium

LIST OF ECETOC PUBLICATIONS (continued inside back cover)

MONOGRAPHS

No.	Title
No. 1	Good Laboratory Practice
No. 2	Contribution to Strategy for Identification and Control of Occupational Carcinogens
No. 2	Definition of a Mutagen, for 6th Amendment
No. 3	Risk Assessment of Occupational Chemical Carcinogens
No. 4	Hepatocarcinogenesis in Laboratory Rodents : Relevance for Man
No. 5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology)
No. 6	Acute Toxicity Tests, $LD_{50}(LC_{50})$ Determinations and Alternatives
No. 7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies
No. 8	Structure-Activity Relationships in Toxicology and Ecotoxicology: An Assessment
No. 9	Assessment of Mutagenicity of Industrial and Plant Protection Chemicals
No. 10	Identification of Immunotoxic Effects of Chemicals and Assessment of their Relevance to Man
No. 11	Eye Irritation Testing
No. 12	Alternative Approaches for the Assessment of Reproductive Toxicity (with emphasis on embryotoxicity/teratogenicity)
No. 13	DNA and Protein Adducts: Evaluation of their Use in exposure Monitoring and Risk Assessment
No. 14	Skin Sensitisation Testing
No. 15	Skin Irritation
No. 16	Mutation Research, Special Issue: Early Indicators of Non-Genotoxic Carcinogenesis
No. 17	Hepatic Peroxisome Proliferation
No. 18	Evaluation of the Neurotoxic Potential of Chemicals
No. 19	Respiratory Allergy
No. 20	Percutaneous Absorption

JACC REPORTS

No.	Title
No. 1	Joint Assessment of Commodity Chemicals, Melamine
No. 2	Joint Assessment of Commodity Chemicals, 1,4-Dioxane
No. 3	Joint Assessment of Commodity Chemicals, Methyl Ethyl Ketone
No. 4	Joint Assessment of Commodity Chemicals, Methylene Chloride
No. 5	Joint Assessment of Commodity Chemicals, Vinylidene Chloride
No. 6	Joint Assessment of Commodity Chemicals, Xylenes
No. 7	Joint Assessment of Commodity Chemicals, Ethylbenzene
No. 8	Joint Assessment of Commodity Chemicals, Methyl Isobutyl Ketone
No. 9	Joint Assessment of Commodity Chemicals, Chlorodifluoromethane
No. 10	Joint Assessment of Commodity Chemicals, Isophorone
No. 11	Joint Assessment of Commodity Chemicals, (HFA-132b) 1,2-Dichloro-1,1-Difluoroethane
No. 12	Joint Assessment of Commodity Chemicals, (HFA-124) 1-Chloro-1,2,2,2-Tetrafluoroethane
No. 13	Joint Assessment of Commodity Chemicals, (HFA-123) 1,1-Dichloro-2,2,2-Trifluoroethane
No. 14	Joint Assessment of Commodity Chemicals, (HFA-133a) 1-Chloro-2,2,2-Trifluoromethane
No. 15	Joint Assessment of Commodity Chemicals, (HFA-141B) 1-Fluoro 1,1-Dichloroethane
No. 16	Joint Assessment of Commodity Chemicals, (HCFC-21) Dichlorofluoromethane
No. 17	Joint Assessment of Commodity Chemicals, (HFA-142b) 1-Chloro-1,1,Difluoroethane
No. 18	Joint Assessment of Commodity Chemicals, Vinylacetate
No. 19	Joint Assessment of Commodity Chemicals, Dicyclopentadiene
No. 20	Joint Assessment of Commodity Chemicals, Tris-/Bis-/Mono-(2-ethylhexyl)phosphate
No. 21	Joint Assessment of Commodity Chemicals, Tris-(2-butoxyethyl)-phosphate
No. 22	Joint Assessment of Commodity Chemicals, Hydrogen Peroxide
No. 23	Joint Assessment of Commodity Chemicals, Polycarboxylate Polymers as Used in Detergents
No. 24	Joint Assessment of Commodity Chemicals, (HFC-125) Pentafluoroethane
No. 25	Joint Assessment of Commodity Chemicals, (HCFC-124) 1-Chloro-1,2,2,2-Tetrafluoroethane

