Difluoromethane (HFC-32)
CAS No. 75-10-5
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CONTENTS

EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It updates an earlier ECETOC review [a] and presents a critical evaluation of the available data on the ecotoxicity, toxicity, environmental fate and impact of difluoromethane (HFC-32). The report includes results of recent and unpublished studies conducted by the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT) [b].

Difluoromethane (HFC-32) is a colourless, flammable gas that is used in refrigerant blends with other hydrofluorocarbons. Any HFC-32 released to the environment will volatilise to the atmosphere where it has been detected. In air, HFC-32 will degrade slowly to carbon dioxide and hydrogen fluoride. HFC-32 does not accumulate in living organisms and there is low risk to the aquatic environment. HFC-32 does not deplete stratospheric ozone because it does not contain chlorine or bromine. The contribution of HFC-32 to global warming is insignificant, due to its low global warming potential and low atmospheric concentration.

HFC-32 is poorly absorbed in the body of mammalian species. Any absorbed HFC-32 is either exhaled unchanged, or rapidly metabolised and excreted, principally as exhaled carbon dioxide.

HFC-32 is essentially non-toxic to laboratory animals. There were minor effects, such as reduced breathing rate and salivation, during brief exposure to high concentrations (86,000 ppm for 4 hours). Once the exposure stopped, animals behaved normally. HFC-32 (up to 350,000 ppm) did not cause cardiac sensitisation to adrenaline, but there were head and limb tremors (pre-narcosis) at 250,000 ppm and above.

Repeated exposure studies in rats (up to 50,000 ppm for 4 or 13 weeks) showed no effects that could be attributed to HFC-32. HFC-32 is not genotoxic *in vitro* or *in vivo*. HFC-32 is poorly absorbed and does not form any toxicologically significant metabolites. As a consequence, HFC-32 is unlikely to be carcinogenic.

In developmental toxicity studies in rats and rabbits, HFC-32 (up to 50,000 ppm) did not interfere with embryo-foetal development or fertility, but foetotoxicity (in the rat) could not be ruled out completely.

There are no known adverse health effects of HFC-32 on humans. In the USA, an occupational exposure limit (8-hour time-weighted-average concentration) of 1,000 ppm is recommended by the American Industrial Hygiene Association.

[a] ECETOC (1995). Joint Assessment of Commodity Chemicals No. 32
[b] A cooperative research effort (1987-2000) sponsored by 16 of the leading CFC producers [www.afeas.org/paft/]

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

This document presents a critical evaluation of the toxicology and ecotoxicology of difluoromethane (HFC-32; CAS No. 75-10-5).

Where relevant, the Task Force has graded the studies by means of a 'code of reliability' (CoR) to reflect the degree of confidence that can be placed on the reported results. The codes and criteria used to assess reliability are included in Appendix A.

1. SUMMARY AND CONCLUSIONS

Difluoromethane (HFC-32 [a]) is a colourless, flammable gas that is sparingly soluble in water. Its main application is as a low-temperature refrigerant, especially in blends with other hydrofluorocarbons. HFC-32, when released to the environment, partitions almost exclusively to the atmosphere. Airborne HFC-32 degrades slowly, by reaction with naturally occurring hydroxyl radicals, to carbon dioxide and hydrogen fluoride. The overall atmospheric lifetime of HFC-32 is 4.9 years. The low octanol-water partition coefficient suggests a low potential for bioaccumulation and there is low risk to the aquatic environment. HFC-32 has no potential to deplete stratospheric ozone, because it does not contain chlorine or bromine. HFC-32 has a global warming potential of 650 relative to a reference value of 1.0 for carbon dioxide (over a 100-year integration time horizon). HFC-32 has been detected in the atmosphere, but actual concentrations are not known.

HFC-32 is poorly absorbed in mammalian species (approximately 1% of the inhaled dose). The absorbed HFC-32 is rapidly excreted unchanged in exhaled air or metabolised via an oxidative pathway and excreted, either in urine as formic acid and compounds arising from incorporation into the C1-pool (more in mice than in rats), or as carbon dioxide (in rats and mice) in exhaled air. There is no significant formation of carboxyhaemoglobin indicating that carbon monoxide formation is not a significant metabolic pathway.

Acute inhalation toxicity in rats is very low: no mortality was seen after 4 hours exposure to 520,000 ppm (1,110,000 mg/m^3). Minor clinical signs were observed in the animals exposed to 86,000 ppm (183,000 mg/m^3) and above during and after exposure: reduced breathing rate, reduced activity, salivation, tail erections. Affected animals showed a rapid reversal of the effects after the end of exposure.

There was no evidence of cardiac sensitisation in the dog in response to exogenous adrenaline challenge at HFC-32 exposure concentrations up to 350,000 ppm (744,000 mg/m^3), the highest concentration tested. Clinical signs indicative of a pre-narcotic response (e.g. head and limb tremors, unsteady gait) were seen at 250,000 ppm (531,000 mg/m^3) and above.

As HFC-32 is a gas, no studies to assess its potential for skin and eye irritation or skin sensitisation have been carried out. No evidence of skin or mucosal irritation was seen in rats exposed by inhalation on an acute or repeated basis. There is no case report in humans.

No toxic effects were seen in rats exposed whole-body to HFC-32 at a concentration of up to 49,500 ppm (105,200 mg/m^3) or 49,100 ppm (104,300 mg/m^3) for 4 weeks or 13 weeks

[a] The naming and numbering convention is explained in Appendix B

respectively. The highest concentration tested (nominal 50,000 ppm; 106,000 mg/m^3) is considered to be a limit concentration for studies of this type on low toxicity, highly volatile fluorocarbons. In both studies, there were no deaths and no treatment-related effects on clinical signs, bodyweights, food consumption, haematological and clinical chemistry parameters, or urine analyses. There were no changes attributable to HFC-32 exposure on group mean organ weights (including testes) or in the incidence of macroscopic or microscopic pathology findings (including reproductive organs) in any exposed group.

HFC-32 has not shown any genotoxic activity both in either *in vitro* or *in vivo* studies. HFC-32 was not mutagenic in the Ames test and not clastogenic in two different mammalian cells assays. *In vivo*, HFC-32 was without effects in the mouse micronucleus assay. The absence of any target organ identified in repeated dose toxicity studies and the lack of genotoxicity show that there is no indication of a carcinogenic potential for HFC-32. There is no evidence that HFC-32 is metabolised via the glutathione pathway in either mice or rats. This is a pathway that would lead to potentially carcinogenic metabolites as in the case of the structurally-related dichloromethane (methylene chloride).

HFC-32 did not induce teratogenic or significant embryo-foetal toxic effects in rats or rabbits exposed to concentrations of up to 50,000 ppm (106,000 mg/m^3) during gestation days 7 to 16 and 6 to 18, respectively. There was evidence of minimal maternal toxicity in both species, and slight foetotoxicity in the rat at 49,800 ppm (105,400 mg/m^3). Based on the results from the 13-week repeated inhalation exposure study in rats including macroscopic and histopathological examinations of the reproductive organs, the available evidence suggests that HFC-32 is unlikely to have the potential to affect fertility at concentrations of up to 50,000 ppm.

No adverse health effects of HFC-32 on humans have been reported.

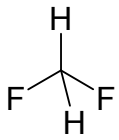
In the USA, an occupational exposure limit (8-hour time-weighted-average concentration) of 1,000 ppm (2,130 mg/m^3) is recommended by the American Industrial Hygiene Association.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name:	Difluoromethane
IUPAC name:	Difluoromethane
Synonyms:	F-32 Fluorocarbon 32 Freon 32 Genetron 32 HFA-32 HFC-32 Methylene difluoride Methylene fluoride R-32 (refrigerant)
CAS name:	Methane, difluoro-
CAS Registry number:	75-10-5
EC (EINECS) Number:	200-839-4
Formula:	CH_2F_2
Molecular mass:	52.02

Chemical structure:



2.2 EU classification and labelling

To date HFC-32 has not been classified by the European Commission under the Dangerous Substances Directive 67/548/EEC and its subsequent amendments.

