1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) CAS No. 306-83-2 (Third Edition)

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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 toxicity and ecotoxicity data on 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123), including results of new toxicological studies conducted by the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT) [b].

HCFC-123 is a volatile liquid that is used, for example, as a refrigerant in air-conditioning installations and as an intermediate in the production of various chemicals. HCFC-123 is a transitional replacement (to be phased out by 2020) for chloro- and bromo-fluorocarbons. It has a low potential for ozone depletion (2% of that of CFC-11, trichlorofluoromethane) and global warming (76 relative to carbon dioxide; this compares to 4,000 for CFC-11).

Any HCFC-123 released to the environment will rapidly volatilise to the atmosphere, where it will be slowly degraded, mainly to trifluoroacetic acid, which will partition into water and possibly accumulate there, although predicted concentrations are below toxic thresholds. HCFC-123 is not readily biodegradable, but is not likely to bio-concentrate in fish and other aquatic organisms. It is slightly to moderately toxic to fish, invertebrates, and algae. Thus, HCFC-123 is unlikely to pose a significant hazard to the aquatic environment; it is also not persistent in water.

HCFC-123 has a low toxicity in laboratory animals upon single brief exposure to the liquid or vapour. The liquid is not irritant or sensitising to the skin, but produces eye irritation. For humans, the most relevant critical effects from single, brief single exposure to HCFC-123, such as from the discharge of a fire extinguisher, are depression of the central nervous system and increased likelihood of cardiac arrhythmia. Repeated exposure to HCFC-123 may yield liver lesions. In reproductive toxicity studies in animals, the growth of neonates was retarded, probably because the milk of the dams contained trifluoroacetic acid, the main metabolite of HCFC-123.

HCFC-123 is not genotoxic *in vivo*, although there was clastogenetic activity at high doses *in vitro*. HCFC-123 caused statistically significant increases in benign tumours in rat liver, testis and pancreas. The formation of liver tumours can be linked with the rodent-specific peroxisome proliferation potential of HCFC-123, while the testicular tumours may have resulted from enhanced hormonal disturbances in senescent rats. Thus, the hepatic and testicular tumours are not relevant for human health hazard assessment. The mechanism of pancreatic acinar cell tumour formation is not understood, and the significance of those tumours for humans remains uncertain.

[a] ECETOC. 1996. Joint assessment of Commodity Chemicals report No. 33

[b] A cooperative research effort (1987-2000) sponsored by 16 of the leading CFC producers [http://www.afeas.org/paft/]

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

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

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

This document presents a critical evaluation of the toxicology and ecotoxicology of 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123) (CAS No. 306-83-2).

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

LIST OF SPECIAL ABBREVATIONS

ALD	Approximate lethal dose
ALP	Alkali phosphatase
ALT	Alanine transferase
AST	Aspartate transaminase
CAS	Chemical Abstracts Service
CCK	Cholecystokinin
CFC	Chlorofluorocarbon
CNS	Central nervous system
CoR	Code fo reliability
EQC	Equilibrium criterion
GGT	γ-glutamyl transpeptidase
GWP	Global warming potential
HCFC	Hydrochlorofluorocarbon
HCG	Human chorionic gonadotropin
HFC	Hydrofluorocarbon
hPa	Hectopascal
HPLC	High-pressure liquid chromatography
i.p.	Intraperitoneal
ITH	Integration time horizon
JACC	Joint Assessment of Commodity Chemicals
K_m	Michaelis-Menten constant
LDHX	Lactate dehydrogenase-X
LHRH	Luteinising hormone-releasing hormone
LOAEL	Lowest-observed-adverse-effect level
MHA	Methaemalbumin
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
ODPs	Ozone depleting potentials
PAFT	Programme for Alternative Fluorocarbon Toxicity Testing
PPAR	Peroxisome proliferator activated receptor
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
TFA	Trifluoroacetic acid
UDS	Unscheduled DNA synthesis
V_{max}	Maximal metabolic rate; velocity at maximal concentration of substrate
WY	Wyeth

1. SUMMARY AND CONCLUSIONS

1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123 [a]) is a non-combustible, volatile colourless liquid with a slight ether odour. HCFC-123 is sparingly soluble in water.

HCFC-123 is produced by hydrofluorination of tetrachloroethylene or hydro-dechlorination of 1,1,1-trichloro-2,2,2-trifluoroethane (CFC-113a). HCFC-123 is used as a refrigerant in commercial and industrial air-conditioning installations, as a foam-blowing agent, in gaseous fire extinguishers, and in metal and electronics cleaning. HCFC-123 is also an intermediate in the production of various agricultural chemicals, trifluoroacetyl chloride, 1-chloro-1,2,2,2-tetrafluoroethane (HCFC-124) and pentafluoroethane (HFC-125).

The ozone-depleting potential of HCFC-123 is 2% of that of CFC-11 (trichlorofluoromethane) and it has a global warming potential of 76 over a 100-year time horizon relative to carbon dioxide. As such, HCFC-123 is a transitional replacement for chlorofluorocarbons and bromofluorocarbons phased out pursuant to the 1987 Montreal Protocol on Substances that deplete the Ozone Layer. According to the 1992 Copenhagen Amendment to the Montreal Protocol HCFC-123 and other hydrochlorofluorocarbons are to be virtually phased out by 2020.

HCFC-123 may be released to the environment as a fugitive emission during production or use. If released to water, it will rapidly volatilise to the atmosphere; the estimated half-life for volatilisation from a model river is 3.6 hours. HCFC-123 is not expected to bio-concentrate in fish and aquatic organisms or adsorb to sediment or suspended organic matter. If released to the atmosphere, HCFC-123 undergoes a slow gas-phase reaction with photochemically produced hydroxyl radicals. Its atmospheric lifetime has been estimated to be 1.3 years.

Closed bottle studies with activated sludge indicate the compound is not readily biodegradable. Fugacity model predictions indicate that it will partition mainly to the air with little entering the water, soil, or sediment compartments.

The main atmospheric breakdown product of HCFC-123 (and other, more widely used fluorocarbons) is trifluoroacetic acid, which will partition into aqueous phases in the environment. Although trifluoroacetic acid is resistant to degradation and may accumulate in certain closed aquatic systems, current and predicted concentrations from HCFC-123 emissions are below toxic thresholds.

HCFC-123 is not readily biodegradable but is not likely to bio-concentrate in fish and other aquatic organisms. It is slightly to moderately toxic to fish, invertebrates, and algae. It exhibits a 96-hour LC_{50} of 55.5 mg/l in rainbow trout, a 48-hour EC_{50} of 17.3 mg/l in *Daphnia*, and a

[a] The naming and numbering system for fluorocarbons is explained in Appendix B

96-hour EC_{50} of 67.8 and 96.6 mg/l for biomass and average specific growth, respectively, in algae. Because of its low aquatic toxicity, HCFC-123 is unlikely to pose a significant hazard to the aquatic environment; it is also not persistent in water.

HCFC-123 has low acute toxicity with an oral approximate lethal dose (ALD) of 9,000 mg/kgbw and a 4-hour inhalation LC_{50} of 32,000 ppm (200,000 mg/m^3) in rats. The dermal LD_{50} in rats and rabbits is > 2,000 mg/kgbw. HCFC-123 was not irritant to rabbit skin, but produced mild to moderate eye irritation in liquid form. It is not a skin sensitiser in guinea pigs. It has a cardiac sensitisation EC_{50} value of 19,500 ppm (122,000 mg/m^3) in dogs. Inhalation for a few minutes to a few hours caused liver lesions in guinea pigs at 1,000 ppm (6,250 mg/m^3), central nervous system (CNS) depression in all species examined at 5,000 ppm (31,300 mg/m^3) and adrenaline-induced cardiac arrhythmia in dogs at 20,000 ppm (125,000 mg/m^3). In the rat and hamster, inhalation of more than 30,000 ppm (188,000 mg/m^3) for 4 hours caused severe CNS depression and death.

In repeated-exposure inhalation toxicity studies lasting 2 to 39 weeks in rats, guinea pigs, dogs, and monkeys, the main target organs were the liver, the hypothalamic-pituitary-gonadal endocrine system, and the CNS. The lowest-observed-adverse-effect level (LOAEL) based on liver effects was 30 ppm (188 mg/m^3). The no-observed-adverse-effect level (NOAEL) was 100 ppm (625 mg/m^3) and 300 ppm (1,880 mg/m^3) for endocrine effects and CNS effects, respectively. HCFC-123 does not induce reproductive or foetal toxicity at levels of exposure lower than those that cause other systemic effects. Growth was retarded in neonatal rats and monkeys reared by dams exposed to HCFC-123, with a LOAEL of 30 ppm (188 mg/m^3). The main metabolite of HCFC-123, trifluoroacetic acid, was found in the milk of the dams.

No developmental toxicity was observed in rabbits (up to 5,000 ppm; 31,300 mg/m^3) or rats (up to 10,000 ppm; 62,500 mg/m^3). In a rat 2-generation reproduction study, HCFC-123 was principally associated with effects on growth and on the liver. Those effects may have been related to peroxisome proliferation. It was not possible to identify a no-effect level as effects were seen in some parameters at the lowest exposure level (30 ppm; 188 mg/m^3). In terms of reproductive performance, there were decreased implantation counts among F_1 females at 1,000 ppm (6,250 mg/m^3). All exposure levels (30, 100, 300 or 1,000 ppm; 188, 625, 1,880 or 6,250 mg/m^3) were associated with impaired pup growth in the offspring of the F_1 generation. Since the metabolite trifluoroacetic acid and/or HCFC-123 itself are present in milk consumed by nursing pups, the decrease in pup weights may have been secondary to hepatic peroxisome proliferation.

Clastogenic activity was observed at cytotoxic doses in three independently conducted *in vitro* chromosome aberration tests with human lymphocytes. However, HCFC-123 was non-mutagenic when tested in the *in vitro* bacterial reverse mutation test. Furthermore, all *in vivo* tests for genetic

toxicity were negative. These *in vivo* studies include the mouse micronucleus test, the unscheduled DNA synthesis test in rat hepatocytes and the rat bone marrow chromosome aberrations assay. Therefore, the evidence suggests that HCFC-123 is unlikely to pose a genotoxic hazard. HCFC-123 was also negative in a cell transformation assay *in vitro* with and without metabolic activation.