TECHNICAL REPORTS

No. Title

No. 1 Assessment of Data on the Effects of Formaldehyde on Humans
No. 2 The Mutagenic and Carcinogenic Potential of Formaldehyde
No. 3 Assessment of Test Methods for Photodegradation of Chemicals in the Environment
No. 4 The Toxicology of Ethylene Glycol Monoalkyl Ethers and its Relevance to Man
No. 5 Toxicity of Ethylene Oxide and its Relevance to Man
No. 6 Formaldehyde Toxicology: an Up-Dating of the ECETOC Technical reports 1 and 2
No. 7 Experimental Assessment of the Phototransformation of Chemicals in the Atmosphere
No. 8 Biodegradation Testing: An Assessment of the Present Status
No. 9 Assessment of Reverse-Phase Chromatographic Methods for Determining Partition Coefficients
No. 10 Considerations Regarding the Extrapolation of Biological Data in Deriving Occupational Exposure Limits
No. 11 Ethylene Oxide Toxicology and its Relevance to Man : An Up-Dating of ECETOC Technical Report n°5
No. 12 The Phototransformation of Chemicals in Water : Results of a Ring-Test
No. 13 The EEC 6th Amendment : A Guide to Risk Evaluation for Effects on the Environment
No. 14 The EEC 6th Amendment : A Guide to Risk Evaluation for Effects on Human Health
No. 15 The Use of Physical-Chemical Properties in the 6th Amendment and their Required Precision, Accuracy and Limiting Values
No. 16 A review of Recent Literature on the Toxicology of Benzene
No. 17 The Toxicology of Glycol Ethers and its Relevance to Man : An Up-Dating of ECETOC Technical Report n°4
No. 18 Harmonisation of Ready Biodegradability Tests
No. 19 An Assessment of Occurrence and Effects of Dialkyl-o-Phthalates in the Environment
No. 20 Biodegradation Tests for Poorly-Soluble Compounds
No. 21 Guide to the Classification of Carcinogens, Mutagens and Teratogens Under the 6th Amendment
No. 22 Classification of Dangerous Substances and Pesticides in the EEC Directives. A Proposed Revision of Criteria for Inhalational Toxicity
No. 23 Evaluation of the Toxicity of Substances to be Assessed for Biodegradability
No. 24 The EEC 6th Amendment : Prolonged Fish Toxicity Tests
No. 25 Evaluation of Fish Tainting
No. 26 The Assessment of Carcinogenic Hazard for Human Beings Exposed to Methylene Chloride
No. 27 Nitrate and Drinking Water
No. 28 Evaluation of Anaerobic Biodegradation
No. 2 9Concentrations of Industrial Organic Chemicals Measured in the Environment: The Influence of Physico-Chemical Properties, Tonnage and Use Pattern
No. 30(5) Existing Chemicals : Literature Reviews and Evaluations
No. 31 The Mutagenicity and Carcinogenicity of Vinyl Chloride : A Historical Review and Assessment
No. 32 Methylene Chloride (Dichloromethane) : Human Risk Assessment Using Experimental Animal Data
No. 33 Nickel and Nickel Compounds : Review of Toxicology and Epidemiology with Special Reference to Carcinogenesis
No. 34 Methylene Chloride (Dichloromethane) : An Overview of Experimental Work Investigating Species, Differences in Carcinogenicity and their Relevance to Man
No. 35 Fate, Behaviour and Toxicity of Organic Chemicals Associated with Sediments
No. 36 Biomonitoring of Industrial Effluents
No. 37 Tetrachloroethylene : Assessment of Human Carcinogenic Hazard
No. 38 A Guide to the Classification of Preparations Containing Carcinogens, Mutagens and Teratogens
No. 39 Hazard Assessment of Floating Chemicals After an Accidental Spill at Sea
No. 40 Hazard Assessment of Chemical Contaminents in Soil
No. 41 Human Exposure to N-Nitrosmaines, Their Effects and a Risk Assessment for n-Nitrosodiethanolamine in Personal Care Products
No. 42 Critical Evaluation of Methods for the Determination of N-Nitrosamines in Personal Care and Household Products
No. 43 Emergency Exposure Indices for Industrial Chemicals
No. 44 Biodegradation Kinetics
No. 45 Nickel, Cobalt and Chromium in Consumer Products: Allergic Contact Dermatitis
No. 46 EC 7th Amendment: Role of Mammalian Toxicokinetic and Metabolic Studies in the Toxicological Assessment of Industrial Chemicals
No. 47 EC 7th Amendment: 'Toxic to Reproduction' - Guidance on Classification
No. 48 Eye Irritation: Reference Chemicals Data Bank
No. 49 Exposure of Man to Dioxins: A Perspective on Industrial Waste Incineration
No. 50 Estimating the Environmental Concentrations of Chemicals Using Fate and Exposure Models
No. 51 Environmental Hazard Assessment of Substances
No. 52 Styrene Toxicology Investigations on the Potential for Carcinogenicity
No. 53 DHTDMAC: Aquatic and Terrestrial Hazard Assessment. CAS No. 61789-80-8
No. 54 Assessment of the Biodegradation of Chemicals in the Marine Environment
No. 55 Pulmonary Toxicity of Polyalkylene Glycols
No. 56 Aquatic Toxicity Data Evaluation
No. 57 Polypropylene Production and Colorectal Cancer
No. 58 Assessment of Non-Occupational Exposure to Chemicals
No. 59 Testing For Worker Protection
No. 60 Trichloroethylene: Assessment of Human Carcinogenic Hazard

Responsible Editor: D. A. Stringer, ECETOC
Av. E. Van Nieuwenhuyse, 4 (Bte 6)
B - 1160 Brussels, Belgium
D-1994-3001-105

Joint Assessment of Commodity Chemicals No. 24

Pentafluoroethane (HFC 125)

CAS No. 354-33-6

May 1994

ISSN-0773-6339-24

Brussels, May 1994

MEMBERS OF THE SCIENTIFIC COMMITTEE
(Peer Review Committee)

W. F. Tordoir, (Chairman), Head Occupational Health and Toxicology Division	SHELL NL - Den Haag
H. Verschuuren, (Vice-Chairman), Head, Toxicology Department	DOW Europe CH - Horgen
O. C. Bøckman, Scientific Advisor	NORSK HYDRO N - Porsgrunn
N. G. Carmichael, Toxicology Director Worldwide	RHÔNE-POULENC F - Lyon
H. De Henau, European Technical Centre Professional and Regulatory Services	PROCTER & GAMBLE B - Brussels
A. de Morsier, Head, Ecotoxicology	CIBA-GEIGY CH - Basel
P. A. Gilbert, Head, Environmetn Division	UNILEVER UK - Port Sunlight
I. J. Graham-Bryce, Head Environmental Affairs	SHELL NL - Den Haag
B. Hildebrand, Director, Experimental Toxicology	BASF D - Ludwigshafen
J. R. Jackson, Director Medicine and Health Science	MONSANTO EUROPE B - Brussels
K. Künstler, Head, Biological Research	HENKEL D - Düsseldorf
H. Lagast, Chief Medical Officer	SOLVAY B - Brussels
E. Löser, Head, Institute of Industrial Toxicology	BAYER D - Wuppertal
R. Millischer[1], Chief Toxicologist	ELF ATOCHEM F - Paris
I. F. Purchase[1], Director, Central Toxicology Laboratory	ZENECA UK - Macclesfield

1 Stewards - responsible for primary peer review.

MEMBERS OF THE TASK FORCE

D. Mayer	HOECHST D - Frankfurt am Main
M. Collins	ICI CHEMICALS AND POLYMERS GB - Cheshire
C. De Rooij	SOLVAY B - Brussels
J. Franklin	SOLVAY B - Brussels
S. Magda	SOLVAY PHARMA DEUTSCHLAND D - Hannover
G. Malinverno	AUSIMONT/MONTECATINI GROUP I - Milan
R. J. Millischer	ELF ATOCHEM F - Paris
G. M. Rusch	ALLIED SIGNAL Inc. USA - Morristown, NJ
H. J. Trochimowicz	E. I. DU PONT DE NEMOURS USA - Newark, DE
W. Haebler	ECETOC B - Brussels

ECETOC JACC Report No. 24

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

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

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced and are continuing to write reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a Producer, Government Official or Consumer can be informed on the up-to-date position with regard to safety, information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed. To assist ourselves and others working in this field we publish annually a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to our Technical Report No. 30 entitled "Existing Chemicals: Literature Reviews and Evaluations".