HFC-32 should be provisionally classified and labelled as follows:

Classification:		R 12	Extremely flammable
Labelling:	Symbol	F+	Extremely flammable
	Risk phrase	R 12	Extremely flammable
	Safety phrases	S 9	Keep container in well-ventilated place
		S 16	Keep away from ignition sources - No smoking
		S 33	Take precautionary measures against static discharges

2.3 Physical and chemical properties

At normal (ambient) temperature and pressure, HFC-32 is a colourless, flammable gas that is sparingly soluble in water. Physical and chemical properties are listed in Table 1. HFC-32 has a slight ether-like odour; this is a characteristic of all HFCs.

Table 1: Physical and chemical properties

Parameter	Value, unit	Reference
Freezing point	–136°C	Dean, 1999
Boiling point at 1,013 hPa	–51.6°C –51.7°C at 1,000 hPa	Dean, 1999; Horvath, 2001 ASHRAE, 2001
Relative density of liquid D_4^{25} (density of water at 4ºC is 1,000 kg/m^3)	0.959	ASHRAE, 2001
Vapour pressure at 25°C	1.69 MPa (16.9 bar)	ASHRAE, 2001
Vapour density at 25°C (air = 1)	1.8	Calculated
Threshold odour concentration	No data	
Solubility in water at 25°C and 1 atm (1,013 hPa) partial pressure of HFC-32	4.39 g/l 3.65 g/l [a] 3.64 g/l [b] 1.57 g/l	Yaws *et al*, 1990 Abraham *et al*, 2001 Maaßen, 1996 Miguel *et al*, 2000
Partition coefficient, log K_{ow} (octanol/water) at 25°C	0.21 [c] 0.21 0.192	Kawahara, 1992 Maaßen, 1996 Abraham *et al*, 2001
log K_{ow}, temperature not stated	0.20	Hansch and Leo, 1987 cited by Sangster, 1989
Partition coefficient, log K_{oc} (organic carbon/water) at 25°C	1.38 [d]	US-EPA, 2003
Henry's Law constant at 25°C	1.45×10^3 Pa·m^3/mol 3.36×10^3 Pa·m^3/mol 1.44×10^3 Pa·m^3/mol	Maaßen, 1996 Miguel *et al*, 2000 Abraham *et al*, 2001
Flash point, closed cup	No data	
Explosion/flammability limits in air at room temperature and 1,013 hPa	12.7 - 33.5% by volume	Richard and Shankland, 1992 [e]
Auto-flammability, ignition temperature	No data	

[a] Calculated from the reported Ostwald solubility coefficient
[b] Calculated from the reported Henry's Law coefficient
[c] Measured
[d] Calculated
[e] The literature has been reviewed by Wilson and Richard, 2002

Typically, commercial HFC-32 has a purity of ≥ 99.9% by weight. Common impurities are various other fluorocarbons and traces of carbon dioxide, methane, nitrogen, oxygen and water, depending on the conditions of the production process (Section 3.1).

2.4 Conversion factors

Conversion factors for HFC-32 concentrations in air at 25°C and 1,013 hPa are:

- 1 ppm = 2.125 mg/m^3
- 1 mg/m^3 = 0.471 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 = 2.162 mg/m^3 and 1 mg/m^3 = 0.463 ppm.

2.5 Analytical methods

Methods for HFC-32 analysis described by Parr-Dobrzanski (1993) are based on gas chromatography with flame ionisation detection.

3. PRODUCTION AND USE

3.1 Production

HFC-32 is manufactured in closed systems. Possible routes are hydrodechlorination of chlorodifluoromethane (HCFC-22) and hydrofluorination of dichloromethane. The annual worldwide production capacity of HFC-32 is estimated to be approximately 15 kt (OECD, 2004).

3.2 Storage

HFC-32 is stored as liquefied gas under pressure in steel cylinders. Recommended storage conditions are: temperatures below 45°C in well-ventilated areas away from sources of heat (to avoid overpressure), naked flames, hot surfaces and other sources of ignition (Arkema, 2002).

3.3 Transport

HFC-32 is transported as liquefied gas under pressure in steel cylinders, under UN number 3252 hazard class 2.1 (flammable gases) (Arkema, 2002).

3.4 Use

HFC-32 is being developed as a substitute for fully or partially halogenated chlorofluorocarbons. The main uses of HFC-32 are in the fields of refrigeration and air conditioning. More than 98% of HFC-32 used in refrigeration and air conditioning is as a substitute for HCFC-22 in blends (because of its flammability) with other hydrofluorocarbons in new stationary domestic air conditioning systems (mainly small and medium size systems). The remainder is used in industrial refrigeration.

HFC-32 is used in the semiconductor, solar panel and flat panel display industries. It is applied as an etchant, particularly in plasma and radio frequency etching. HFC-32 is also used to clean deposition and etch tools or used as a constituent of other hydrofluorocarbon mixtures (Spectra Gases, 2006).

Analysis of sales data collected by the United Nations Framework Convention on Climate Change leads to a total European consumption of 2.3 kt in 2005, which was slightly lower than in 2004. Consumption in the USA in 2005 was 2.8 kt. Data for other countries with potentially significant consumption are not available (UNFCCC, 2007).

Global annual demand for HFC-32 has been estimated at 3 kt in 2002 and 25 to 28 kt in 2015 (IPCC/TEAP, 2005).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, TRANSFORMATION AND IMPACT

4.1 Emissions

4.1.1 Natural sources

There is no known natural source of HFC-32.

4.1.2 Emissions during production and use

HFC-32 is manufactured and stored in closed systems. Therefore, under normal conditions of manufacturing and handling, HFC-32 releases should be negligible.

Emissions of HFC-32 to air mainly originate from releases during its use in stationary air conditioning systems of medium size (power 5 to 100 kW) where it is a component of blended refrigerants. Large air conditioners are designed to meet the requirements of the buildings in which they are located, while smaller units are chosen to meet the requirements of the rooms in which they are situated; their maintenance should only be carried out by professionals. Airborne emissions from small domestic air conditioners (hermetically sealed units < 5 kW) are low. The information in UNFCCC (2007), although incomplete, indicates that global cumulative emissions over the whole time that HFC-32 has been used in those air conditioning systems up to the year 2005 amount to less than 9 kt.

Global annual emissions of HFC-32 have been estimated at 1 kt for 2002 and 6 to 8 kt for 2015 (IPCC/TEAP, 2005).

On the basis of a single day's atmospheric measurements, Yokouchi *et al* (2005) estimated that emissions of HFC-32 from Japan were 230 t in 2003. The short time-base explains the difference between this estimate and the data submitted by Japan to UNFCCC (2007), i.e. 53 t in 2003 (followed by 92 t in 2004 and 112 t in 2005).

Assuming that emission scenarios for HFC-32 releases follow those for stationary cooling (IPCC, 2001), the background concentration of HFC-32 in the atmosphere would rise to between 1 and 2 ppt (pmol/mol) by 2010.

4.2 Environmental distribution

HFC-32 is a gas at room temperature and normal atmospheric pressure. Its vapour pressure (1.69 MPa at 25 °C) and water solubility (4.4 g/l) suggest an almost exclusive partitioning of HFC-32 into the atmosphere, when it is released in the environment.