HCFC-123 induced benign hepatic tumours in female rats and benign acinar cell tumours of the pancreas in male rats exposed by inhalation to 0, 300, 1,000 or 5,000 ppm (0, 1,880, 6,250 or 31,300 mg/m^3) for 2 years. In addition, equivocal increases in benign interstitial cell tumours of the testes occurred in male rats. The lowest concentration (300 ppm) was above the no-observed-effect level (NOEL) as effects at this concentration were observed on clinical chemistry parameters, lower body weight and body weight gain, increased incidence of neoplastic and non-neoplastic morphological changes, and higher hepatic peroxisomal β-oxidation activity. The incidence of hepatocellular adenomas in male rats seen at 5,000 ppm was not statistically significant, whereas, in female rats, the observed increased incidences at 300 and 5,000 ppm were. There was no significant increase in hepatocellular adenomas at 1,000 ppm. The incidence of benign pancreatic acinar cell adenomas was increased in all exposed males in a dose-dependent manner. Benign testicular interstitial cell adenomas were also statistically significant at 300 and 5,000 ppm. However, when adjusted for survival, the increase in interstitial cell adenomas was equivocal. It is likely that the tumours observed involve one or more non-genotoxic mechanisms, including peroxisome proliferation and β-oxidation, hepatocellular necrosis and regenerative proliferation. It is noted that these hepatic, pancreatic and testicular tumours were all benign, appeared late in life (primarily in males) and were not life threatening to the animals. The formation of hepatic tumours can be linked with the rodent-specific peroxisome proliferation potential of HCFC-123, while the testicular tumours may have resulted from enhanced hormonal disturbances in senescent rats. Thus, the hepatic and testicular tumours are not relevant for human health hazard assessment. The mechanism of pancreatic acinar cell tumour formation is not understood, and the significance of those tumours for humans remains uncertain.

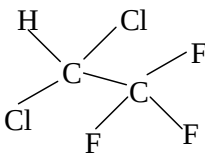
Exposure of the general public to HCFC-123 is minimal. There is a significant database on human exposure to varying concentrations of HCFC-123, but no information on exposure during its use as an intermediate. Processes where HCFC-123 is used as an intermediate are closed systems, and exposure should be much less than established occupational exposure limits. Nonetheless, there is the potential for occupational exposure during the manufacture of HCFC-123 and its use as an intermediate. Cases of dizziness, headache, and nausea following a single exposure to unknown levels of airborne HCFC-123 have been reported. The most relevant critical effects from a single, brief exposure to HCFC-123, such as from the discharge of a fire extinguisher, are CNS depression and an increased likelihood of adrenaline-induced cardiac arrhythmia.

The most critical effect resulting from repeated exposure to HCFC-123 was development of lesions in the liver, which have been reported in workers exposed to average air levels above 5 ppm (31 mg/m^3) for 1 to 4 months. Other reported cases of liver toxicity associated with repeated occupational exposures to HCFC-123 vapours lacked concurrent exposure measurement and adverse health effects were coupled with poor industrial hygiene practices. In all of the cases cited, the exposures were probably high. In exposure scenario models or re-created levels that cause liver effects, concentrations are much higher than established occupational exposure limits.

As noted in the WEEL Guide (AIHA, 2001), ‘A common theme for all of the documented human liver disease cases associated with HCFC-123 is the lack of concurrent exposure measurement with adverse health effects and poor industrial hygiene practices. In all of the cases cited, it is probable that exposures were very high for undetermined periods of time.’ In cases where the exposure scenario was modelled or re-created, levels that caused liver effects were much higher than established exposure limits when calculated or measured.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name:	1,1-Dichloro-2,2,2-trifluoroethane
IUPAC name:	Ethane, 2,2-dichloro-1,1,1-trifluoro-
Synonyms:	Arcton 123
	2,2-Dichloro-1,1,1-trifluoroethane
	Ethane, dichlorotrifluoro-
	F-123
	FC-123
	Fluorocarbon 123
	Freon 123
	Genetron 123
	HCFC-123
	HFA-123
	Propellant 123
	R-123
	Refrigerant 123
	Suva 123
CAS name:	Ethane, 2,2-dichloro-1,1,1-trifluoro-
CAS registry number:	306-83-2
EC (EINECS) number:	206-190-3
Formula:	$C_2HCl_2F_3$
Molecular mass	152.93
Chemical structure:	

2.2 EU classification and labelling

HCFC-123 is not classifiable according to the Dangerous Substances Directive 67/548/EEC and its subsequent amendments (EC, 2001).

2.3 Physical and chemical properties

HCFC-123 is a non-flammable, volatile, colourless liquid at room temperature and normal atmospheric pressure. It has a faint ethereal odour. HCFC-123 is slightly soluble in water. Physical and chemical data for HCFC-123 are given in Table 1.

Table 1: Physical and chemical properties

Property	Value, unit	Reference
Boiling point at 1,013 hPa	27.6°C	Du Pont, 2002
	27.9°C	Honeywell, 2000
Freezing point	–107°C	Honeywell, 2000
Relative density D_4^{25} at 21.1°C	1.46	Du Pont, 2002
(density of water at 4°C is 1,000 kg/m^3)	1.47	Honeywell, 2000
Viscosity at 20°C	No data	
Refractive index n_D at 20°C	No data	
Vapour pressure at 21.1°C	786 hPa [a]	Du Pont, 2002
at 25°C	896 hPa [a]	Honeywell, 2000
Vapour density (air = 1)	5.3	Du Pont, 2002
		Honeywell, 2000
Threshold odour concentration	No data	
Surface tension at 20°C	No data	
Solubility in water at 25°C	3.9 g/l	Du Pont, 2002
at 21.1°C	2.1 g/l	Honeywell, 2000
Solubility in organic solvents	Miscible with acetone, ethanol, vegetable oil and petroleum solvents	Du Pont, 1987
Partition coefficient, log K_{ow} (octanol/water) at 20°C	2.0 - 2.8	ECETOC, 1996
	2.3 - 2.9	NICNAS, 1996
	2.307 (estimated)	Honeywell, 2000
Partition coefficient, log K_{oc} (organic carbon/water) at 20°C	No data	
Henry's Law constant at 25°C	3,557 Pa·m^3/mol (4.3 g/l/bar)	ECETOC, 1996
	3,513 Pa·m^3/mol	Calculated [c]
	3,140 Pa·m^3/mol	Interpolated [d]
Flash point (closed cup)	None	Du Pont, 2002
		Honeywell, 2000
Flammability limits in air at 1,013 hPa, at ambient temperature	Non-flammable	Du Pont, 2002
		Honeywell, 2000
Flammability limits in air, up to 100°C	None [b]	Du Pont, 2002
		Honeywell, 2000
Explosion limits in air at 1,013 hPa, at ambient temperature	No data (not applicable)	
Auto-flammability, ignition temperature	770°C	Honeywell, 2000

[a] Reported, respectively, as 11.4 and 13 psia (pounds/inch^2) absolute pressure; 1 bar = 1,000 hPa = 14.5 psia

[b] However, mixtures of HCFC-123 with high concentrations of air at elevated pressure and/or temperature can become combustible. HCFC-123 can also become combustible in an oxygen enriched atmosphere

[c] Derived from Du Pont vapour pressure and solubility values: 89,600 Pa / 3,900 g/m^3 (or 25.50 mol/m^3)

[d] Between experimental measurements carried out as a function of temperature (Chang and Criddle, 1995)

Commercial HCFC-123 typically has a purity of ≥ 99.9. Common impurities are various other fluorocarbons, depending on the conditions of the production process (Section 3.1).

2.4 Conversion factors

Conversion factors for HCFC-123 concentrations in air at standard conditions (25°C and 1,013 hPa) are:

- 1 ppm = 6.251 mg/m^3
- 1 mg/m^3 = 0.160 ppm

In this report, converted values are given in parentheses.

The generic formula, from which the conversion factors for vapour concentrations in air are derived, is given in Appendix C. According to European standard conditions (20°C and 1,013 hPa) these would be: 1 ppm = 5.573 mg/m^3 and 1 mg/m^3 = 0.157 ppm.

2.5 Analytical methods

A method for analysis has been described for HCFC-123 that involves gas chromatography with dual flame ionisation detection (Rusch *et al*, 1994).

There are no validated methods for biological monitoring of HCFC-123, although urinary excretion of trifluoroacetic acid (TFA) has been used as an indicator of exposure (Tanaka *et al*, 1998).

3. PRODUCTION AND USE

3.1 Production

Possible routes for the production of HCFC-123 are hydrofluorination of tetrachloroethylene and hydro-dechlorination of 1,1,1-trichloro-2,2,2-trifluoroethane (CFC-113a). An estimate of the current worldwide, commercially available production volume of HCFC-123 is not available, but total emissions are assumed to be 2.5 kt/y at most by 2010 (Section 4.1).

The manufacture, import and export of HCFC-123 and other hydrochlorofluorocarbons are regulated under the Montreal Protocol on Substances that Deplete the Ozone Layer. These should be phased out, virtually (95.5% relative to a 1996 cap) by 2020, in all signatory states, and completely by 2030, in countries that have ratified the Copenhagen Amendment to the Montreal Protocol. For information on the Montreal Protocol and subsequent amendments, see UNEP (2000).

3.2 Use

The principal use for HCFC-123 is as a substitute refrigerant for trichlorofluoromethane (CFC-11) in commercial and industrial air-conditioning installations, in gaseous fire extinguishers, as a foam-blowing agent, and in metal and electronics cleaning. These uses are primarily as a temporary replacement for chlorofluorocarbons and bromofluorocarbons phased out pursuant to the 1987 Montreal Protocol.

HCFC-123 may also be used as a chemical intermediate in the production of trifluoroacetyl chloride, various agricultural chemicals, HCFC-124 and HFC-125.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, TRANSFORMATION AND IMPACT

4.1 Sources

There is no known natural source of HCFC-123. Emissions of HCFC-123 will occur from its use in the different applications (Section 3.2).

The worldwide emission of HCFC-123 is estimated to reach 2.5 kt/y at most by 2010 (Calm *et al*, 1999).

Yokouchi *et al* (2005) estimated HCFC-123 emissions from Japan based on measurements of the enhancement of concentrations in boundary-layer air compared to the free troposphere. Using chlorodifluoromethane (HCFC-22) as a reference compound for which the emissions are assumed to be known, the annual emissions of HCFC-123 in 2002-2003 were estimated to be 40 to 50 t/y, compared to a value of 70 t/y taken from the OECD Pollutant Release and Transfer Register 2002 – Japan, 2004.