This document presents a critical assessment of the toxicology and ecotoxicology of Pentafluoroethane (HFC 125; CAS No. 354-33-6).

PENTAFLUOROETHANE (HFC 125)

CONTENTS

SECTION 1 SUMMARY

Pentafluoroethane is a non-flammable colourless gas, which is currently under development as a CFC alternative and is not yet available in commercial quantities.

The low octanol/water partition coefficient indicates that pentafluoroethane is unlikely to bioaccumulate in environmental organisms. The physical properties (gas and low water solubility) suggest a low risk to the aquatic environment.

The atmospheric degradation of pentafluoroethane will take place mainly in the troposphere by reaction with naturally occurring hydroxyl radicals. The atmospheric lifetime is estimated to be 40.7 years. Pentafluoroethane has no effect on stratospheric ozone since it contains neither chlorine nor bromine. Pentafluoroethane has a Global Warming Potential of 0.84 relative to a reference value of 1.0 for trichlorofluoromethane (CFC 11). Pentafluoroethane degrades in the atmosphere to CO_2 and HF.

In limited metabolic studies *in vivo* in the rat, the metabolism of pentafuoroethane was negligible. Toxicokinetic studies are in progress.

The acute inhalation toxicity of pentafluoroethane is very low. The 4-hour LC_{50} in the rat is greater than 3,928,000 mg/m^3 (800,000 ppm). During the exposure the only clinical signs were ataxia, decrease of locomotor activity and dyspnoea.

As with many other fluorocarbons, inhalation of high concentration of pentafluoroethane, followed by an intravenous epinephrine challenge to simulate stress, can induce a cardiac sensitisation response in dogs. The threshold concentration for this effect was 491,000 mg/m^3 (100,000 ppm) and the No Observed Effect Concentration (NOEC) was 368,250 mg/m^3 (75,000 ppm).

Exposure by inhalation up to 245,000 mg/m^3 (50,000 ppm) 5 days a week for 4 to 13 consecutive weeks, did not induced any toxic effect and the NOEC was greater than 245,000 mg/m^3 (50,000 ppm).

Developmental toxicity studies by inhalation route were carried out in both rats and rabbits. No evidence of embryotoxicity or teratogenicity was seen even at exposure levels as high as 245,000 mg/m^3 (50,000 ppm).

Pentafluoroethane was not mutagenic both in *vitro* and *in vivo* studies using bacteria, mammalian cell lines and in the mouse micronucleus assay.

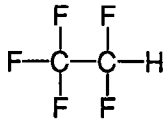
There are no reported effects of pentafluoroethane in man.

An occupational exposure limit (8-hour time weighted average) of 1,000 ppm (4,910 mg/m^3) is recommended by producers.

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

2.1 IDENTITY

Chemical structure:



Chemical Formula: CHF_2-CF_3

Common Name: 1,1,1,2,2 pentafluoroethane

Common synonyms: pentafluoroethane; ethane pentafluoro
HFC 125[1] , HFA 125 , R 125

CAS Registry Number: 354-33-6

EINECS Number: 2065578

Conversion factors: 1 ppm = 4.91 mg/m^3 at 25 °C
1 mg/m^3 = 0.204 ppm at 25 ° C

2.2 PHYSICAL AND CHEMICAL PROPERTIES

Pentafluoroethane is a non-flammable, colourless gas which can be liquified under its autogenous pressure. Some physical and chemical properties are given in Table 1.

1 Abbreviations mean : Hydro-Fluoro-Carbon : C_2HF_5
First figure = Number of C-atoms minus 1 = 1
Second figure = Number of H-atoms plus 1 = 2
Third figure = Number of F-atoms = 5
= HFC 125

Table 1 Physical and Chemical Properties of Pentafluoroethane

Molecular weight:	120
Physical form:	Gas at room temperature
Colour:	Colourless
Boiling point, °C at 1013 hPa:	-48.5
Freezing point, °C at 1013 hPa:	-103
Liquid density at 25°C, g/ml:	1.19
Vapour density (air = 1):	4
Vapour pressure at 25°C, kPa:	1,381
Solubility in water at 25°C, g/l:	0.97
Flammability:	Non flammable
Octanol/Water partition coefficient (log P_{ow})	1.48*

Data from Ausimont (1993), Product brochure Meforex 125, except * which is given by Kawara and Tsutsumi (1992)

2.3 ANALYTICAL METHODS

Methods for pentafluoroethane analysis are described by Nakayama *et al* (1992a) and are based on gas chromatography with flame ionisation detection and liquid chromatography.

SECTION 3. PRODUCTION AND USE

Processes for the production of pentafluoroethane are still under development. Possible routes are hydrofluorination of 1,1-dichloro-2,2,2-trifluoroethane (HCFC 123) and hydrodechlorination of chloropentafluoroethane (CFC 115).

Currently pentafluoroethane is produced only on a small scale, in the order of a few kt/y for development purposes. Pentafluoroethane is being developed as a substitute for fully halogenated chlorofluorocarbons and halons. Its main potential applications are likely to be as a component for low-temperature refrigerant blends and as a total flooding fire extinguishing agent.

SECTION 4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

There is no natural source of pentafluoroethane. The production figure of 25 kt/y is adopted here to represent a conservative upper limit to possible future annual man-made emissions, in order to assess certain aspects of the potential environmental impact of pentafluoroethane.