The environmental partitioning of HFC-32 was assessed (Binaglia, 2007) by means of the fugacity-based equilibrium criteria (EQC) Level I and 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-32 using the following values for physico-chemical properties: melting point –136 °C, water solubility 4.4 g/l, vapour pressure 1.69 MPa, log K_{ow} 0.2 (all listed in Table 1), and an atmospheric lifetime of 4.9 years, corresponding to a half-life of 3.4 years (Section 4.3.1). Degradation in other media was not taken into account. Two simulations were considered at Level III, assuming emission (1,000 kg/h) to air alone or to water alone. The results are shown in Table 2.

Table 2: Partitioning (%) into the environment

Compartment	Level I	Level III	
		Emission to air alone	Emission to water alone
Air	99.979	99.999	19.9
Water	0.0207	0.000015	79.9
Soil	0.000029	0.0036	0.0007
Sediment	0.0000006	0.00000003	0.161

The Level III model simulation with emissions to air alone and the Level I simulation predicted a distribution of HFC-32 almost exclusively into the atmosphere. However, when the emissions are to water alone, a significant proportion of HFC-32 is expected to partition to the aqueous compartment at the steady-state. This is due to the resistances in the water-to-air transfer rate introduced in the Level III default parameters.

In conclusion, HFC-32 released to air is predicted to remain almost exclusively in that compartment and any HFC-32 emitted to water will ultimately be found in the air.

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric fate and impact

Atmospheric lifetime [a]

Atmospheric degradation of HFC-32 is mainly attributable to reaction with the hydroxyl radical ($^{\bullet}OH$) in the lower part of the atmosphere (troposphere). The rate constant for this reaction at 25°C is 1.1×10^{-14} cm^3/molecule/s (NASA/JPL, 2003). Possible reactions in the stratosphere with $^{\bullet}OH$, the excited oxygen radical [$O(^1D)$] and by photolysis were estimated to make only a minor contribution to the atmospheric removal of HFC-32 (IPCC, 2001). The overall atmospheric lifetime of HFC-32 has been determined to be 4.9 years (WMO, 2002; IPCC/TEAP, 2005); the corresponding half-life is 3.4 years.

Stratospheric ozone depletion

Since HFC-32 contains neither chlorine nor bromine, it has no effect on stratospheric ozone.

Global warming potential

The global warming potential (GWP) 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' to accommodate the long and complex environmental lifetime of the reference compound (CO_2).

HFC-32 is a greenhouse gas. Its GWP relative to carbon dioxide has been calculated to lie between 550 and 670 for an integration time horizon of 100 years. The variation results from changes in values of properties determined for both CO_2 and HFC-32. The highest value was published in IPCC/TEAP (2005). However, the official GWP used in the Kyoto protocol is 650 (IPCC, 1995) and this value is used as the standard for Kyoto protocol compliance. Subsequently, the Intergovernmental Panel on Climate Change in its 'Third Assessment Report'

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

adopted a GWP of 550 for HFC-32 (IPCC, 2001). This value is used as a reference in the European Regulation on certain fluorinated greenhouse gases (EU, 2006).

The impact of HFC-32 on global warming depends on its atmospheric concentration and therefore on the actual quantity emitted to the atmosphere. Based on emission scenarios for stationary cooling (IPCC, 2001), the concentration of HFC-32 in the atmosphere would be about 0.25 ppt in 2010 (Section 4.1.2). On the basis of the radiative efficiency of 0.11 $W/m^2 \cdot ppb$ (IPCC/TEAP, 2005), the contribution of HFC-32 to radiative forcing would be 1.1×10^{-4} W/m^2 in 2010. The expected overall radiative forcing in 2010 from the different emission scenarios, which include all contributions from greenhouse gases and direct or indirect effects of aerosols, is estimated to range from 1.63 to 1.85 W/m^2 (IPCC, 2001). In comparison, the HFC-32 contribution of 1.1×10^{-4} W/m^2 (0.01%) is currently insignificant.

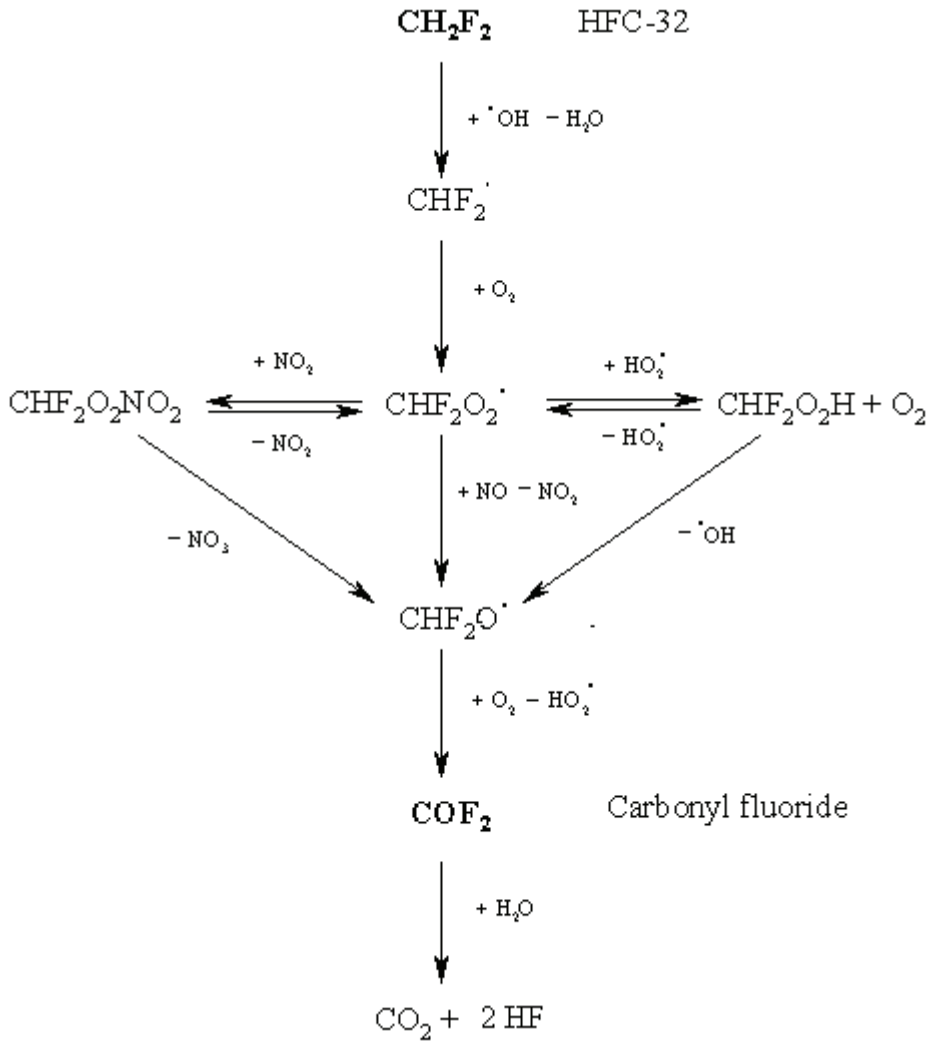
Tropospheric ozone formation

Because of its low reactivity with $^{\bullet}OH$, HFC-32 will not contribute significantly to the formation of ground-level ozone. Its photochemical ozone creation potential (POCP) has been calculated to be 0.2 relative to a reference value of 100 for ethylene (Hayman and Derwent, 1997; IPCC/TEAP, 2005).

Degradation mechanism and products

By analogy with other hydrochlorofluorocarbons or hydrofluorocarbons for which detailed mechanistic studies exist (WMO, 1989a; WMO, 1991; Wallington *et al,* 1994), the following atmospheric degradation scheme can be proposed for HFC-32 (Figure 1).