4.2 Environmental distribution

The environmental partitioning of HCFC-123 has been assessed (Libre, 2004) using the equilibrium criterion (EQC) Level I and III models (Mackay *et al*, 1996). The Level I model calculates the partitioning at equilibrium between the different environmental media (air, water, soil, sediment) for a fixed quantity of a supposedly non-degradable substance introduced into an evaluative environment (Table 2).

In the Level III EQC simulation, continuous amounts are emitted to air and water, while degradation is taken into account. Thus, the Level III model yields the stationary partitioning of a substance in each compartment, as shown in Table 2 for HCFC-123. The calculations were based on the physical properties listed in Table 1 and a lifetime of 1.3 year, corresponding to a half-life of 0.9 year (Section 4.3).

Table 2: Partitioning (%) into the environment (Libre, 2004)

Compartment	EQC Level I	EQC Level III [a]
Air	99.9	47.2
Water	0.085	50.4
Soil	0.015	2.064
Sediment	0.000335	0.323

[a] Assuming equal emissions to air, water and soil

The Level I results show that HCFC-123 would preferentially stay in the air compartment. Level III modelling indicates almost equal partitioning between air and water, and a small fraction to soil, due to the resistances to inter-media transfer (in particular from water to air) introduced in the Level III model.

4.3 Atmospheric lifetime [a]

The atmospheric degradation of HCFC-123 occurs mainly in the troposphere, being initiated by attack of naturally occurring hydroxyl radicals. A few percent of ground-level emissions will reach the stratosphere and be degraded there by photolysis and reaction with hydroxyl radicals. The latest estimation of HCFC-123 atmospheric lifetime is 1.3 years (WMO, 2002), corresponding to a half-life of 0.9 year.

4.4 Ozone depleting potential

Ozone depleting potentials (ODPs) express the stratospheric ozone loss due to emission of a unit mass of a given compound, divided by the ozone loss due to emission of the same mass of a reference compound. Trichlorofluoromethane (CFC-11) is used as a reference compound.

The most recent model calculation for the ODP of HCFC-123 is 0.012 (WMO, 1999). Since 1992 semi-empirical model calculations have been considered more reliable and were introduced in the revision of the Montreal Protocol (Copenhagen amendment). The semi-empirical ODP value for HCFC-123 is 0.02, i.e. 2% of that of CFC-11 (WMO, 2002) and this is the official value for the Montreal Protocol.

4.5 Global warming potential

The global warming potential (GWP) of a greenhouse gas is the time-integrated radiative forcing resulting from emission to the atmosphere of a unit mass of a given substance, divided by the same quantity calculated for a reference substance. The radiative forcing is the additional earthward infrared radiation flux arising from the presence of the substance in the atmosphere. The GWP calculation is performed for a given 'integration time horizon (ITH)'. Depending on the reference substance, the ITH may be chosen to be finite (e.g. for CO_2) or infinite (e.g. for CFC-11). Today, GWP values are almost invariably expressed relative to CO_2, for an ITH of 100 years.

[a] The 'lifetime' is the time necessary for 63% degradation; it is equal to the 'half-life' divided by ln2 (= 0.69)

In the latest scientific assessment on ozone (WMO, 2002) a value of 76 has been calculated using the most recent data on lifetime and radiative forcing efficiency of HCFC-123.

4.6 Tropospheric ozone formation

Due to its low atmospheric reactivity, HCFC-123 is not a significant contributor to ground ozone formation. Its photochemical ozone creation potential has been calculated to be 0.3 by reference with 100 for ethylene (Hayman and Derwent, 1997).

4.7 Degradation mechanism and products

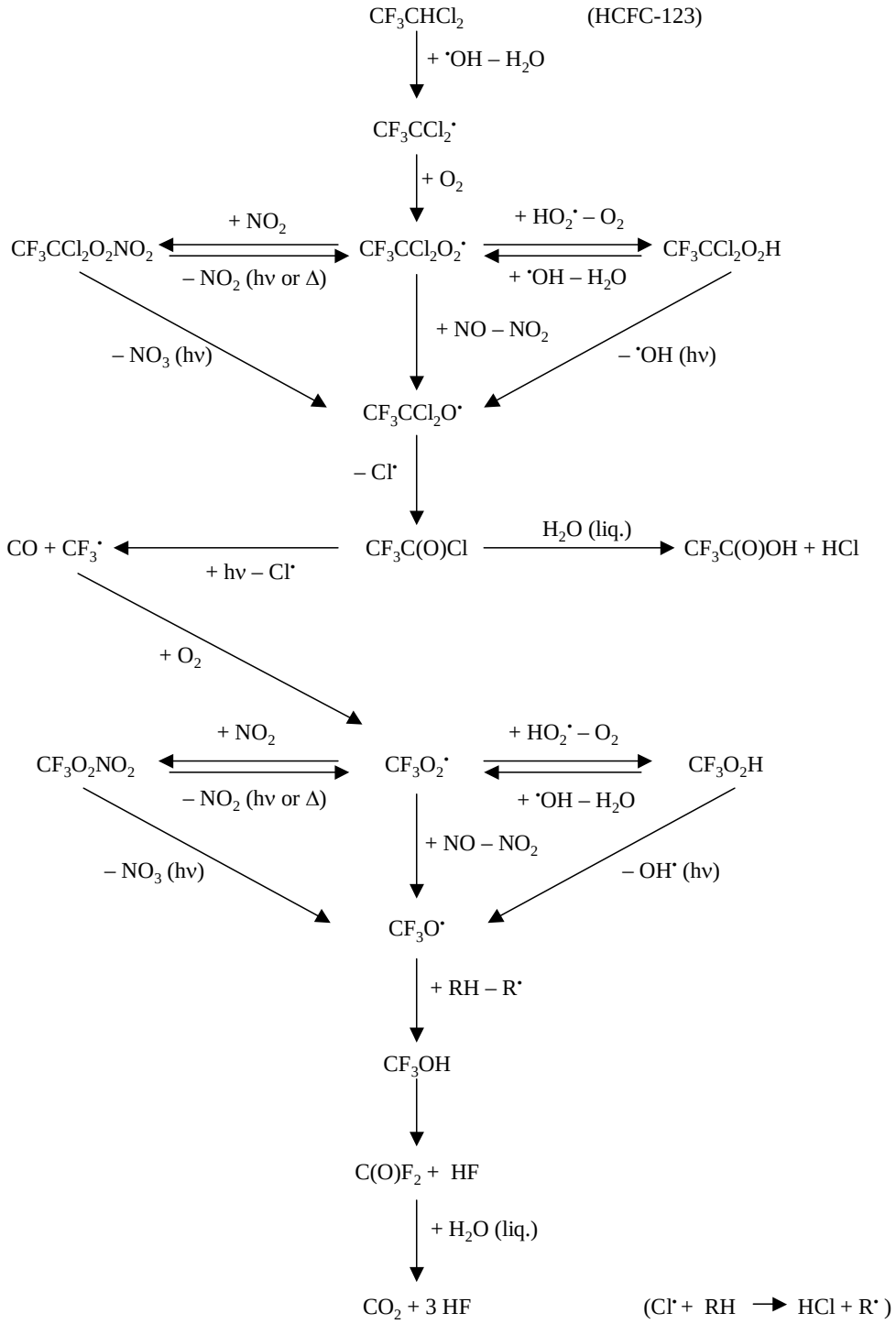
Support for the basic tropospheric degradation mechanism for HCFC-123 proposed by WMO (1989a) has been provided by several laboratory studies (Edney *et al*, 1991; WMO, 1991; WMO, 1994; Tuazon and Atkinson, 1993; Hayman *et al*, 1994).

Breakdown of HCFC-123 in the troposphere (Figure 1) will be initiated by OH radicals and will proceed via various free-radical and short-lived molecular intermediates to give HCl and CF_3COCl. The latter molecules are expected to be removed from the atmosphere within a few days to a few months by uptake into clouds, rain and the oceans, CF_3COCl then being rapidly hydrolysed to TFA and HCl (AFEAS, 1992).

Photolysis of CF_3COCl will compete to some extent with its hydrolysis and will ultimately lead to CO, CO_2, HCl and HF. It has been estimated that the fraction of CF_3COCl photolysed is about 25 to 40% (Rodriguez *et al*, 1993; Hayman *et al*, 1994).

Although peroxynitrates ($CF_3CCl_2O_2NO_2$, $CF_3O_2NO_2$) and hydroperoxides ($CF_3CCl_2O_2H$, CF_3O_2H) may be formed during the degradation of HCFC-123, they are not thought to play a significant role in its atmospheric chemistry, probably being rather short-lived intermediates.

Figure 1: Tropospheric degradation mechanism



[a] NO_2, NO and NO_3, free radicals
[b] R, alkyl

4.8 Contribution of degradation products to environmental chloride, fluoride and trifluoroacetate and to the acidity of rainwater

Assuming an atmospheric release and degradation rate of 2.5 kt HCFC-123 per year (conservative upper limit, Section 4.1), conversion of two thirds of the latter into TFA + 2 HCl and one-third into CO_2 + 2 HCl + 3 HF, followed by uniform scavenging of the acids produced into the global average rainfall of 5 x 10^{11} kt/y, it follows that the levels of chloride, fluoride and the acidity thus formed are low compared with those arising from other known sources:

- Chlorine yield from 2.5 kt/y HCFC-123 would be 1.2 kt/y, i.e. insignificant compared with the natural atmospheric chloride flux of roughly 1 x 10^7 kt/y, mainly arising from sea-salt aerosols (WMO, 1989a).
- Fluoride production would be 0.3 kt/y, i.e. very small compared with the estimated atmospheric fluoride flux of 1,000 to 8,000 kt/y (WMO, 1989b); the contribution of HCFC-123 to the fluoride concentration in rainwater would be 0.6 ppt by weight (0.6 pg/l). This should be compared with typical fluoride concentrations in 'background' rainwater of around 10 ppb by weight (10 ng/l), i.e. 17,000 times greater, and with levels of about 1 ppm by weight (1 µg/l) used for the fluoridation of drinking water, i.e. 1,700,000 times greater (WMO, 1989a).
- The HCl, HF and TFA acids formed from HCFC-123 and scavenged in rainwater would represent an acidity of 6 x 10^7 mol H^+/y, i.e. 170,000 times less than the acidity arising from natural and anthropogenic emissions of SO_2 and NO_x (UK-RGAR, 1990). Thus, the contribution of 2.5 kt/y HCFC-123 to acid rain would be negligible.