4.1 ENVIRONMENTAL DISTRIBUTION

On the basis of its physical properties pentafluoroethane may be expected, when released to the environment, to partition almost exclusively into the atmosphere for the following reasons :

- it is a gas at room temperature and normal atmospheric pressure, boiling at - 49 °C;

- its Henry's Law constant for dissolution in water is 0.97 g/l.bar at room temperature; for an atmospheric concentration of 50 pptv (i.e. the calculated steady-state concentration resulting from emissions of 25 kt/y), the equilibrium concentration in cloud and surface waters would thus be about 0.05 pptw.

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

Pentafluoroethane present in surface or ground waters would have little tendency to partition onto biota and soil:

- the measured log P_{ow} is 1.48 (Kawara and Tsutsumi, 1992), indicating the absence of a significant potential for passive bioaccumulation; accumulation in environmental organisms is therefore unlikely;

- from various correlations, $\log K_{oc}$ may be estimated to lie in the range of 1.3-1.7, which means that pentafluoroethane would be moderately to highly mobile in soils.

As the atmospheric lifetime of pentafluoroethane (about 41 y, see Section 4.2) is much longer than either the intrahemispheric or interhemispheric mixing times, this compound will ultimately become more or less uniformly distributed in the atmosphere on a global scale. The upper-limit steady state

concentration of 50 pptv, referred to above, would be attained only after many decades of emissions at the assumed 25 kt/y level.

4.2 ATMOSPHERIC LIFETIME[1]

The atmospheric degradation of pentafluoroethane will occur mainly in the troposphere, being initiated by attack by naturally occurring hydroxyl radicals. The lifetime with respect to this process is estimated to be 40.7 y (WMO, 1991). Although some pentafluoroethane will be transported to the stratosphere, its degradation there, by reaction with hydroxyl radicals and oxygen atoms, will not make a significant contribution to the overall atmospheric loss, almost all of which will occur in the troposphere, according to data reported by Talukdar *et al* (1991).

4.3 OZONE DEPLETING POTENTIAL

Since pentafluoroethane contains neither chlorine nor bromine, it has no effect on stratospheric ozone.

4.4 GLOBAL WARMING POTENTIAL

Global Warming Potentials (GWPs) express the radiative forcing (increase in earthward infra-red radiation flux) due to emission of a unit mass of a given compound, divided by the radiative forcing due to emission of the same mass of a reference compound.

Based on the lifetime quoted above, the Halocarbon Global Warming Potential (HGWP) of pentafluoroethane is 0.84 relative to a reference value of 1.0 for CFC 11. This assessment assumes a pulse emission and an infinite Integration Time Horizon (ITH), which is mathematically equivalent to a steady-state calculation (AER, 1992).

GWPs may also be expressed with CO_2 as the reference substance and assessed over a finite ITH. For pentafluoroethane the corresponding values are 5,200, 3,400 and 1,200 (relative to reference values of 1.0 for CO_2 taken at each ITH), for ITHs of 20, 100 and 500 y respectively (WMO, 1991; IPCC, 1992).

1 Lifetime (LT) is calculated according to the formula $LT = 1 / (k_{OH\cdot} \times c_{OH\cdot})$ where $k_{OH\cdot}$ is the rate constant for the reaction of the chemical with OH-radicals, and $c_{OH\cdot}$ the global mean of OH-radicals in the troposphere. In this period approx. 63% decomposition is achieved (WMO, 1989).

4.5 TROPOSPHERIC OZONE FORMATION

As discussed in WMO (1989) pentafluoroethane is too unreactive in the atmosphere to make any significant contribution to local urban tropospheric ozone formation, and the related "photochemical smog", near the emission sources.

4.6 DEGRADATION MECHANISM AND PRODUCTS

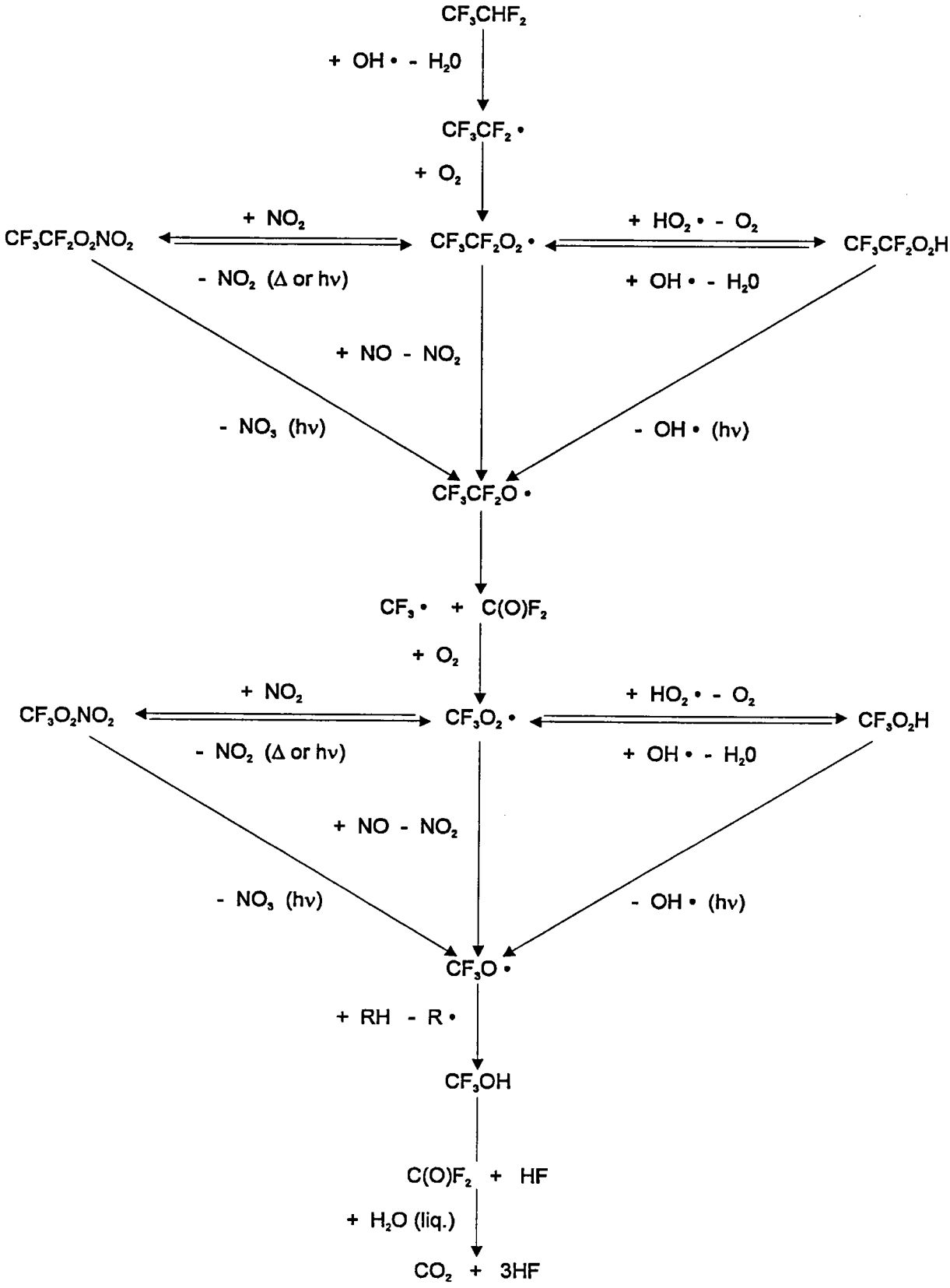
Support for the basic tropospheric degradation mechanism for pentafluoroethane proposed in WMO (1989) has been provided by recent laboratory studies (see for example: WMO, 1991, Edney and Driscoll, 1992; Tuazon and Atkinson, 1993, Sehested *et al*, 1993).