Figure 1: Tropospheric Degradation Mechanism for HFC-32[a]



NO, NO_2 and NO_3, free radicals

As stated above, breakdown of HFC-32 will occur almost exclusively in the troposphere and will be initiated essentially by ·OH. It will proceed via various free-radical or short-lived molecular intermediates to give carbonyl fluoride (COF_2). Support for this mechanism is provided by experimental observations on the analogous chlorine-atom initiated oxidation of HFC-32, in which COF_2 is the sole carbon-containing product formed (Nielsen *et al,* 1992).

COF_2 as an intermediate product will be further converted to HF and carbon dioxide by hydrolysis in atmospheric condensed water. By analogy with phosgene, the atmospheric lifetime of COF_2 by wet removal can be estimated at 70 days (half-life 48.5 d) as an average value

(WMO, 1998). On the basis of the relative lifetimes of HFC-32 and COF_2, it can be estimated that the tropospheric concentration of COF_2 due to HFC-32 alone would be about 0.04 ppt in 2010.

The peroxynitrate ($CHF_2O_2NO_2$) and hydroperoxide (CHF_2O_2H) that may be formed during the degradation of HFC-32 are rather short-lived intermediates. Those compounds are not thought to play a significant role in the atmospheric chemistry of HFC-32 (Wallington *et al,* 1994).

4.3.2 Environmental impact of atmospheric degradation products of HFC-32

Contribution to acid rain and environmental burden of fluoride ion

Assuming an atmospheric release and degradation rate of 8 kt HFC-32 per year (Section 4.1.2 – Maximum estimated emissions for 2015), 100% conversion into COF_2, uniform scavenging of the latter into the global average rainfall of 5×10^{11} kt/y, followed by hydrolysis to carbon dioxide (CO_2) and hydrogen fluoride (HF), leads to the conclusion that:

- fluoride (F^-) production would be 6 kt/y, i.e. small compared with the estimated atmospheric fluoride flux of 1,000 to 8,000 kt/y (WMO, 1989b);
- the contribution of HFC-32 to the fluoride concentration in rainwater would be 12 ng F^-/l. This should be compared with typical fluoride concentrations in 'background' rainwater of around 10 µg/l, i.e. over 800 times greater, and with levels of about 1 mg/l used for the fluoridation of drinking water, i.e. over 80,000 times higher (WMO, 1989b);
- the hydrogen fluoride formed from HFC-32 and scavenged in rainwater would represent an acidity of 3.2×10^8 mol H^+/y, i.e. more than 25,000 times less than the acidity arising from the global natural and anthropogenic emissions of SO_2 and NO_x, i.e. 9×10^{12} mol H^+/y (Galloway, 1995). Thus the contribution of HFC-32 to acid rain would be negligible.

In all, the levels of fluoride and acidity produced by HFC-32 are low compared with those arising from other sources.

4.3.3 Aquatic and terrestrial fate

Only accidental releases of HFC-32 to water may be expected. In the water compartment rapid volatilisation will occur (Section 4.2). The half-life for volatilisation of HFC-32 from water was calculated, using EpiWin software (US-EPA, 2003), to be 44 minutes for a river or 2.8 days for a lake (wind speed 5 or 0.5 m/s, flow 1 or 0.05 m/s, respectively, and 1 m depth).

Due to its low log K_{ow} (0.21 in Table 1), no bioconcentration or bioaccumulation is expected to occur for HFC-32.

4.3.4 Biodegradation

HFC-32 was not readily biodegradable in the closed bottle test, where 3 to 5% ultimate degradation was observed after 28 days (Tobeta, 1992). Although this test, based on oxygen consumption in aerobic conditions is stringent, it is unlikely that microbial biodegradation is a significant environmental elimination process for HFC-32 (Berends *et al*, 1999).

4.3.5 Summary and evaluation

When released to the environment, HFC-32 will partition almost exclusively to the atmosphere, where it degrades slowly to carbon dioxide and HF mainly by tropospheric reaction with naturally occurring OH radicals. The overall atmospheric lifetime is 4.9 years (half-life 3.4 y). HFC-32 has no potential to deplete stratospheric ozone, because it does not contain chlorine or bromine. The official GWP is 650 compared to 1.0 for carbon dioxide (over a 100-year integration time horizon).

Any HFC-32 accidentally released into the aquatic environment is not expected to undergo abiotic or biotic degradation. Rapid volatilisation will be the dominant removal process. In view of its low octanol-water partition coefficient (log K_{ow} = 0.21), HFC-32 is not expected to bioconcentrate or bioaccumulate in aquatic organisms.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

Yokouchi *et al* (2005) estimated annual emissions of HFC-32 from Japan in 2003 (Section 4.1.2) from measurements of HFC-32 in the atmospheric boundary layer and in the free troposphere. The concentrations on which this estimate was based were not reported in the publication.

Miller *et al* (2008) measured a concentration of 2.3 ppt HFC-32 at Trinidad Head, California, USA in mid-2006. This level is higher than postulated in Section 4.1.2. However, the air sampled at Trinidad Head may not be truly representative of background air (Li *et al*, 2005).

No other observations of HFC-32 in background air or other environmental compartments have been reported.

5.2 Human exposure levels and hygiene standards

5.2.1 Non-occupational exposure

Consumer exposure has not been measured directly.

5.2.2 Occupational exposure

No published sources of industrial hygiene monitoring data are available.

5.2.3 Hygiene standards

The American Industrial Hygiene Association's Workplace Environmental Exposure Level (WEEL) Committee has assigned HFC-32 an occupational exposure limit of 1,000 ppm (2,130 mg/m^3) as an 8-hour time-weighted-average concentration. This is the highest level given for substances of very low toxicity. It is based on the good housekeeping principle that exposures to all substances except carbon dioxide should be maintained at or below 1,000 ppm (AIHA, 1997).

Arkema (formerly Elf Atochem) has set an internal occupational exposure limit of 1,000 ppm (2,130 mg/m^3) (Elf Atochem, 1995).

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Due to the specific physico-chemical properties of HFC-32, no aquatic or terrestrial toxicity testing has been carried out. Specific containment techniques would have to be used to obtain and maintain adequate concentrations in such test systems, and these would cause artefacts (e.g. O_2 depletion and increases in carbon dioxide concentration) not representative of the natural environment.

In the absence of experimental data, a modelling approach has been used to assess the effects of HFC-32 on aquatic and terrestrial organisms.

6.1 Micro-organisms

No data are available.

6.2 Aquatic toxicity

EcoSar software (US-EPA, 2000; CoR 2f) was used to predict the effects of HFC-32 on green algae, daphnids and fish. The measured log K_{ow} of 0.21 (Table 1) was used for the calculations. EcoSar predictions are based on actual toxicity data for classes of compounds with similar modes of action, i.e. narcosis in the case of fluorocarbons (Boethling *et al*, 1994) (Table 3).

Table 3: Predicted acute toxicity to aquatic organisms

Species	Duration (h)	Effect / parameter	Concentration (mg/l)
Freshwater		**Growth inhibition**	
Green alga	96	EC_{50}	360
		Immobility	
Daphnia	48	EC_{50}	620
		Lethality	
Fish	96	LC_{50}	630
Marine		**Lethality**	
Shrimp	96	LC_{50}	460
Fish	96	LC_{50}	80

Furthermore, a low aquatic toxicity may be expected for HFC-32 in view of the test results obtained for its structural analogue chlorodifluoromethane (HCFC-22) (DuPont, 1994; Hoke, 1997).

6.3 Terrestrial organisms

A value of 800 mg/kgbw is predicted for the 14-day LC_{50} in earthworms, using the EcoSar program (US-EPA, 2000; CoR 2f).