The contribution of HCFC-123 to trifluoroacetate in rainwater would be 2.5 ppt by weight (2.5 pg/l). Extensive environmental studies on the possible impact of TFA on the environment have been conducted by AFEAS (Alternative Fluorocarbon Environment Acceptability Study). The results of these studies were used to conduct a risk assessment of TFA impact on the environment and humans (Boutonnet *et al*, 1999). No expected adverse effects are foreseen from the contribution of CFC replacements (including HCFC-123) on the environment or humans. Moreover, it has been confirmed that TFA is a naturally occurring substance homogeneously present in ocean waters at concentrations of 200 ng/l, down to 4,000 m, which corresponds to an environmental burden of about 268 millions of tonnes of TFA (Frank *et al*, 2002). A more detailed discussion of those studies is presented in Section 4.3.3 of ECETOC (2005).

4.9 Biodegradability

To assess its biodegradability potential, a sample of HCFC-123 was incubated with activated sludge in a sealed bottle for 28 days. It was estimated that 24% of the compound had degraded during that time (Jenkins, 1992a). Aerobic degradation by the methanotrophic bacterium

Methylosinus trichosporium was not detected (De Flaun *et al*, 1992). When using a mixed culture (MM1), a slow methanotrophic biotransformation occurred (Chang and Criddle, 1995). Berends *et al* (1999) reported the biodegradation of a number of fluorocarbons including HCFC-123 in closed bottle test system to be less than 60% after 28 days. These results indicate that HCFC-123 is not readily biodegradable.

Microbial transformation involving reductive dechlorination to 2-chloro-1,1,1-trifluoroethane was observed in anoxic freshwater and salt-marsh sediments, whereas no degradation was observed in aerobic soils (Oremland *et al*, 1996).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

HCFC-123 was detected in non-urban ambient air in Australia at levels less than 0.01 ppt (62.5 pg/m^3) (Fraser, 1994 cited by IPCS, 2000). WMO (2002) cites a value of 0.03 ppt (0.19 pg/m^3) for air sampled at Cape Grim (Tasmania) in 1996.

Other data on background air levels indicate a mean baseline value of 0.12 ppt (0.75 pg/m^3) at Cape Grim during the second half of 1998 (Sturrock *et al*, 2001) and an annual mean of 1.06 ppt (6.63 pg/m^3) for 2002 at the Zeppelin Mountain station Svalbard (Spitzbergen), Norway (Stordal *et al*, 2003).

Information on levels of HCFC-123 in water, wildlife or food is not available.

5.2 Consumer exposure

HCFC-123 is used as a blowing agent in polyurethane foam insulation of refrigerators.

Indirect exposure via the environment is low as the concentration in ambient air is less than 0.01 ppt (62.5 pg/m^3), and HCFC-123 is unlikely to persist in other media because of its limited solubility and high volatility. Therefore, exposure of the general population to HCFC-123 is expected to be minimal.

5.3 Occupational exposure

There is potential for occupational exposure, predominantly via inhalation, during the manufacture of HCFC-123 and the manufacture and use of products containing HCFC-123. This includes the operation and maintenance of air-conditioning installations running on HCFC-123, the discharge of the chemical from fire protection systems, and the use of liquid in metal and electronic cleaning.

In an HCFC-123 manufacturing plant in Canada, two operators monitored over 165 to 480 minutes on 4 separate days had time-weighted breathing-zone levels of HCFC-123 ranging from 1.16 to 8.94 ppm (7.25 - 55.9 mg/m^3). On one occasion, a drum-filling lance failure resulted in a level in excess of 33 ppm (206 mg/m^3) (Du Pont, 1999 cited by IPCS, 2000). No monitoring data were available for the manufacture of products containing HCFC-123.

Several studies have measured HCFC-123 levels in chiller machinery rooms during normal operations as well as maintenance and repair activities. In four of twelve un-manned machinery rooms containing air-conditioning, equipment running on HCFC-123, air levels were below 1 ppm (6.25 mg/m^3) (4-h TWA) at three sites. At one site, where samples were taken near a leak and a half-empty HCFC-123 drum, levels of 5.9 to 13.6 ppm (36.9 - 85.0 mg/m^3) (20-min TWA) were recorded. At the other eight sites, machinery room air levels were below the limit of detection of 0.2 to 0.4 ppm (1.3 - 2.5 mg/m^3) (Trane Company, 1991 cited by IPCS, 2000).

Breathing-zone levels of HCFC-123 during routine chiller maintenance operations, including refrigerant transfer, were measured at nine US installations. Two-hour to 12-hour TWA concentrations were less than 1 ppm (6.25 mg/m^3) in five cases, less than 2 ppm (12.5 mg/m^3) in 3 cases, and in the range of 2 to 5 ppm (12.5 - 31.3 mg/m^3) in one case (MRI, 1991; Sibley, 1992; Trane Company, 1992; all cited by IPCS, 2000).

In Australia, 4- to 6-hour TWA concentrations were less than 1 ppm (6.25 mg/m^3) during repair work at a single installation. In these studies, continuous area monitoring showed TWA air concentrations below 1 ppm (6.25 mg/m^3), with activity-related instantaneous peaks ranging from 30 to 500 ppm (188 - 3,125 mg/m^3) (NICNAS, 1996 cited by IPCS, 2000).

Air levels resulting from the use of a fire extinguisher containing 93% HCFC-123 were measured during fire control exercises in which the fire fighters wore a self-contained breathing apparatus. Outdoor discharge resulted in maximum breathing-zone levels ranging from 7 to 870 ppm (44 - 5,440 mg/m^3), depending on the type of fire hazard. Inside an aircraft hangar, the discharge of hand-held extinguishers resulted in a breathing-zone concentration of 20 ppm (125 mg/m^3) during discharge, with average static air levels ranging from 29 to 114 ppm (181 - 713 mg/m^3) over the following 30 minutes. With a large semi-portable fire extinguisher, breathing-zone concentrations during discharge reached 180 to 300 ppm (1,125 - 1,880 mg/m^3), whereas average static air levels ranged from 165 to 557 ppm (844 - 3,482 mg/m^3) over the following 30 minutes (MRI, 1993a,b cited by IPCS, 2000).

In the US, a factory which converted to using HCFC-123 in its degreaser operations, showed 5.5-hour TWA levels of HCFC-123 that ranged from 5.3 to 12.0 ppm (33.1 - 75.0 mg/m^3) throughout the facility (personal and area samples were taken). Charging and unloading the degreaser resulted in short-term breathing-zone levels ranging from 160 to 460 ppm (1,000 - 2,875 mg/m^3). Some employees developed elevations of serum hepatic enzyme levels. These effects were reversed when the use of HCFC-123 was discontinued (Boucher *et al*, 2003).

As noted in the WEEL Guide (AIHA, 2001), ‘A common theme for all of the documented human liver disease cases associated with HCFC-123 is the lack of concurrent exposure measurement with adverse health effects and poor industrial hygiene practices. In all of the cases cited, it is

probably that exposures were very high for undetermined periods of time.' In cases where the exposure scenario was modelled or re-created, levels that caused liver effects were much higher than established exposure limits when calculated or measured. Boucher *et al* (2003) measured exposure levels of up to 460 ppm (2,875 mg/m^3) for brief time periods (21 minutes) and modelling suggested that levels could have been as high as 252 to 1,630 ppm (1,575 - 10,190 mg/m^3). However, most 8-hour TWA samples were in the range of 5 to 12 ppm (31.2 - 75 mg/m^3). Shin *et al* (2002a) have subsequently developed a sampling and analytical method for HCFC-123 in the workplace atmosphere; the method meets NIOSH sampling and analytical criteria. Liver toxicity has not been reported in workers where appropriate industrial hygiene measures and/or personal protective equipment has been used to ensure compliance with the 50 ppm (310 mg/m^3) 8-hour TWA exposure limit set by the AIHA WEEL Committee.

Shin *et al* (2002b) investigated four factories in South Korea that manufactured large-sized industrial air-conditioners. In the study, conducted in 1998, 12 male workers (27 - 47 years old) intermittently exposed between 1.2 to 17.5 years (mean 6.8 ± 5.3) were investigated. The geometric mean 8-hour TWA levels at the first and second factory were 2.2 ppm (range 0.89 - 4.2 ppm) (12.5, 5.56 - 26.3 mg/m^3) and 32.5 ppm (range 4.9 - 113.9 ppm) (203, 30.6 - 712 mg/m^3). The authors estimated that the levels at the other two factories were lower than the reported for the first two. There were no adverse health effects noted and liver function was within the normal range in all exposed workers. The levels of aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transferase in blood were used as indicators of liver function / dysfunction. The authors conclude that liver damage did not occur at exposure levels less than 32.5 ppm (8-h TWA) HCFC-123.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Micro-organisms

No data are available.

6.2 Aquatic organisms

The effects of HCFC-123 on the growth of the unicellular green alga, *Selenastrum capricornutum*, were determined over a period of 96 hours. The measured concentrations causing a 50% reduction in growth rate and biomass were 96.6 mg/l (nominal concentration 736 mg/l) and 67.8 mg/l (nominal concentration 476 mg/l), respectively. The wide difference between measured and nominal concentration is probably reflective of the low solubility and high volatility of the compound (Jenkins, 1992b).

With the water flea, *Daphnia magna*, the mean measured concentration causing a 50% reduction in activity during a 48-hour exposure was 17.3 mg/l. There were no significant effects on mobility at 2.24 mg/l (Jenkins, 1992c).

In a study with rainbow trout (*Salmo gairdneri*), fish were exposed under semi-static conditions to HCFC-123 (purity not specified) in sealed vessels at nominal concentrations of up to 133 mg/l (measured 90.6 mg/l). No lethality occurred at concentrations below 33.3 mg/l (measured), while 100% lethality occurred at the highest concentration measured (90.6 mg/l). Treatment-related effects were seen at all exposure levels. Fish exhibited darkened pigmentation, lethargic behaviour and loss of co-ordination. The no-observed-effect concentration (NOEC) was < 15.3 mg/l (mean, measured). Since lethality was not progressive during the test, an asymptotic LC_{50} was thought to have been attained (Jenkins, 1992d) (Table 3).