Breakdown of pentafluoroethane in the troposphere will be initiated by OH-radicals and will proceed via various free-radical intermediates to give COF_2 and the CF_3O radical (see reaction scheme). COF_2 is expected to be removed from the atmosphere, within a few days to a few months, by uptake into clouds in rain and the oceans, followed by rapid hydrolysis to CO_2 and HF (AFEAS, 1992; STEP/AFEAS,1993; Franklin, 1993). The probable fate of the CF_3O radical has recently been reviewed by Franklin (1993). It is believed to be converted, by reaction with hydrocarbons or other species, to CF_3OH. The latter may decompose either in the gas phase to COF_2 and HF, or more likely after uptake into the aqueous phase, to CO_2 and HF. Thus, overall, the sole major degradation end products from pentafluoroethane would be CO_2 and HF.

Although peroxynitrates ($CF_3CF_2O_2NO_2$, $CF_3O_2NO_2$) and hydroperoxides ($CF_3CF_2O_2H$, CF_3O_2H) may be formed during the degradation, they are not thought to play a significant role in the atmospheric chemistry of pentafluoroethane, probably being rather short-lived intermediates.

No information is available on biodegradation and possible bioaccumulation in the environment. Experimental studies demonstrate that the compound is not readily biodegradable in the closed bottle test. A 4% degradation was observed after 28 days (Tobeta, 1992).

TROPOSPHERIC DEGRADATION MECHANISM FOR HFC-125



4.7 CONTRIBUTION OF DEGRADATION PRODUCTS TO ENVIRONMENTAL FLUORIDE AND TO THE ACIDITY OF RAINWATER

Assuming an atmospheric release rate of 25 kt pentafluoroethane/y (conservative upper limit), complete conversion into HF (5 mol/mol pentafluoroethane) and uniform scavenging of the HF produced into the global average rainfall of 5 x 10^{11} kt/y, it follows that the levels of fluoride and acidity thus produced are low compared with those arising from existing sources:

- F^- production would be 20 kt/y. i.e. insignificant compared with the estimated atmospheric fluoride flux of 1,000-8,000 kt/y (WMO, 1989);

- the contribution of pentafluoroethane to the fluoride concentration in rainwater would be 40 pptw; this should be compared with typical fluoride concentrations in "background" rainwater of around 10 ppbw, i.e. 250 times greater, and with levels of about 1 ppmw used for the fluoridation of drinking water, i.e. 25,000 times greater (WMO, 1989).

- the hydrofluoric acid formed from pentafluoroethane and scavenged in rainwater would represent an acidity of 10^9 mol H^+/y , i.e. 10,000 times less than the acidity arising from natural and anthropogenic emissions of SO_2 and NO_x (UKRGAR, 1990); thus the contribution of pentafluoroethane to acid rain would be negligible.

SECTION 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

No observations of pentafluoroethane in the atmosphere or other environmental compartments have yet been reported.

SECTION 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

No data available

SECTION 7. KINETICS AND METABOLISM

Harris *et al* (1992) demonstrated that pentafluoroethane is very slowly metabolised *in vivo* in the rat. Urinary trifluoroacetic acid concentration in rats exposed to pentafluoroethane was 40-50 fold less than in rats exposed to halothane or 1,1-dichloro-2,2,2-trifluoroethane (CFC-123) and 10 fold less than in rats exposed to 1-chloro-1,2,2,2-tetrafluoroethane (CFC-124).

Nakayama (1993) reported no detectable plasma or urinary fluoride levels in rats after exposure by inhalation for 4 and 13 weeks up to concentration of 245,500 mg/m^3 (50,000 ppm) pentafluoroethane. The author concluded that metabolism if any was very low.

A pharmacokinetic study is in progress. Preliminary results from rats exposed for 6h to concentration of 0, 4,910, 24,500 or 245,500 mg/m^3 (0, 1,000, 5,000 or 50,000 ppm) indicates that the uptake and metabolic transformation are negligible at all the concentration levels (PAFT, 1989).

SECTION 8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEM

8.1 SINGLE EXPOSURE

Groups of 5 male rats were exposed by inhalation for 4 h to concentrations of either 2,469,730 mg/m^3 or 3,481,190 mg/m^3 (504,000 ppm or 710,000 ppm). No mortality or clinical signs were seen at either exposure level. A transient body weight loss was observed (Panepinto, 1990).