HFC-32 has been found to be a reversible inhibitor of methane (CH_4) oxidation by methanotrophic *Methylococcus capsulatus* in soil. Consumption of methane was blocked by levels of HFC-32 (0.03 kPa), and the inhibition was reversed following HFC-32 removal. Although a small quantity of HFC-32 was consumed during these incubations, its remaining concentration was sufficiently high to sustain inhibition. Methanogenesis in anaerobic soil slurries, including acetoclastic methanogenesis, was unaffected by levels of HFC-32 which inhibited methanotrophy. Low levels of HFC-32 (0.03 kPa) also inhibited nitrification and nitrous oxide (N_2O) production by soils (Miller *et al*, 1998).

7. KINETICS AND METABOLISM

7.1 Animal studies

Gas uptake, air-tissue partition coefficients and kinetic parameters of dihalomethanes were studied in 3 male Fischer 344 rats exposed to HFC-32 concentrations of 8.5, 64 or 155 mg/m^3 (4, 30, 73 ppm) for 2 to 6 hours. The sample of HFC-32 used was a 30:70 mixture with chlorofluoromethane (HCFC-31). HFC-32 was not metabolised and kinetic constants could not be determined. Partition coefficients were measured at 37°C as 1.31 ± 0.05 (n = 4), 4.76 ± 0.75 (n = 3), 1.60 ± 0.10 (n = 4), 1.43 ± 0.31 (n = 4), 2.75 ± 0.39 (n = 4) and 1.44 ± 0.25 (n = 3) in 0.9% saline, olive oil, blood, fat, liver and muscle, respectively (Gargas *et al*, 1986).

Air-tissue partition coefficients of pure HFC-32 were 1.13 ± 0.05, 2.28 ± 0.42, 1.25 ± 0.17, 1.63 ± 0.52 and 1.79 ± 0.53 in 0.9% saline, olive oil, and in rat blood, liver and fat, respectively (Ellis *et al*, 1994; Ellis *et al*, 1996b).

Uptake of radiolabelled ^{14}C-HFC-32 (specific activity 19.0 mCi/mmol, radiochemical purity > 97%) was measured in male Wistar derived rats exposed to concentrations of 10,000, 25,000 or 50,000 ppm HFC-32 (21,300, 53,250 or 106,500 mg/m^3) for up to 6 hours. Blood levels of HFC-32 were determined at 2, 4 and 6 hours. Exhaled carbon dioxide (as $^{14}CO_2$) was determined during exposure and up to 11.5 hours post-exposure. Blood levels of HFC-32 increased in a linear manner with exposure concentration and were 23.7 ± 1.4, 62.5 ± 2.6 and 120.2 ± 5.2 µg/ml at 10,000, 25,000 and 50,000 ppm, respectively. The amount of HFC-32 metabolised and exhaled as carbon dioxide increased in proportion to the exposure concentration, reaching a maximum of 667 µmol/kgbw/h at 50,000 ppm by 4 to 5 hours and declining rapidly on cessation of exposure. This indicated that metabolism of HFC-32 was not saturated at exposure concentrations of up to 50,000 ppm. It was concluded that the body burden of HFC-32 and its metabolism are dependent on the partitioning between alveolar airspace and blood (Ellis *et al*; 1994; Ellis *et al*, 1996b).

Wistar derived rats and Swiss derived mice (4 males/group/species) were housed individually in glass metabolism cages. Prior to the beginning of the study, fluoride ion was determined in (control) urine. Each animal was then placed in an inhalation chamber and exposed to 10,000 ppm ^{14}C-HFC-32 (21,300 mg/m^3) (specific activity of 5.27 to 7.38 µCi/mmol) for 6 hours. During the exposure period urine and faeces were collected. Following exposure, animals were rapidly transferred back to their metabolism cages where urine, faeces, and any exhaled organic metabolites, e.g. carbon dioxide and carbon monoxide, were collected. After 4 days, the animals were killed. One rat and one mouse were used to measure total carcass radioactivity. From the remaining animals, samples of blood (whole and plasma), liver, kidneys, lungs, heart, brain, testes, muscle, renal fat, spleen and bone (femur) were taken for radioactivity measurements. In

addition, rats and mice of the same strains (4/group/species) were exposed to 10,000 ppm unlabelled HFC-32 for 6 hours. Four males of each species were used as controls. Animals were subsequently killed and blood collected for carboxyhaemoglobin assays. Analysis showed that the target concentration of 10,000 ppm HFC-32 had been reached and maintained. The inhaled dose was estimated to be 79 to 84 mmol HFC-32/kgbw in rats and 122 to 129 mmol/kgbw in mice. The following results are expressed in terms of this inhaled dose.

Only 0.89% and 1.13% of the inhaled dose was actually absorbed in rats and mice, respectively. Most of the absorbed dose was eliminated within one hour of exposure. Of the recovered absorbed HFC-32, 55.7% and 39.8% was eliminated from rats and mice, respectively, in the faeces, urine and expired air. The levels of organic material collected in traps (containing acetone) were too small to identify and this material was therefore assumed to be HFC-32. Urinary and faecal excretion of the radiolabel was extremely rapid and began during exposure. Approximately half of the total urinary excretion of radiolabel occurred in the first hour after exposure. Urinary excretion of HFC-32 and its metabolites was more prominent in mice (0.34%) than in rats (0.13%). Faecal excretion was minimal and accounted for only 0.03% and 0.07% in rats and mice respectively.

Exhalation of carbon dioxide was the major route of excretion of metabolised HFC-32 in both rats and mice. Of the inhaled dose of HFC-32, 0.23% and 0.27% was recovered as the carbon dioxide in rats and mice, respectively. Carbon monoxide could not be detected as a metabolite of HFC-32, either in the form of carboxyhaemoglobin in the blood or as ^{14}C carbon monoxide in exhaled air. Therefore, the formation of carbon monoxide was assumed to play an insignificant or no role in HFC-32 metabolism.

At the end of the study (after 4 days) only small amounts of radiolabel remained in the carcass and accounted for 0.11% and 0.12% of the dose in rats and mice, respectively. The highest concentrations were present in the lungs, liver and kidneys but the distribution was relatively uniform in both species. These non-volatile metabolites were presumed to be either formic acid or compounds arising from its incorporation into the C1-pool.

Metabolism of HFC-32 was expected to result in the excretion of fluoride ion into the urine. Of the inhaled dose of HFC-32, 0.51% and 0.80% was shown to be metabolised in rats and mice, respectively, and carbon dioxide was the major metabolite in both species. It was proposed from the metabolism study that oxidative metabolism was the main route of biotransformation of HFC-32. The expected major urinary metabolite from this process would be formic acid and a radiolabel arising from the incorporation of formic acid into endogenous material.

In all, HFC-32 was not readily absorbed by the body but rapidly excreted unchanged or metabolised via an oxidative pathway. Approximately 1% of the inhaled dose was absorbed and

excreted, principally in urine (more in mice than rats) and by exhalation as carbon dioxide (in rats and mice) (Ellis *et al*, 1992, 1996a,b; CoR 1b).