Table 3: Lethality to rainbow trout (Jenkins, 1992d)

Parameter	Duration	Concentration	
		Nominal (mg/l)	Measured (mg/l)
LC_0	96	42.5	33.3
LC_{100}	96	133	90.6
LC_{50}	24	83.5	64.1
LC_{50}	48	69.2	59.4
LC_{50}	72	65.4	55.5
LC_{50}	96	65.4	55.5
NOEC	96	< 13.3	< 15.3

Berends *et al* (1999) also reported the above data for algae, *D. magna* and rainbow trout in comparison with data for other HFCs and HCFCs.

The above studies indicate low to moderate toxicity to environmental organisms.

6.3 Terrestrial organisms

No data are available.

7. KINETICS AND METABOLISM

7.1 Animal studies

7.1.1 Absorption

Dose-dependent increases in urinary fluoride levels were observed in 90-day inhalation studies with rats and dogs and in the 2-year inhalation study with rats indicating that absorption and some metabolic transformation of HCFC-123 occurred in these species (Section 8.3 and 8.5).

The partition coefficients of HCFC-123 in various tissues have been determined by a number of investigators (Dekant, 1994; Loizou *et al*, 1994; Vinegar *et al*, 1994) utilising the vial-equilibration method of Gargas *et al* (1989). Based on the results of these studies, HCFC-123 was less lipophilic than halothane (2-bromo-2-chloro-1,1,1-trifluoroethane, HCFC-123B1), the bromine analogue.

Because of its lipophilic characteristics, however, absorption would be expected to occur readily. Indeed, studies by several investigators (below) indicate that HCFC-123 absorption occurs rapidly. The partition coefficients for HCFC-123 are shown in Table 4.

Table 4: Partition coefficients in rats [a]

Partition between:	Coefficient
Blood/Air	4.06
Liver/Air	1.15
Lean tissue/Air	1.20
Fat/Air	15.4

[a] From Dekant (1994), Loizou *et al* (1994) and Vinegar *et al* (1994)

Male and female Sprague-Dawley rats were exposed for 6 hours to HCFC-123 starting concentrations of 500, 1,000, 2,000, 3,000, 4,000 or 5,000 ppm (3,126, 6,250, 12,500, 18,800, 25,000 or 31,300 mg/m^3). Uptake was measured as the loss of HCFC-123 from a recirculating inhalation chamber by gas chromatography. A PBPK model to describe the uptake, distribution and metabolism was constructed with the Advanced Continuous Simulation Language program (Loizou *et al*, 1994; Dekant, 1994). The data were fitted to the model. The kinetic constants obtained from this modelling are shown in Table 5.

Table 5: Metabolic constants [a]

Metabolic constant	Male rats	Female rats
Vmax (mg/h)	2.34	2.34
Vmax (mg/kg/h)	7.20 ± 0.28	7.97 ± 0.30
Km (mg/l)	1.2	1.2

[a] From Loizou *et al* (1994)

A single saturable component model best described the uptake of HCFC-123, although the model did not accurately predict the uptake in female rats at HCFC-123 concentrations of greater than 4,000 ppm. First order kinetics describe the uptake at lower concentrations, whereas a transition to zero order uptake appears to occur at about 4,000 ppm. This concentration limiting process may be by suppression of metabolism (Vinegar *et al,* 1994), or due to a perfusion limiting process in tissues, e.g. liver.

In another study by Dekant (1994), male Sprague-Dawley rats and male Hartley guinea pigs were exposed by inhalation to ^{14}C-radiolabelled HCFC-123 for 6 hours at a concentration of 4,000 ppm (25,000 mg/m^3). This investigator measured the disappearance of HCFC-123 from the inhalation chamber and found that approximately 50 to 60% of the radiolabelled material was lost from the chamber of exposed rats, whereas about 95% of the applied dose was lost from the chamber of exposed guinea pigs. Only 20 to 30% of the applied radiolabel was recovered in these studies and, in the absence of a mass balance, the loss of the remaining radiolabel was unknown but presumably absorbed.

In separate studies, Dodd *et al* (1993) and Vinegar *et al* (1994) exposed Fischer 344 rats to HCFC-123 concentrations of 100 to 10,000 (625 - 62,500 mg/m^3) for 2 to 6 hours. Vinegar *et al* (1994) reported that the uptake of HCFC-123 was biphasic with a rapid initial uptake over 30 to 45 minutes followed by a slower absorption phase. Both groups of investigators also indicated that uptake reached saturation at concentrations greater than 2,000 ppm (12,500 mg/m^3), a finding consistent with Dekant (1994). As the concentration approached 10,000 ppm, there appeared to be a suppression of the production of TFA. Concurrent with the uptake of HCFC-123, TFA blood concentrations rose during exposure to the compound (Vinegar *et al,* 1994). Following a 4-hour exposure to 1,000 ppm (6,250 mg/m^3), the HCFC-123 and TFA blood concentrations were about 15 and 93 mg/l, respectively. However, by the end of the 4-hour exposure to an HCFC-123 concentration of 10,000 ppm, the HCFC-123 and TFA blood concentrations were about 94 and 38 mg/l, respectively. These data suggest that at 10,000 ppm suppression of the oxidative metabolic pathway occurs, apparently due to substrate inhibition and not to killing of the metabolic enzyme. Indeed less than 24 hours later, the TFA blood concentrations rebounded and approached 100 mg/l at the exposure concentration of 10,000 ppm. Since the reversible inhibition of metabolising enzyme by HCFC-123 results in lower TFA concentrations, it is reasonable to

assume that as HCFC-123 related inhibition declines, the TFA concentrations will rebound. This is because TFA is formed only as HCFC-123 is metabolised.

7.1.2 Distribution

Dodd *et* al (1993) reported that following a 2-hour exposure to HCFC-123 at a concentration of 10,000 ppm (62,500 mg/m^3) to Fischer 344 or Sprague-Dawley rats, the material was detected in all tissues sampled (tissues were not identified). At 24 hours post-exposure, small amounts of metabolites (not identified) were detected in the liver, kidney, muscle and skin.

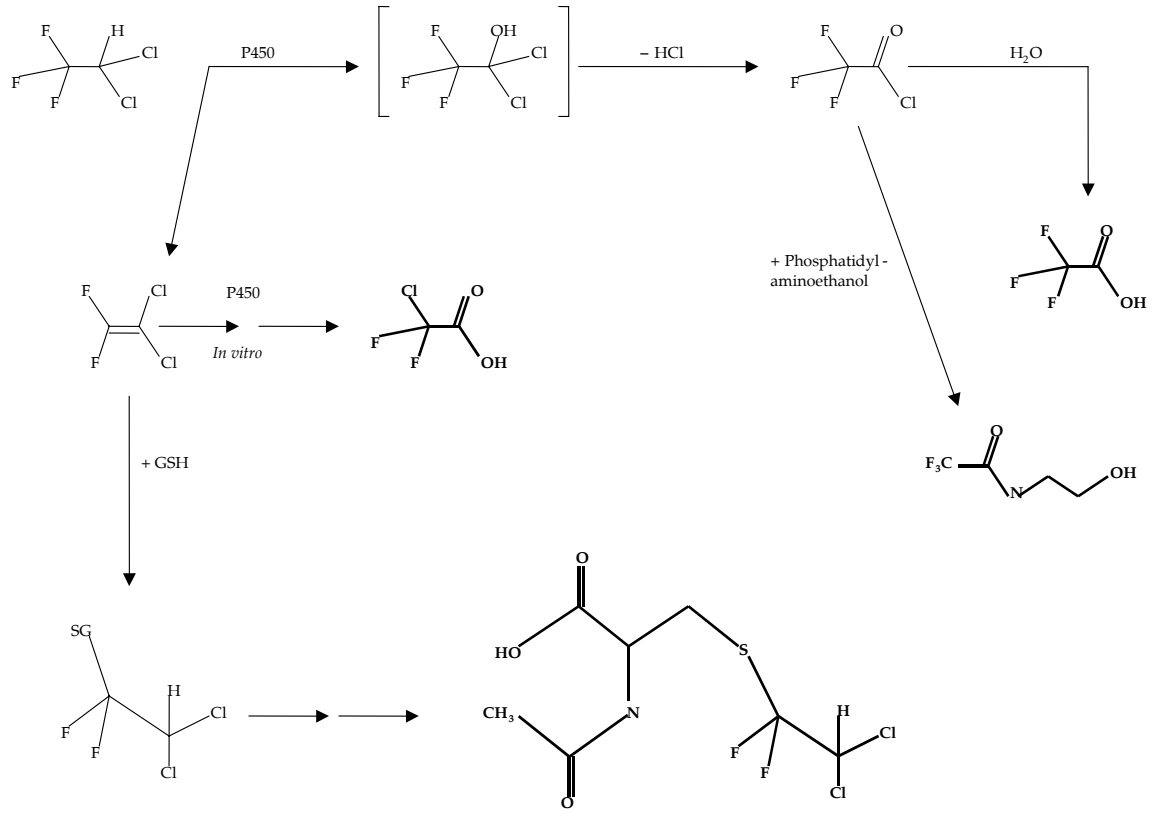
Dekant (1994) examined the tissue and organ distribution of ^{14}C-HCFC-123 in 2 male Sprague-Dawley rats or 2 male Hartley guinea pigs exposed by inhalation to ^{14}C-HCFC-123 at a concentration of 4,000 ppm (25,000 mg/m^3) for 6 hours. After the exposure, the animals were placed in glass metabolism cages and excreta collected for 48 hours. The animals were subsequently killed and radioactivity determined in selected tissues and organs.

After 48 hours, only low levels of radioactivity remained in the organs and tissues. Low amounts of radioactivity (pmol/mg protein) were bound to plasma proteins and erythrocytic proteins. Guinea pigs showed a greater variation in this binding than rats. In both species, the liver contained the highest concentration of radioactivity, representing 5- to 10-fold higher levels than those found in other tissues and organs. HCFC-123 is rapidly removed from the fatty tissue and none would be expected 48 hours post-exposure. The metabolite, trifluoroacetate, can bind with liver protein and therefore the label will be found in the liver. Protein binding and partitioning are separate physical phenomena. Partitioning is independent of concentration or protein binding and therefore the greater binding of HCFC-123 radioactive material (probably TFA) is not related to partitioning of HCFC-123 in lipid tissue.) The kidney and lung contained lower concentrations of radioactivity, but still somewhat higher than the other organs examined (testes, brain, pancreas and spleen).