One group of 5 male and 5 female Sprague-Dawley rats was exposed for 4 h to an atmosphere containing 3,928,000 mg/m^3 (800,000 ppm) or 80 % of pentafluoroethane (the remaining 20 % was oxygen). A control group of 5 males and 5 females was exposed to air only. During the pentafluoroethane exposure almost all rats showed ataxia, decreased locomotor activity and dyspnea. No mortality occurred. All clinical signs disappeared completely within one hour of terminating exposure. No other clinical signs were seen during the 14-d observation period. No effect was seen on body weight and no changes were seen at necroscopy at the end of the observation period. The 4-h LC_{50} was greater than 3,928,000 g/m^3 (800,000 ppm) (Nakayama *et al*, 1992a).

8.2 REPEATED EXPOSURE

Four groups of 10 male and 10 female Sprague-Dawley rats were exposed to pentafluoroethane 6 h/d, 5 d/wk for 4 consecutive weeks at target concentrations of 0 (air), 24,500, 73,650 and 245,500 mg/m^3 (0, 5,000, 15,600 and 50,000 ppm). In addition ten rats from control and high dose groups were kept for an additional 2-wk after the end of exposure. All rats survived to the end of the observation period. There were no compound-related effects on body weight, food consumption, clinical signs, haematology, biochemistry, urinalysis, organ weight or tissue morphology at any exposure level. Based on this study the No Observed Effect Concentration (NOEC) was considered to be greater than 245,500 mg/m^3 (50,000 ppm) (Nakayama *et al*, 1992b).

Four groups of 20 male and 20 female Sprague-Dawley rats were exposed to pentafluoroethane 6 h/d, 5 d/wk for 13 consecutive weeks at target concentration of 24,500; 73,650 and 245,500 mg/m^3 (5,000, 15,600 and 50,000 ppm). Ten rats per sex at each concentration level were kept untreated for 4 weeks after the end of exposure. No mortality occurred; there were no compound-related effects on any of the parameters examined namely, body weight, clinical signs, haematology, biochemistry, urinalysis, organ weight and tissue morphology. No increase in plasma and urinary

fluoride concentration was seen. Levels of peroxisomal ß-oxidation activity of the liver were comparable to controls at all exposure concentrations. Based on the results of this study the NOEC was considered to be greater than 245,500 mg/m^3 (50,000 ppm) (Nakayama *et al*, 1993).

8.3 LONG TERM EXPOSURE

No data are available

8.4 SKIN AND EYE IRRITATION/SKIN SENSITISATION

As pentafluoroethane is a gas at ambient temperature, studies to assess skin and eye irritation as well as skin sensitisation have not been carried out. No evidence of skin or mucosal irritation was seen in rats exposed by inhalation on an acute or a repeated basis (see section 8.2).

8.5 SPECIAL STUDIES : CARDIOVASCULAR EFFECTS

The assessment of cardiac sensitisation potential was investigated in Beagle dogs (Hardy *et al*, 1992; Hardy and Kieren, 1993). The test was carried out according to well established methods. (Reinhardt *et al*, 1971; Beck *et al*, 1973). The effect of pentafluoroethane was compared to trichlorofluoromethane (CFC 11) and bromotrifluoromethane (Halon 13B1) which are known cardiac sensitisers. The concentration in air which caused cardiac sensitisation in 50 % of the dogs treated by i.v. injection of epinephrine (EC_{50}) was calculated to be 682,490 mg/m^3 (140,000 ppm). The threshold concentration was 491,000 mg/m^3 (100,000 ppm) with a NOEC equal to 368,250 mg/m^3 (75,000 ppm). The compound was far less potent than trichlorofluoromethane but more active than bromotrifluoromethane.

8.6 REPRODUCTIVE EFFECTS, EMBRYOTOXICITY AND TERATOGENICITY

8.6.1 Reproductive effects

No data are available.

8.6.2 Embryotoxicity and Teratogenicity

The effects of pentafluoroethane on pregnancy and *in utero* development of the *conceptus* were investigated in both rats and rabbits.

The rat study was carried out administering the compound by inhalation (whole body) to females for 6 h/d from day 6 to 15 (inclusive) *post coitum* (Master *et al*, 1992). Pentafluoroethane was administered to groups of 40 pregnant Sprague-Dawley rats, at target concentrations of 0 (air), 24,500, 73,650 or 245,500 mg/m^3 (0, 5,000, 15,600 or 50,000 ppm). Treatment with pentafluoroethane at 245,500 mg/m^3 (50,000 ppm) was associated with unsteady gait during the exposure. No other clinical signs were seen at any exposure level. Litter parameters appeared to be unaffected at all the exposure levels, as judged by *in utero* survival, foetal growth and morphological development. It was concluded that pentafluoroethane was neither teratogenic nor embryotoxic in the rat, even at maternally toxic levels.

The rabbit study was carried out administering the compound by inhalation to females for 6 h/d from day 6 to day 18 *post coitum* (inclusive) (Brooker *et al*, 1992). Pentafluoroethane was administered to groups of 24 pregnant rabbits at target concentrations of 0 (air), 24,500, 73,650 or 245,500 mg/m^3 (0, 5,000, 15,600 or 50,000 ppm). Treatment with pentafluoroethane at 245,500 mg/m^3 (50,000 ppm) was associated with slightly lower food consumption during the treatment period and slightly lower weight gain during the first few days of treatment . No other clinical signs attributable to the treatment was seen at any exposure level. *In utero* survival, fetal growth and morphological development were unaffected at all exposure levels.

It was therefore concluded that pentafluoroethane was neither teratogenic nor embryotoxic in the rat and the rabbit, even at exposure concentrations that elicited some signs of maternal toxicity.

8.7 MUTAGENICITY

The mutagenic effects of pentafluoroethane were investigated *in vitro* and *in vivo*. A summary of the results is given in Table 2.

In vitro studies

The bacterial assay was carried out in *Salmonella typhimurium* and *Escherichia coli* using the Ames test (May *et al*, 1992) with pentafluoroethane as a vapour at concentrations up to 100% v/v. No increases in reversion to prototrophy were observed with any of the strains either with and without metabolic activation. It was concluded that pentafluoroethane was devoid of mutagenic activity under these test conditions.