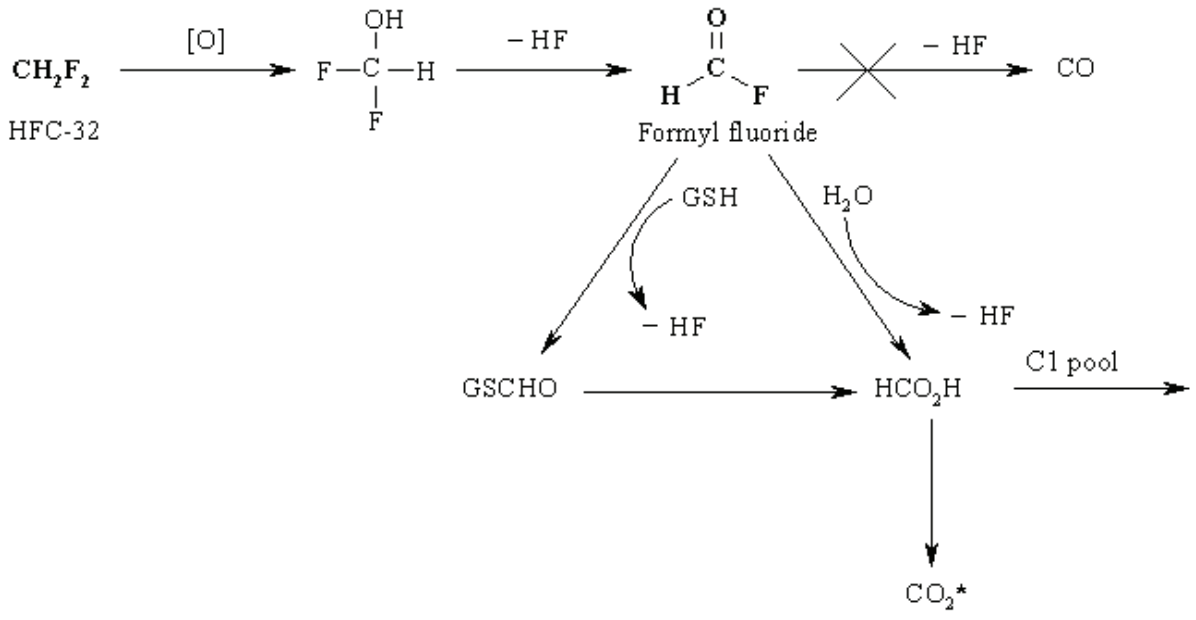
7.2 Human studies

No data are available on the absorption, distribution, metabolic transformation or elimination of HFC-32 in humans.

7.3 Conclusion

Kinetic and metabolic studies in rats and mice indicate that following inhalation exposure, HFC-32 is poorly absorbed (about 1%), is eliminated mainly via exhalation unchanged or as carbon dioxide (Figure 2). The remaining non-volatile metabolites are excreted in the urine and are presumed to be either formic acid, or compounds arising from its incorporation into the C1 pool. The equilibration of HFC-32 levels in blood is reached after 2 hours of exposure.

Figure 2: Postulated route of oxidation of HFC-32 (from Ellis et al, 1992)



*Denotes metabolite identified

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

No specific oral and dermal toxicity data are available (HFC-32 is a gas at room temperature).

8.1 Single exposure

Wistar derived rats (5/sex/group) were exposed by inhalation (nose-only) to measured concentrations of 0, 7,510 ± 4,700, 85,900 ± 29,400 or 520,000 ± 19,200 ppm HFC-32 (16,000, 183,000, 1,110,000 mg/m^3) for 4 hours. A mixture of nitrogen and oxygen was added to maintain the oxygen level at 20%. The animals were observed for 14 days after exposure during which time daily clinical examinations were carried out. At the end of this period necropsy was performed. Lungs were removed and weighed, as were any abnormally appearing body organs.

There were no deaths. Treatment-related clinical abnormalities observed during the 4-hour treatment period occurred only in animals treated with middle and high dose HFC-32. All animals treated with the middle dose showed reduced response to sound. All rats exposed to the high dose showed an absence of response to sound and some showed an increased breathing depth and reduced breathing rate, and tail erections. Following treatment, tail erections and an increased period of piloerection were observed in animals treated with middle and high doses of HFC-32. Reduced activity, salivation and shaking were observed for one day only in the highest treatment group. Animals treated with 520,000 ppm demonstrated reduced splaying reflex but this was thought to be an artefact as it is reported to be found frequently in untreated rats of that strain and age. One male (85,900 ppm) demonstrated reduced stability for the 2-week observation period, as did 2 females at the highest dose for one day only.

The lungs of all treated animals appeared healthy at necropsy. One or two males showed slight abnormalities in the bladder, kidney, liver, and/or seminal vesicles at the highest dose only. No such abnormalities were noticed in any females. No toxicologically significant changes were observed in bodyweight, bodyweight gain, or absolute or relative lung weight.

Under the conditions of this study, the LD_{50} for HFC-32 was > 520,000 ppm (Parr-Dobrzanski, 1992a; Ellis *et al*, 1996b; CoR 1a).

8.1.1 Cardiac sensitisation

The potential of HFC-32 to sensitise the heart to adrenaline (epinephrine) was investigated in 8 beagle dogs. Each dog was assessed for the effect of adrenaline on its response to the known cardiac sensitiser trichlorotrifluoromethane (CFC-11). Exposures to HFC-32 commenced at

150,000 ppm (319,000 mg/m^3) and, in the absence of a positive response, further exposures were carried out at increments of 50,000 ppm (106,000 mg/m^3) to a maximum of 350,000 ppm (744,000 mg/m^3). Adrenaline was administered before exposure to provide a baseline response, and after 5 minutes exposure to HFC-32. A positive cardiac sensitisation effect was not seen in any animal at any concentration of HFC-32. It was concluded that HFC-32 did not have a cardiac sensitisation potential in the dog at concentrations from 150,000 to 350,000 ppm (Hardy and Kieran, 1992; Ellis *et al*, 1996b)

In this study, clinical signs indicative of a pre-narcotic response (e.g. head and limb tremors, unsteady gait) were seen in all eight animals at 350,000 ppm HFC-32. Five of the animals were affected at a concentration of 300,000 ppm (638,000 mg/m^3), and only one affected at 250,000 ppm (531,000 mg/m^3).

8.2 Skin, respiratory tract and eye irritation, sensitisation

As HFC-32 is a gas at room temperature and pressure, no studies to assess its potential for skin and eye irritation or skin sensitisation have been carried out. No evidence of skin or mucosal irritation was seen in rats exposed by inhalation on an acute or a repeated basis. There is no case report in humans (internal report or published).

8.3 Repeated exposure

Trochimowicz *et al* (1977; CoR 4a) described a study in which male rats were exposed (6 h/d, 5 d/wk) to HFC-32 at a concentration of 200,000 ppm (425,000 mg/m^3) for 2 weeks. There were no changes in clinical signs, haematology, urine or blood biochemistry during the study and no histopathological changes were detected following termination.

Wistar rats (5/sex/group) were exposed (whole-body, 6 h/d, 5 d/wk) to measured concentrations of 0, 2,010, 9,870 or 49,500 ppm HFC-32 (0, 4,270, 20,970, 105,200 mg/m^3) for 4 weeks. There were no deaths, no clinical abnormalities or biologically significant variations in body weights, food consumption, urinalysis and haematological parameters, and no ophthalmic changes that could be attributed to treatment. Increases in plasma potassium (1.2 fold over control), measured at the end of the exposure period in males exposed to 49,500 ppm, were not considered as biologically significant. No changes in organ weights of treated animals compared to controls occurred and no macroscopic findings were noted that suggested a treatment-related effect. Microscopic findings also indicated an absence of treatment-related effects. In conclusion, treatment of rats with 2,010, 9,870 or 49,500 ppm HFC-32 for 4 weeks resulted in a few minor and probably biologically insignificant changes (Parr-Dobrzanski, 1992b; CoR 1b).