7.1.3 Metabolism

Routes of metabolism for HCFC-123 are shown in Figure 2.

Figure 2: Oxidative metabolic pathways [a] (after Dekant, 1994)



[a] Metabolic pathways of HCFC-123 in rats *in vivo* and in rat liver microsomes; metabolites identified are emboldened.

In vitro

Dekant (1994) and Urban *et al* (1994) examined the metabolism of HCFC-123 in rat and human liver microsomal fractions. The final concentration of HCFC-123 in the microsomal fractions was 3.3 mmol/l (4.32 µmol in final volume of 1.3 ml); the actual exposure concentration, relevant for the determination of rate constants, is unknown since the air/microsomal partition coefficient was unknown. In these studies, TFA was the primary metabolite that was oxidatively formed. In the absence of NADPH or with the use of heat inactivated microsomes, only a small amount of TFA was observed, indicating the involvement of cytochrome P450. Chlorodifluoroacetic acid (a minor metabolite), inorganic fluoride and a minor unidentified metabolite were also detected in both rat and human liver microsomal fractions. In human cells, the microsomal oxidation of HCFC-123 was significantly greater than in rats (about 10 times).

These investigators also examined the effects of inducing and inhibiting cytochrome P450 on the metabolism of HCFC-123. In these studies, rats were pre-treated with either ethanol (10%, w/v) in drinking water for 10 days or intraperitoneally (*i.p.*) with pyridine (100 mg/kgbw) once daily for 4 consecutive days. With pre-treatment, the rate of TFA formation was increased approximately 10-fold compared to control values. Inclusion of diethyldithiocarbamate (300 µmol/l), a cytochrome P450 inhibitor, into the microsomal reaction inhibited induction of TFA formation by approximately 60%. A similar inhibition of TFA formation was observed with human microsomes. These results suggested that HCFC-123 was metabolised by a specific isoenzyme of cytochrome P450 known as cytochrome P450 2E1. In humans, there was considerable heterogeneity among liver specimens. In the rat, relatively high concentrations of P450 2E1 and P450 281/2 were identified in the liver, compared low levels in the lung and kidney. No cross-reactivity was observed in the testes or pancreas.

Godin *et al* (1993) examined the *in vitro* metabolism of HCFC-123 in rat liver microsomal preparations by varying the concentration of oxygen to simulate anaerobic metabolism. At 0% oxygen concentrations, HCFC-133a (2-chloro-1,1,1-trifluoroethane) was detected. When microsomes from rats treated with either phenobarbital (0.1% solution in drinking water for 7 days) or pyridine (200 mg/kgbw *i.p.* for 4 days) were utilised, an increase in HCFC-133a formation, compared to controls, occurred at oxygen concentrations of 2 to 5%. However, no HCFC-133a formation was evident in either control or induced microsomes at oxygen concentrations greater than 5%. Another microsomal metabolite, 2-chloro-1,1-difluoroethylene was also detected, but only in induced microsomes at 0% oxygen concentrations. Under low oxygen anaerobic (5% O_2, 95% argon) conditions *in vitro*, Dekant (1994) and Urban *et al* (1994) found no volatile metabolites.

In separate studies presented in an abstract, HCFC-123 (1 - 20 mmol/l, final concentrations) was incubated with rat liver microsomal preparations from either phenobarbital or pyridine induced microsomes (Ferrara *et al*, 1995). The formation of reactive intermediates was studied by measuring the depletion of added glutathione . After 30 minutes of incubation, a 32 to 47% loss of added glutathione was observed with phenobarbital-induced microsomes. The loss was dose-dependent. With pyridine-induced microsomes, a 57 to 65% loss was observed, but no dose dependency was observed.

Saturating concentrations of carbon monoxide or N-*tert*-butyl-α-phenyl nitrone (a free radical scavenger) afforded nearly complete protection from glutathione loss in both phenobarbital and pyridine induced microsomes at 20 mmol HCFC-123/l. These data suggested that HCFC-123 under anaerobic conditions might be reductively metabolised to reactive intermediates that inactivate cytochrome P450, either P450 2E1 or P450 2B.

The formation of the oxidative metabolite, TFA, has been observed in all metabolic studies conducted with HCFC-123. In the studies of Godin *et al* (1993), TFA formation was detected in microsomal preparations from control and induced animals, and at oxygen concentrations of 0%, 2%, 5% and 21%. The amount of TFA formation at 0% oxygen levels was low (0.07 ± 0.05 nmol/3 min/mg protein). At higher oxygen concentrations, TFA was formed in much higher quantity. However, the TFA amounts were not significantly different one from another between 2, 5 and 21% oxygen. Both pyridine and phenobarbital induced microsomes increased the levels of TFA production, although the increase in TFA was not significant with increasing levels of oxygen concentrations. These data indicate that oxidative metabolism of HCFC-123 to TFA is a saturable process at low oxygen concentrations. The same authors showed that small changes in oxygen concentrations might have a greater influence on the formation of reductive metabolites than on oxidative metabolites (see above description of reductive metabolism).

In another study, the metabolism of HCFC-123 in microsomes prepared from rat kidney and liver was examined (Huwyler *et al,* 1992). In this study, the release of Cl was measured as reflecting the metabolism of HCFC-123. Compared to liver metabolism, the kidney was a poor metabolic tissue with the metabolic capacity being approximately 10-fold less than the liver. The authors did not attempt to identify any metabolites.

In vivo

Loizou *et al* (1994) examined the *in vivo* metabolism of HCFC-123 in rats. In this study, male and female Sprague-Dawley rats were exposed (whole-body) once for 6 hours to starting concentrations of 500, 1,000, 2,000, 3,000, 4,000 or 5,000 ppm (3,125, 6,250, 12,500, 18,800, 25,000 or 31,200 mg/m^3). After exposure, the animals were transferred to metabolism cages and urine was collected for determination of TFA. There were no sex-related differences in formation of TFA, but there was a dose-dependent increase in the amount of TFA formed. This increase in TFA formation was also reported by Dodd *et al* (1993). In the latter study, Fischer 344 or Sprague-Dawley rats were exposed nose-only for 2 hours to an HCFC-123 concentration of 1,000 ppm. No strain differences in TFA formation were observed, and TFA was found to be the most abundant metabolite. Blood level saturation of TFA appeared by the end of 4 hours exposure at all concentrations. In addition, the reductive metabolites HCFC-133a and 2-chloro-1,1-difluoroethylene were identified in the liver and HCFC-133a was also identified in the kidney of the exposed rats (Vinegar *et al,* 1994). Metabolism appears to reach saturation with exposures in the range of 1,000 to 2,000 ppm (Dodd *et al,* 1993), although Loizou *et al* (1994) reported that metabolic saturation occurs at about 3,000 ppm.

Dekant (1994) also examined the *in vivo* metabolism of HCFC-123. In this study, 2 male Sprague-Dawley rats and 2 male Hartley guinea pigs were exposed whole-body for 3 hours to

2,000 ppm (12,500 mg/m^3) of ^{14}C-HCFC-123. After 3 hours, a second injection into the chamber of ^{14}C-HCFC-123 was made; the total exposure duration was 6 hours. TFA was the major metabolite for both species. In rats, approximately 25% of the administered radiolabel was recovered in the urine as TFA. In the guinea pig about 20 to 30% of the administered label appeared in the urine as TFA. Other minor metabolites were also detected. One metabolite identified was N-acetyl-S-(2,2-dichloro-1,1-difluoroethyl)-L-cysteine, which can be formed through reductive metabolism of HCFC-123, possibly to 1,1-dichloro-2,2-difluoroethene, and conjugation with glutathione, a metabolic process observed *in vitro* (Ferrara *et al*, 1995). In addition, N-trifluoroacetyl-2-aminoethanol was also identified in the urine of rats and guinea pigs. Two other minor metabolites were only identified in urine collected in the first 24 hours. TFA was identified in the urine collected throughout the 48-hour collection period.

Dekant (1994) and Loizou *et al* (1994) pre-treated rats *i.p.* with diallyl sulphide, a cytochrome P450 2E1 inhibitor (Brady *et al*, 1988), at doses of 10, 20 or 50 mg/kgbw 14 hours prior to a 6-hour exposure to HCFC-123 at a concentration of 1,000 ppm. A dose-dependent reduction in HCFC-123 uptake was observed, with a significant reduction occurring at 20 and 50 mg/kgbw of diallyl sulphide. Further, a dose-dependent reduction in urinary TFA excretion (22% at 50 mg/kgbw) was observed, providing further evidence of the involvement of cytochrome P450 2E1 in the metabolism of HCFC-123.

7.1.4 Elimination

Data from pharmacokinetic and biotransformation studies with HCFC-123 and the urinary excretion of TFA indicate that hepatic elimination is the rate limiting step in the biotransformation of HCFC-123.

The major route of elimination was rapid exhalation of unchanged HCFC-123. This route eliminated about 90% or more. Within a period of 8 hours, 98% of inhaled HCFC-123 was cleared from the blood. This is in agreement with the disappearance of clinical symptoms after about 15 minutes of cessation of exposure. The majority of metabolised HCFC-123 was excreted as TFA in the urine (Vinegar *et al*, 1994). In a study by Dekant *et al* (1994), male and female Sprague-Dawley rats were exposed whole-body to ^{14}C-HCFC-123 concentrations of 1,000, 1,500, 2,000, 3,000, 5,000 ppm (6,250, 9,380, 12,500, 18,800 or 31,300 mg/m^3) for 6 hours. Male Hartley guinea pigs were exposed to 2,000 ppm (12,500 mg/m^3) for 6 hours. Urine was collected for 48 hours after exposure, and TFA levels determined. An increase in urinary TFA excretion was observed. The kinetic constant for urinary TFA excretion for male rats was 75.2 µmol/l (K_m), and the V_{max} was 292 µmol/kg/24 h. For female rats, the K_m was 24.4 µmol/1 and the V_{max} was 232 µmol/kg/24 h.