The clastogenic activity of vapours of pentachloroethane at concentrations up to 60% v/v was studied in Chinese hamster ovary cells. No biologically or statistically significant increases in

aberrant cell frequencies were apparent at any tested concentration after 4 h (± S 9)and 24 h (± S 9) of exposure . Following 48 h of exposure to 60 % v/v (highest concentration) a statistically significant increase of aberrant cell frequencies both including and excluding gaps, was apparent. This was associated with clear evidence of toxicity of pentafluoroethane to cells. Moreover, a marked increase of the incidence of polyploid cells was apparent in cultures exposed to the highest concentration (Dance and Hodson-Walker, 1992).

Pentafluoroethane was therefore capable of inducing aberrant cells but this occurred only at unrealistically high concentrations (60% v/w) when there was significant cytotoxicity. Under normal test conditions, pentafluoroethane was non clastogenic.

In the human lymphocyte *in vitro* cytogenic assay, pentafluoroethane was tested as a vapour at concentrations up to 70% v/v. After 3 hours of exposure at a concentration of 35 % and in the presence of metabolic activation, a statistical increase of aberrant cell frequencies was observed. This was considered by the authors to be non-treatment related since it was not present at the highest concentration. The increase was due to an increased incidence in one of the two cultures. Moreover, the value was within the historical background control range and furthermore no biologically and no statistically significant increase was apparent if the gaps were excluded. After 3 h exposure and in the absence of S 9 mix a statistically significant increase in the aberrant cell frequencies in cultures exposed to 70 % was seen, including and excluding gaps. The aberrant cell frequencies including gaps in one culture were within the historical control range. No biologically or statistically significant increases were seen in cultures exposed at any pentafluoroethane concentration for 24 or 48 hours without metabolic activation (Dance *et al* , 1997).

The increase in aberrant cell frequencies was not reproducible in this series of experiments, hence pentafluoroethane is not clastogenic to human lymphocytes.

In conclusion pentafluoroethane, under these test conditions, did not show conclusive evidence of clastogenic activity.

In vivo studies

Edwards *et al* (1992) studied the *in vivo* clastogenic activity of pentafluoroethane. Male and female CD 1 mice were exposed by the inhalation to concentrations of 0 (air), 117,840, 589,200 and 2,946,000 mg/m^3 of pentafluoroethane for 6 h. Groups of male and female animals were killed 24, 48 and 72 h after treatment for micronucleus analysis. All mice exposed to the high concentration showed transient hunched posture, tremors and hypoactivity; additionally one animal showed slow

respiration; all animals killed after 24 hours had lost weight. There was no evidence of a dose-related reduction in bone marrow proliferation following exposure to pentafluoroethane. Frequencies of micronucleated polychromatic erythrocytes in animals killed 24, 48 and 72 h after exposure were similar to controls. It was concluded that, under the test condition, pentafluoroethane was devoid of any clastogenic activity *in vivo*.

The overall weight of evidence from preceding variety of mutagenic evaluations demonstrates that pentafluoroethane is not mutagenic either in *in vitro* nor *in vivo* assays with or without metabolic activation.

Table 2. Pentafluoroethane Mutagenicity

Assay	Strain/Type	Test conditions	Results	Comments	References
Ames test *S. Typhimurium* *E. Coli*	TA 98, TA 100, TA 1535, TA 1537, TA 1538 WP2 uvr	± S9; Vapour phase concentration 20, 40, 60, 80, 100%	Negative		May *et al*, 1992
Chromosomal Aberration	CHO cells	± S9; Vapour phase concentration up to 60%	Increase of aberrant cell frequencies at 60% v/v after 48h exposure (± S9). Increase of polyploid cell at 60% v/v after 48h exp.	Clear cytotoxicity was evident at 60% v/v No clear evidence of clastogenic activity	Dance and Hodson-Walker, 1992
Chromosomal Aberration	Human Lymphocytes	± S9; Vapour phase concentration up to 70%	Increase of aberrant cells at 35% v/v after 3 hours of exposure (±S9) Increase of aberrant cells at 70% v/v after 3 hours of exposure (±S9)	No concentration related relationship level of increase within background data No effect at 24 and 48 hours (± S9). No real evidence of clastogenic activity	Dance *et al*, 1992
Bone marrow micronucleus	Mice (Cd-1)	± S9; dose levels 0, 24,000, 120,000, 601,000ppm	Negative		Edwards *et al*, 1992

SECTION 9 EFFECTS ON MAN

There are no reported adverse health effects which can be attributed to pentafluoroethane exposure.

BIBLIOGRAPHY

AER, 1992. Atmospheric and Environmenal Research. Cambridge, Massachusetts, USA. Private communication to AFEAS, 23 January 1992.

AFEAS, 1992. Proceedings of the AFEAS Workshop: Atmospheric Wet and Dry Deposition of Carbonyl and Haloacetyl Halides. Brussels, 22 September 1992.

Beck PS, Clark DG and Tinston DJ, 1973. The pharmacological action of Bromochlorodifluoromethane (BCF). Toxicol.Appl.Pharmac., 24,1-10.

Brooker AJ, Brown RJ, John DM, Coombs DW, 1992. The effect of HFC 125 on pregnancy of the rabbit (ALS 10/920856). Huntingdon Research Centre Ltd. Cambridgeshire, England

Dance CA and Hodson-Walker G, 1992. In vitro assessment of the clastogenic activity of HFC 125 in cultured chinese hamster ovary (CHO)cells (LSR Rep. 91/PAR006/1015a). Life Science Research Ltd. Eye, Suffolk, England.

Dance CA, Beach KE and Hodson-Walker G, 1992. In vitro assessment of the clastogenic activity of HFC 125 in cultured human lymphocytes (LSR Rep. 91/PAR005/1014a) Life Science Research Ltd. Eye, Suffolk, England.