Wistar rats (10/sex/group) were exposed (whole-body, 6 h/d, 5 d/wk) to measured concentrations of 0, 4,940, 14,600 or 49,100 ppm HFC-32 (0, 10,500, 31,030, 104,300 mg/m^3) for 13 weeks. Ten additional animals from the control and highest dose groups were used as a satellite group and were kept for observation for 28 days after the completion of the 90-day exposure period. Necropsy was performed in week 14 for the main study group and in week 18 for the satellite group. There were no deaths, no clinical abnormalities and no ophthalmic changes that could be attributed to treatment. No biologically significant and/or treatment-related variations occurred in body weights, food consumption, urinalysis, haematological or blood clinical chemistry parameters. Triglyceride levels were increased (1.4 fold) in males exposed to 49,100 ppm at weeks 5 and 15. There was also an increase (1.3 fold) of serum alanine transferase activity in females from all exposure groups at week 5. Both increases were judged not to be biologically significant. No changes in organ weights of treated animals compared to controls occurred and no macroscopic findings were noted that suggested a treatment-related effect. Microscopic findings suggested an absence of treatment-related effects. In conclusion, the treatment of rats with 4,940, 14,600 and 49,100 ppm HFC-32 for 90 days resulted in a few minor or biologically insignificant changes (Parr-Dobrzanski, 1993; Ellis *et al*, 1996b; CoR 1b).

8.3.1 Conclusion

HFC-32 shows a low toxicity when administered daily via inhalation at concentrations up to 49,100 ppm for up to 90 days.

8.4 Genotoxicity and cell transformation

8.4.1 *In vitro*

HFC-32 was tested for its ability to cause gene mutations in the *Salmonella typhimurium* and *Escherichia coli* bacterial reverse mutation assay (Ames test). The concentrations of HFC-32 selected for the study were 0, 50,000, 100,000, 250,000, 500,000, 750,000 or 1,000,000 ppm (0, 106,000, 213,000, 531,000, 1,060,000, 1,590,000, 2,130,000 mg/m^3). *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strains WP2P and WP2P uvrA were used, in the presence or absence of liver microsomal S9 [a] metabolic activation. The positive controls produced marked increases in the number of revertant colonies within the anticipated range. No significant increases in the number of revertant colonies of bacteria were recorded for any of the strains of *S. typhimurium* or *E. coli* used, at any dose level of the test substance, with or without metabolic activation. HFC-32 caused some toxicity to *S. typhimurium* at the 750,000 or 1,000,000 ppm. The results indicated that HFC-32 was not genotoxic toward *Salmonella typhimurium* or

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

Escherichia coli under the conditions employed in this study (Callander, 1992; Ellis *et al*, 1996b; CoR 1b).

HFC-32 was investigated for its potential to cause chromosomal aberrations in cultured Chinese hamster lung cells, with and without exogenous metabolic activation. The lung cells were exposed to HFC-32 at 100,000, 200,000, 400,000 or 800,000 ppm HFC-32 (213,000, 425,000, 850,000, 1,700,000 mg/m^3) for 24 or 48 hours without metabolic activation and for 6 hours with metabolic activation. Chromosomal aberrations were very low in the negative controls whereas induction was clearly observed in the positive control groups. No statistically significant chromosomal aberrations were observed in any of the tests using HFC-32. In conclusion, under the conditions of this study, HFC-32 did not cause chromosomal aberrations in cultured Chinese hamster lung cells (Asakura, 1993; Ellis *et al*, 1996b; CoR 1a).

An evaluation of the clastogenic potential of HFC-32 was made using human lymphocytes (from 1 female and 1 male donor) tested at 0, 100,000, 500,000 or 1,000,000 ppm HFC-32 (0, 213,000, 1,060,000, 2,130,000 mg/m^3). No significant reductions in mitotic index compared to air controls were found in treated cells harvested at 72 and 96 hours after culture initiation, either in the absence or presence of metabolic activation. The 96-hour incubation was performed using lymphocytes from the female donor only and at the highest concentration. No statistically or biologically significant increases in chromosomal aberration frequencies (including or excluding gap-type aberrations) compared to air control values were seen at any of the exposure level tested in either donor, in the presence or absence of metabolic activation, at either sampling time. The test system was shown to be sensitive to gaseous and liquid phase direct acting clastogens (Mackay and Howard, 1992; Ellis *et al*, 1996b; CoR 1a).

8.4.2 *In vivo*

HFC-32 was investigated for its potential to induce micronuclei in bone marrow polychromatic erythrocytes of 6-week old Charles River strain mice (5/sex/group) exposed (whole-body) to 132,150 ppm HFC-32 (281,000 mg/m^3) for 6 hours. A single preliminary experiment was performed to determine the protocol of the main experiment. At 24 or 48 hours after treatment, the animals were killed and the bone marrow cells were collected for micronucleus analysis. No cytotoxic effects were observed as indicated by the absence of an increase in the ratio of polychromatic to normochromatic erythrocytes in treated animals compared to controls. No increase in the frequency of micronucleated polychromatic erythrocytes occurred in animals treated with HFC-32 compared to controls. In contrast, a distinct increase in the number of micronuclei was noted in animals treated with the positive control cyclophosphamide. In conclusion, under the conditions of this study HFC-32 was found not to cause chromosomal

damage in bone marrow cells of mice *in vivo* (Randall and Mackay, 1993; Ellis *et al*, 1996b; CoR 1b).

8.4.3 Summary and evaluation

HFC-32 was not mutagenic in *Salmonella typhimurium* or *Escherichia coli*. HFC-32 was neither clastogenic in polychromatic erythrocytes of mouse bone marrow *in vivo*, nor in human peripheral blood lymphocytes or Chinese hamster lung cells *in vitro*.

8.5 Chronic toxicity and carcinogenicity

No carcinogenicity study is available.

The absence of any target organ identified in the repeated dose toxicity studies in rats exposed up to 49,100 ppm for 13 weeks, and the absence of any genotoxic activity *in vitro* or *in vivo*, show that there is no indication of a carcinogenic potential for HFC-32.

HFC-32 has a chemical structure comparable to dichloromethane (methylene chloride). In lifetime inhalation studies, exposure to very high levels of dichloromethane significantly increased the incidence of liver and lung tumours in mice and benign mammary gland tumours in rats (NTP, 1986). Like dichloromethane, HFC-32 could, theoretically, be metabolised by oxidative metabolism. In the case of HFC-32, this would lead to the formation of formyl fluoride, which could, in theory, subsequently dissociate to carbon monoxide and HF. Formyl fluoride is a relatively stable molecule and there is no evidence of carbon monoxide formation in either the mouse or the rat (Section 7.1). On the contrary, the most significant excreted metabolite was shown to be carbon dioxide, suggesting that hydrolysis of formyl fluoride was the most likely metabolic pathway.

8.6 Embryotoxicity, teratology and reproductive performance

8.6.1 Embryotoxicity and teratology

HFC-32 was investigated for its potential to cause foetotoxicity or teratogenicity in a modified Chernoff-Kavlock assay. Female Wistar derived rats (10/group) were exposed (whole-body, 6 h/d) to 0, 9,930 or 49,600 ppm HFC-32 (0, 21,100, 105,400 mg/m^3) during days 7 to 16 of gestation (period of organogenesis). Animals then littered and reared their young to 5 days *post partum.* Pups were weighed on days 1 and 5, and the number of dead and live animals was recorded. There was no effect on maternal body weight gain. One female showed signs of

urinary incontinence on days 8 to 10 of gestation. No other clinical signs were observed in the animals during exposure. One female at 9,930 ppm was unable to sustain its litter to day 5 *post partum*. One control female and two 49,600 ppm exposed females showed a high incidence of pup mortality to day 5 *post partum* (57%, 64%, and 55% respectively) compared to other females in the study. The percentage of animals surviving to day 5 was 96% for both groups when the 3 litters with increased mortality were removed. No pups were dead at birth. However the litter size was statistically lower in the two treated groups than controls (9.3 compared to 10.7 for the 9,930 ppm group). The average pup weight at birth was the same in each group but at day 5, pups in the 50,000 ppm group were of low weight compared to controls. The pups from the 49,600 ppm group showed only 31% weight gain from birth compared to the 40% gain of control animals to day 5. In conclusion, under the conditions of this test HFC-32 was not considered to be a foetotoxicant or a teratogen (Moxon, 1992; CoR 1b).