Other investigators have reported similar results. Dodd *et al* (1993) and Vinegar *et al* (1994) reported separately on exposures of Fisher 344 rats to HCFC-123 concentrations of 100, 1,000 or 10,000 ppm (625, 6,250 or 62,500 mg/m^3) for 4 hours. Vinegar showed that the major route of elimination was through exhalation of unchanged HCFC-123. Indeed, about 90% or more is eliminated by this route. These investigators also followed the time course of TFA elimination for 24 hours. They showed that blood TFA concentrations initially increased for about 5 hours post-exposure followed by a slow elimination. They further reported that the venous blood concentration of HCFC-123 after a 4-hour exposure to 1,000 ppm decreased from 4.5 mg/l to 1.5 mg/l in about 1 hour, and the concentration decreased further (to 0.024 mg/l at 8 hours post-exposure) during the remainder of the study. The blood elimination half-life ($t_{1/2}$) was estimated to be 2 to 4 hours (Dodd *et al,* 1993). Fat concentrations of HCFC-123 decreased in a manner similar to the blood levels. However this source of HCFC-123 influenced the post-exposure elimination kinetics by serving as a source of additional material.

Buschmann *et al* (2001) conducted a study in Sprague-Dawley rats (Crl:CD BR) to differentiate between the effects of HCFC-123 on the lactating dam and on the foetus. Pregnant and/or lactating dams without the pups were exposed (6 h/d; whole-body) by inhalation to 0 or 1,000 ppm (0, 6,250 mg/m^3) from day 6 to 19 post-conception or from day 5 to 21 post-partum. Pups were cross-fostered to new dams within the first 2 days. TFA was detected in the milk of lactating rats (52.1 ± 11.9 μg/ml; *n* = 10) and in the urine of litters (9.21 ± 3.1 μg/ml; n = 9) that had been nursed by treated dams. Rat milk was not analysed for HCFC-123 or for any other metabolites. Toxicity seen in the litters including decreased pup weight was attributed to the presence of TFA in maternal milk.

Lactating rhesus monkeys (*Macaca fascicularis*) (4/group) and neonates were exposed (6 h/d) to 0 or 1,000 ppm HCFC-123 (0, 6,250 mg/m^3) for 21 consecutive days. There were no observed effects on milk composition, a number of clinical chemistry parameters or body weight, but there were liver lesions in biopsies obtained at the end of the study. Milk from exposed mothers contained HCFC-123 and TFA at concentrations of 1 to 5 μg/ml and 17 to 30 μg/ml, respectively. The monkey milk was not analysed for other metabolites. In the blood, HCFC-123 was not detected, but TFA was present at concentrations of 9 to 70 μg/ml in mothers and 17 to 90 μg/ml in neonates. In this study, the average growth rate was lower in exposed neonates than controls (Cappon *et al*, 2002).

7.1.5 Covalent binding

Metabolic studies reveal the potential for formation of a reactive intermediate, trifluoroacetyl chloride, in *in vitro* studies (see above). Since halothane forms the same reactive intermediate, which has previously been shown to bind to liver macromolecules, several investigators have

focused on the covalent binding of HCFC-123 metabolites to liver macromolecules. Furthermore, with halothane, this binding has been shown to result in an immuno-reactive product responsible for halothane-induced hepatitis (Pohl *et al*, 1988).

Harris *et al* (1991) exposed male Fischer 344 rats to approximately 7,000 or 11,000 ppm HCFC-123 (43,800 or 68,800 mg/m^3) for 2 hours. After exposure, microsomes were prepared, and the level of binding determined by immuno-blotting. These authors identified a trifluoroacetylated lysine cross-link that was identical to the TFA-protein cross-link found with halothane. In an extension of these studies, Harris *et al* (1992) exposed male Fischer 344 rats for 6 hours to concentrations of 100, 1,000 or 10,000 ppm HCFC-123 (625, 6,250 or 62,500 mg/m^3) and to 10,000 ppm halothane [a] (80,670 mg/m^3). Twelve hours after exposure, liver sub-cellular fractions were prepared for immuno-blotting. TFA-proteins were detected in the liver of animals exposed to both compounds. A similar degree of cross-linking was seen in rats exposed to 1,000 ppm of halothane and 1,000 or 10,000 ppm of HCFC-123. Less TFA-protein cross-link was detected at 100 ppm.

Huwyler and Gut (1992) and Huwyler *et al* (1992) examined the binding of HCFC-123 or halothane to macromolecules in the liver, kidney and heart. In each of these studies, a 10 mmol/kgbw dose of HCFC-123 (1,529 mg/kgbw) or halothane (1,974 mg/kgbw) was administered *i.p.* to male Sprague-Dawley rats in sesame oil. Kidney, heart and liver sub-cellular fractions were prepared 6 hours after treatment. TFA-protein cross-links were determined by immuno-blotting sequentially using anti-TFA-antibody, goat anti-rabbit HAP conjugated second antibody and enhanced chemiluminescence. TFA-protein cross-links were detected in each of these tissues for both compounds, although the intensity of the kidney and heart cross-linking was much less than that in the liver; about 5% and < 0.5% of the amount formed in the liver was found in kidney and heart, respectively. Prior treatment of the homogenate with piperidine (1 mol/l) or glutathione (5 and 10 mmol/l) abolished the reactivity with protein indicating that cytochrome dependent metabolism of HCFC-123 was occurring in the kidney. The half-life of the cross-links in the kidney was estimated to be between 18 and 90 hours, and in the heart about 12 hours. This is in contrast to the apparent half-life in the liver that was longer than 90 hours but less than 10 days. Cryosections of the kidney tissue revealed that the tubular proteins of the renal cortex were the prime targets of acylation. In the liver, there was a gradient of staining that occurred from the central vein to the portal triad, with the central vein containing the greater staining intensity. These data confirm the ability of the liver and kidney to transform HCFC-123 into a potentially reactive metabolite that can bind to tissue macromolecules.

Zanovello *et al* (2003) investigated the activation of HCFC-123 by methaemalbumin (MHA), a synthetic complex of haem with human albumin that is often used as a model for the inactivation

[a] $C_2HBrClF_3$, molecular mass 197.38 (Appendix C)

of the natural cytochrome P450 haemoprotein. The investigators found that MHA can reductively activate HCFC-123 to reactive species resulting in the loss of its haem group. During anaerobic incubation of MHA with 10 mmol HCFC-123/l, a typically reduced difference spectrum was observed with a 470-nm peak that increased with time, which is indicative of the interaction of HCFC-123 or metabolite(s) with the haem. In similar anaerobic incubations, a significant loss of haem was determined by both the pyridine-haemochromogen technique and ion-pairing reverse-phase HPLC (37 and 30%, respectively). The loss of haem was time-, but not dose-dependent. No statistically significant loss of protoporphyrin IX, as measured by a fluorescence technique, or of the absolute haem spectrum produced in presence of CO (CO-haem complex) was observed up to 10 mmol HCFC-123/l. Small but statistically significant levels of inorganic fluoride were detected in the presence of 20 mmol HCFC-123/l using an F^--specific electrode. The authors concluded that incubation of the non-enzymatic P450 model MHA with HCFC-123 under anaerobic conditions leads to reductive activation of the substrate, resulting in haem modification, as was previously shown to occur for halothane. These data confirm the hypothesis that the suicidal destruction of haem is the mechanism of action for HCFC-123-dependent loss of the enzyme's content and catalytic function.

TFA-protein adducts were investigated by immuno-blotting in liver and plasma of guinea pigs treated with halothane or HCFC-123. Male outbred Hartley guinea pigs were administered HCFC-123 (1, 5, 10 and 15 mmol/kgbw) or halothane (positive control, 10 mmol/kgbw) *i.p.* in corn oil. Blood and liver samples were collected 24 hours after administration. Immuno-reactive bands were demonstrated in liver microsomes at all HCFC-123 and halothane concentrations, and in plasma of animals treated with 10 and 15 mmol/kgbw HCFC-123 and 10 mmol/kgbw halothane; there was no change in microsomal P450 content or mono-oxygenase activity of the P450 2A, 2E1 and 2B iso-enzymes. Instead, when HCFC-123 was administered at doses of 1 and 5 mmol/kgbw, the 2E1-dependent *p*-nitrophenol hydroxylase activity was enhanced. The mild liver damage seen in some animals treated with 1 or 5 mmol/kgbw HCFC-123 was not associated with the presence of TFA-proteins in plasma, which is normally the case. The authors concluded that the lower threshold dose for the appearance of TFA-proteins or damage in the liver (1 mmol/kgbw) than for the presence of TFA-proteins in plasma (10 mmol/kgbw) would suggest that the presence of TFA-proteins in plasma may be the result of liver damage (Bortolato *et al*, 2003).

7.1.6 Summary

Overall, HCFC-123 appears to be easily and quickly absorbed via the respiratory route. It undergoes a biphasic uptake that is saturable in the rat at concentrations greater than 2,000 ppm (12,500 mg/m^3). It is distributed in all tissues/organs and found in greatest quantity in the liver. Due to volatility, elimination will be rapid. Under aerobic conditions, it undergoes cytochrome

P450 2E1 mediated oxidative metabolism resulting in the formation of trifluoroacetyl chloride and TFA. Reductive metabolism to HCFC-133a could be detected only under anaerobic conditions and this pathway seems of little relevance for human hazard assessment. The major route of elimination is rapid exhalation of unchanged HCFC-123. About 90% was eliminated by this route in the rat. Within a period of 8 hours, 98% of inhaled material was cleared from the blood. The majority of the metabolised HCFC-123 was excreted in the urine as TFA. TFA was also present in rat and monkey milk. Similar to halothane, trifluoroacetylated proteins can be detected *in vitro* and *in vivo.*

7.2 Human studies

There is limited information on the toxicokinetics of HCFC-123 in humans *in vivo*.

Tanaka *et al* (1998) reported the detection of TFA in the urine of 4 volunteers exposed by inhalation to 6,073 ppm HCFC-123 (37,960 mg/m^3) for 6 hours. The metabolite peaked at 10 to 27 mg/l by 20 to 30 hours and returned to non-detectable levels 96 hours post-exposure with an elimination half-life of 25 hours.

Williams *et al* (1996) utilised physiologically-based pharmacokinetics modelling for halothane in humans and for halothane and HCFC-123 in rats to deduce a model in humans for HCFC-123 and its main metabolite TFA.

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

8.1 Acute toxicity

8.1.1 Oral toxicity

The approximate lethal dose is reported to be 9,000 mg/kgbw for male rats administered a corn oil solution of HCFC-123 by intra-gastric intubation (Henry, 1975).