Edney EO and Driscoll DJ ,1992. Chlorine Initiated Photooxidation Studies of Hydrochlorofluorocarbons (HCFCs) and Hydrofluorocarbons (HFCs). Results for HCFC-22 ($CHClF_2$); HFC-41 (CH_3F); HCFC-124 ($CClFHCF_3$); HFC-125 (CF_3CHF_2); HFC-134a (CF_3CH_2H); HCFC-142b ($CClF_2CH_3$); and HFC-152a (CHF_2CH_3). Int. J. Chem. Kinet., 24, 1067-1081.

Edwards CN, Hodson-Walker G and Cracknell S, 1992. HFC 125: assessment of clastogenic action on bone marrow erythrocytes in the micronucleus test (LSR Rep. 92/PAR004/0148). Life Science Research Ltd. Eye, Suffolk, England.

Franklin J, 1993. The Atmospheric Degradation and Impact of 1,1,1,2-Tetrafluoroethane (hydrofluorocarbon 134a). Chemosphere, 27 (8), 1565-1601.

Hardy CJ and Kieren PC, 1993. Halon 13B1, Freon 23 and mixture of Freon 23 and HFC 125. Assessment of Cardiac Sensitisation Potential in Dogs (DPT 273/921009). Huntingdon Research Centre Ltd. Cambridgeshire, England.

Hardy CJ, Kieren PC, Sharman IJ and Clark GC, 1992. Assessment of Cardiac Sensitisation Potential in Dogs. Comparison of HFC 125 and Halon 13B1 (ALS 11/920116). Huntingdon Research Centre Ltd. Cambridgeshire, England.

Harris JW, Jones JP, Martin JL, La Rosa AC, Olson MJ, Polh LR and Anders MW, 1992. Pentahaloethane-based chlorofluorocarbons substitutes and halothane: correlation of *in vivo* hepatic protein trifluoroacetylation and urinary trifluoroacetic acid excretion with calculated enthalpia. Chemical Research in Toxicology, 5, 720-725.

IPCC, 1992. Intergovernmental Panel on Climate Change. Climate Change, 1992. The Supplementary Report to the IPPC Scientific Assessment. Houghton JT, Callander BA and Varney SK, Eds. Cambridge University Press. Cambridge, England.

Kawara K and Tsutsumi Y, 1992. Test on 1-octanol/water partition coefficient of HFC 125. Kurume Research Laboratories. Fukuoka, Japan.

Master RE, Brown RJ, John DM and Coombs DW, 1992. A study of the effect of HFC 125 on pregnancy of the rat (inhalation exposure)(ALS 9/920434). Huntingdon Research Centre Ltd. Cambridgeshire, England.

May K, Watson D and Hodson-Walker G, 1992. HFC 125 in gaseous phase : assessment of mutagenic potential in amino acid auxothrophs of Salmonella typhimurium and Escherichia coli (the Ames test)(LSR Rep. 91/PAR003/1152a). Life Science Research Ltd. Eye, Suffolk, England.

Nakayama E, Nagano K, Ohnishi M, Katagiri S and Motegi O, 1992a. Acute inhalation toxicity study of 1,1,1,2,2 pentafluoroethane in rats. Japan Bioassay Laboratory. Hirasawa, Japan.

Nakayama E, Nagano K, Ohnishi M and Motegi O, 1992b. Four week inhalation study of 1,1,1,2,2,pentafluoroethane (HFC 125) in rats. Japan Bioassay Laboratory. Hirasawa, Japan.

Nakayama E, Nagano K, Ohnishi M and Motegi O, 1993. Thirteen week inhalation toxicity study of 1,1,1,2,2,pentafluoroethane (HFC 125) in rats. Japan Bioassay Laboratory. Hirasawa, Japan.

PAFT, 1989. Programme for Alternative Toxicology Testing. Toxicology Forum, European Symposium, Toulouse, France.

Panepinto AS, 1990. Four hours inhalation approximate lethal concentrations (ALC) of HFC 125, HLR 582-90. Haskell Laboratory, DuPont. USA.

Reinhardt CF, Azar A, Maxfiled MD, Smith PE and Mullin LS, 1971. Cardiac arrhythmias and aerosol sniffing. Arch.Environ. Health, 22, 265-279.

Sehested J, Ellerman T, Nielsen OJ, Wallington TJ and Hurley MD, 1993. UV Absorption Spectrum, and Kinetics and Mechanism of the Self Reaction of $CF_3CF_2O_2$ Radicals in the Gas Phase at 295°K. Int. J. Chem. Kinet., 25, 707-717.

STEP/AFEAS, 1993. Proceedings of the STEP-HALOCSIDE/AFEAS Workshop. Kinetics and Mechanisms for the Reactions of Halogenated Organic

Compounds in the Troposphere. Dublin, 23-25 March 1993.

Talukdar R, Mellouki A, Gierczak T, Burkholder JB, McKeen SA and Ravishankara AR, 1991. Atmospheric Fate of CF_2H_2, CH_3CF_3, CHF_2CF_3, and CH_3CFCl_2. Rate Coefficients for Reactions with OH and UV Absorption Cross Sections of CH_3CFCl_2. J. Phys. Chem., 95 (15), 5815-5821.

Tobeta Y., 1992. Test on biodegradability of HFC 125 by microorganisms (closed bottle method). Kurume Research Laboratories. Fukuoka, Japan.

Tuazon EC and Atkinson R, 1993. Tropospheric Transformation Products of a Series of Hydrofluorocarbons and Hydrochlorofluorocarbons. J. Atmos. Chem., 17 (2), 179-199.

UKRGAR, 1990. Acid Deposition in the United Kingdom 1986-1988. Third Report of the United Kingdom Review Group on Acid Rain. September 1990.

WMO, 1989. Global Ozone Research and Monitoring Project, Report No. 20. Scientific Assessment of Stratospheric Ozone, II, Appendix (AFEAS Report). World Meteorological Organisation. Geneva, Switzerland.

WMO, 1991. Global Ozone Research and Monitoring Project, Report No. 25. Scientific Assessment of Ozone Depletion. World Meteorological Organisation. Geneva, Switzerland.