In a further study, HFC-32 was also investigated for its potential to cause foetotoxicity or teratogenicity. Female Wistar derived rats (24/group) were exposed (whole-body, 6 h/d) to 0, 5,000, 15,000 or 49,800 ppm HFC-32 (0, 10,600, 31,900, 105,400 mg/m^3) on days 7 to 16 of gestation. On day 22 of gestation, the animals were killed and necropsied. None of the animals showed any clinical change during the course of the study. The maternal bodyweights were slightly lower than the control animals at 15,000 and 49,800 ppm. Animals exposed to 49,800 ppm had a reduced food consumption during days 7 to 16 compared to controls. No abnormal macroscopic changes were noted *post mortem* and maternal performance seemed unaffected by exposure.

Two animals exposed to 49,800 ppm and one each exposed to 5,000 or 15,000 ppm HFC-32 totally resorbed their litters. There was a slight but not statistically significant increase in the number of early intra-uterine deaths amongst the other animals exposed to 49,800 ppm but the number of litters affected was the same as in the controls. There was a reduction in the mean number of live foetuses in the 49,800 ppm group due to the higher incidence of pre-implantation loss (occurring prior to HFC-32 exposure) and slightly but not statistically higher post-implantation loss. A similar reduction in the 15,000 ppm group was considered incidental due to a lower number of *corpora lutea* compared to controls.

HFC-32 had no effect on foetus weight. Neither the type nor the incidence of major foetal abnormalities was associated with HFC-32. A number of foetuses amongst the 49,800 ppm treated group had minor external or visceral defects which consisted of dilated ureters, mottled livers and hepatic cysts. Collectively these defects occurred in statistically significant numbers compared to the control animals, but as individual deformities they did not. There was also an increase in the number of foetuses in the higher treatment group with kinked ureters. HFC-32 resulted in an increased incidence of partial ossification of the parietal bones in animals exposed to 5,000 and 49,800 ppm, but not 15,000 ppm. These may have occurred as a result of maternal

toxicity. Several other skeletal defects were also increased in exposed groups compared to controls. These defects were reduced bone ossification and shortened ribs. No effect on the manus or pes of the rat was evident.

In conclusion, exposure of pregnant females to HFC-32 at levels of up to 15,000 ppm caused no maternal or foetal toxicity. At higher concentrations, the findings were of low incidence and were typical of the general minor changes seen in the presence of maternal toxicity. This slightly increased incidence of minor variants/defects compared to control was considered, at most, to indicate minimal foetotoxicity at 49,800 ppm in the presence of slight maternal toxicity (Moxon, 1993; Ellis *et al*, 1996b; CoR 1b).

A teratology study was conducted in New Zealand white rabbits (24 females/group). Dams were exposed (6 h/d) to 0, 5,000, 15,000 and 50,000 ppm HFC-32 (0, 10,600, 31,900, 106,300 mg/m^3) (measured concentrations very close to the target levels) from gestation days 6 to 18. Mothers were killed on day 29. Due to limited availability of exposure chambers in relation to the number of animals used, the study was conducted in two phases of three consecutive batches. Statistical analyses of bodyweight and litter data showed that there was no interaction between exposure and phase allowing a combined presentation of the data from the two phases. There were no exposure-related effects on mortality or clinical signs. There was a slight and statistically significant decrease in bodyweight during days 8 to 10 but recovery was recorded from day 10, weight gains being generally comparable to controls. Thus maternal effects were minimal and confined to the highest exposure level group.

There were no treatment-related changes in any of the litter parameters: *corpora lutea*, implantation sites, resorptions, number of live foetuses or foetal weight. Although the incidence of malformed foetuses at 50,000 ppm was slightly (but not statistically significantly) higher than in controls, this was essentially due to 4 foetuses with microphthalmia, confined to 2 litters out of 20 and only observed in study phase 2. Moreover, there was no consistent pattern to the types of structural defects observed among foetuses from HFC-32 exposed mothers and no contributory evidence in less severe changes (anomalies, variants, foetal weight). Consequently, this finding was considered likely to be coincidental. There were no treatment-related effects on the incidence of foetuses showing visceral or skeletal anomalies or with skeletal variants. The no-observed adverse effect level (NOAEL) in that study for developmental effects and for maternally toxic effects were considered to be both equal to 50,000 ppm (Meyers, 1994; Ellis *et al*, 1996b; CoR 1a).

Conclusion

HFC-32 was not teratogenic in the rat or rabbit at any exposure level. There was evidence of minimal maternal toxicity in both species, and slight foetotoxicity in the rat at 49,800 ppm.

8.6.2 Reproductive performance

No specific fertility study is available on HFC-32.

Relevant information is provided from the 28-day and the 13-week repeated toxicity studies in rats. In these studies, Wistar derived rats were exposed (whole-body, 6 h/d, 5 d/wk) to concentrations up to 50,000 ppm for 28 days or 13 weeks respectively. In neither study were there significant changes observed at the macroscopic examination, or in the histopathological examination of the reproductive organs or on testes weight. Based on these limited data, the available evidence suggests that HFC-32 is unlikely to have the potential to affect fertility.

8.6.3 Conclusion

In developmental toxicity studies, HFC-32 did not induce teratogenic or significant embryo-foetal toxic effects in rats or rabbits exposed up to 50,000 ppm during gestation days 7 to 16 and 6 to 18, respectively. Based on the results from the 13-week repeated inhalation exposure study, including macroscopic and histopathological examinations of the reproductive organs, the available evidence suggests that HFC-32 is unlikely to have the potential to affect fertility in rats up to 50,000 ppm. Thus, the NOAEL for fertility and developmental endpoints were both established at 50,000 ppm.

8.7 Special studies

8.7.1 Peroxisome proliferation and hypolipidaemia

A peroxisome proliferation assay was performed in hepatocytes from a Sprague-Dawley male rat. The cells were cultured *in vitro* and exposed to concentrations of 400,000, 500,000, 600,000, 700,000 and 800,000 ppm HFC-32 (850,000, 1,060,000, 1,280,000, 1,490,000, 1,700,000 mg/m^3) for 4 days. No increase in the palmitoyl-CoA-oxidase activity was observed at any of the tested concentrations (Elf Atochem, 1993; CoR 1b).

9. EFFECTS ON HUMANS

There are no reports of adverse health effects due to HFC-32.

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

APPENDIX B: 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 (DuPont, 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' and 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 $\rightarrow C_2F_6$
- HFC-23 = 3 Fs, 1 H, 1 C, and 0 Cls $\rightarrow CF_3H$
- PFC-1216 = 6 Fs, 0 Hs, 3 Cs, 0 Cls with 1 double bond $\rightarrow C_3F_6 \rightarrow CF_2 = CF\text{-}CF_3$

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 → c-C_4F_8.

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-CFH_2, 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 → $C_5H_2F_{10}$

- m indicates CF_3 . . . CF_3
- e indicates CHF, so CF_3CHF
- e indicates CHF, so $CF_3CHFCHF$
- HFC-43-10mee → $CF_3CHFCHFCF_2CF_3$.

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 $–CF_2CF_3$).

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.

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

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

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

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

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