8.1.2 Dermal toxicity

Two acute dermal toxicity studies were performed. In the first study (Trochimowicz, 1989), a single dose of 2,000 mg/kgbw of HCFC-123 was applied to the clipped, intact skin of 5 male and 5 female New Zealand white rabbits. The application sites were occluded for a period of 24 hours and the rabbits were observed for 14 days post-treatment. One day following treatment, 6 of 10 rabbits had slight to moderate erythema, which resolved by day 5. No deaths occurred in this study and no gross pathological abnormalities were found in any of the rabbits. It was concluded that the dermal LD_{50} for HCFC-123 was greater than 2,000 mg/kgbw for rabbits.

In the second acute dermal toxicity study (Trochimowicz, 1989), the 2,000 mg/kgbw of HCFC-123 was applied undiluted to the backs of 5 male and 5 female Crl:CD BR rats. The application sites were also occluded for a period of 24 hours. No dermal irritation was observed and no deaths occurred during 14 days post-dosing. The only clinical signs in this study consisted of red nasal or ocular discharges noted in only 1 male and 1 female rat and slight to moderate body weight losses (described as up to 12% of initial body weights). As with the rabbits, no gross pathological abnormalities were observed in the treated rats. The dermal LD_{50} was determined to be greater than 2,000 mg/kgbw for rats.

Based on these two studies, HCFC-123 is considered as a substance with a low order of acute dermal toxicity.

8.1.3 Inhalation toxicity

The results of inhalation toxicity studies are summarised in Table 6 (where converted values are given).

From an acute inhalation toxicity study of HCFC-123 using Chinese hamsters, the 4-hour LC_{50} was determined to be approximately 28,400 ppm HCFC-123, indicating a low order of acute inhalation toxicity. Surviving animals were anaesthetised, and recovered upon cessation of

exposure. All animals died at 31,000 ppm (194,000 mg/m^3) and no mortality was observed at approximately 26,000 ppm (162,500 mg/m^3), indicating a steep dose-response curve (Darr, 1981).

Table 6: Acute toxicity

Concentration		Exposure	LC_{50}		Remark	Reference
(ppm)	(mg/m^3)	time	(ppm)	(mg/m^3)		
Rat						
20,700, 32,000, 33,700, 42,100, 52,500, 55,000	(129,400, 200,000, 210,700, 263,000, 344,000)	4 h	32,000	(200,000)	Loss of mobility, lethargy, unresponsiveness to sound, dyspnoea after 5 min exposure; no clinical signs 30 min post-exposure	Hall, 1975
7,800 - 123,000	48,600 - 767,000	6 h	52,800	(329,900)	Mild convulsions after 3 h exposure to 23,200 ppm (145,000 mg/m^3)	Coate, 1976
0, 1,000, 2,500, 5,000, 10,000	0, 6,250, 15,600, 31,300, 62,500	15 min	NS [a]	NS	Behavioural parameters adversely affected at 5,000 ppm and above, but full recovery within 5 to 15 min post-exposure; NOEL 2,500 ppm	Trochimowicz, 1989
Mouse						
NS	NS	30 min	74,000	(463,000)	AC_{50} 24,000 ppm (150,000 mg/m^3)	Raventos and Lemon, 1965
Hamster						
10,000 - 31,000	(62,500 - 194,000)	4 h	28,400	(177,500)	Survivors anaesthetised reversibly; 100% mortality at 31,000 ppm, 0% mortality at 26,000 ppm (162,500 mg/m^3)	Darr, 1981
Guinea pig						
2,000	12,500	6 h	NS	NS	Rapid metabolism, no clinical signs	Dekant, 1994
0, 1,000, 10,000, 20,000, 30,000	0, 6,250, 62,500, 125,000, 188,000	4 h	NS	NS	Liver changes at all concentrations (centrilobular vacuolisation; degeneration, necrosis)	Marit *et al*, 1994

[a] Not stated

Another acute inhalation study found the LC_{50} to be 32,000 ppm in Sprague-Dawley rats exposed for 4 hours. The animals showed signs of anaesthesia: loss of mobility, lethargy, prostration, unresponsiveness to sound, and dyspnoea within 5 minutes after initiation of exposure to concentrations of HCFC-123 ranging from approximately 20,700 to 55,000 ppm. Surviving rats showed no clinical signs 30 minutes after the cessation of exposure (Hall, 1975).

A 6-hour LC_{50} was determined to be approximately 52,800 ppm for rats. One group of rats exposed to a concentration of about 23,200 ppm experienced mild convulsions after 3 hours of exposure (Coate, 1976).

Behavioural effects were evaluated in rats before, during and after 15-minute exposures to HCFC-123 at concentrations of 0, 1,000, 2,500, 5,000 or 10,000 ppm. The exposures were carried out in a 'glove box' thereby allowing the measurement of unconditioned reflexes, locomotor activity and co-ordination. At concentrations of 5,000 and 10,000 ppm these behavioural parameters were affected. At 5,000 ppm the animals recovered fully within 5 to 15 minutes and at the high dose the animals recovered fully within 30 minutes post-exposure. The NOEL was 2,500 ppm (Trochimowicz, 1989).

An LC_{50} of approximately 74,000 ppm was reported for mice exposed to HCFC-123 vapours for 30 minutes. The median anaesthetic concentration (AC_{50}) in mice was 24,000 ppm, also for a 30-minute exposure (Raventos and Lemon, 1965).

Dekant (1994) exposed guinea pigs to a level of 2,000 ppm of HCFC-123 for 6 hours in a closed recirculating exposure system. No effects were reported.

The acute toxicity of HCFC-123 to guinea pigs was evaluated in a series of 4-hour exposures at levels of 1,000 to 30,000 ppm. At 48 hours post-exposure, animals from all exposure groups showed significant signs of hepatotoxicity, centrilobular vacuole (fatty) change, multi-focal random degeneration and necrosis. No effects were seen in the heart and kidney (Marit *et al*, 1994).

The above results demonstrate that HCFC-123 has a rather low order of acute inhalation toxicity with the primary toxic effect being central nervous system depression.

8.1.4 Cardiac sensitisation

Early studies on the toxicity of certain hydrocarbons, especially anaesthetics, showed that they could render the mammalian heart abnormally reactive or sensitive to adrenaline (epinephrine) resulting in cardiac arrhythmia. In one study described by Foll (1976), a concentration of

10,000 ppm (62,500 mg/m^3) of HCFC-123 was listed as the concentration that will induce cardiac sensitisation in the dog. No details of the experimental conditions were provided.

In another study in Beagle dogs, the cardiac sensitisation potential of HCFC-123 was evaluated using exposure levels of 10,000, 20,000 or 40,000 ppm (62,500, 125,000 or 250,000 mg/m^3). After approximately 5 minutes of exposure the dogs were given an intravenous injection of epinephrine (8 µg/kgbw) and monitored for cardiac arrhythmia. All 3 dogs developed cardiac arrhythmia at an exposure level of 40,000 ppm and 4 out of 6 dogs after exposure to 20,000 ppm. A concentration of 10,000 ppm was tolerated without any signs of cardiac arrhythmia. The EC_{50} was estimated to be approximately 19,000 ppm (119,000 mg/m^3) and the NOEL was 1,000 ppm for HCFC-123 (Trochimowicz and Mullin, 1973).

8.2 Skin, respiratory tract and eye irritation, sensitisation

8.2.1 Skin irritation and sensitisation

HCFC-123 was tested for acute skin irritation potential using 4 male and 2 female New Zealand rabbits. HCFC-123 produced no skin irritation when 0.5 ml/6 cm^2 were applied for 4 hours to clipped, intact skin in any of the treated animals (Brock, 1988; Trochimowicz, 1989).

HCFC-123, when applied topically to the backs of male guinea pigs as 10% and 50% solutions in propylene glycol, produced no skin irritation or sensitisation. Sensitisation was tested 2 weeks after administering 4 sacral intradermal injections (0.1 ml of a 1% v/v solution of HCFC-123 in dimethyl phthalate) given over a 3-week period (Goodman, 1975; Trochimowicz, 1989).

8.2.2 Eye irritation

Undiluted (0.1 ml) HCFC-123 instilled into the conjunctival sac of the rabbit eye without subsequent washing produced mild to moderate conjunctival irritation. Washing the eye immediately after dosing still resulted in mild to moderate conjunctival irritation, as well as a slight corneal opacity. In both cases, complete recovery occurred within 3 to 7 days (Brittelli, 1975; Trochimowicz, 1989).

8.3 Subacute/subchronic toxicity

Groups of 10 male rats were exposed (6 h/d, 5 d/wk) by inhalation to either air (controls) or to 10,000 ppm HCFC-123 (62,600 mg/m^3) for 2 weeks. Except for weak anaesthetic effects during

exposure, there were no adverse compound-related effects relative to haematological, blood, chemical, urine analytical or histopathological indices (Kelly and Trochimowicz, 1976).

Crl:CD BR rats (10/sex/group) were exposed (6 h/d, 5 d/wk) by inhalation to concentrations of 1,000, 5,000, 10,000 or 20,000 ppm HCFC-123 (6,250, 31,300, 62,500 or 125,000 mg/m^3) for 4 weeks. At 5,000 ppm and above, rats exhibited dose-related anaesthetic effects during exposure. A decreased rate of weight gain was seen in all female exposure groups (not dose-related) and in the two highest male exposure groups (dose-related). No compound-related mortality occurred during the 4-week study. A dose-related increase in liver-to-body-weight ratios was observed for all females (up to a maximum of 27% for high dose females) and for high dosed males (18%), without any accompanying histopathological change. Elevations in transaminases were seen in male rats only at the 20,000 ppm level. In addition, a dose-related decrease in cytochrome P450 occurred in all female exposure groups and in males at the highest two exposure levels. Increases in urinary fluoride at the highest exposure concentrations were also observed. Finally, there were no histopathologic effects seen in this study (Rusch *et al*, 1994).

Sprague-Dawley rats (27/sex/group) and 4 male Beagle dogs were exposed (6 h/d, 5 d/wk) by inhalation to HCFC-123 at concentrations of 0, 1,000 or 10,000 (0, 6,250 or 62,500 mg/m^3) for 90 days. At the high dose level, both species exhibited lack of motor co-ordination soon after the start of exposure. This was followed by reduced motor activity and a reduction in responsiveness to noise. After removal from exposure, co-ordination and activity returned to normal within 20 minutes. In rats, there were no adverse effects other than a reduction of final body weight, increase in relative liver weight and elevated urinary fluoride concentration at the two test levels. At the high dose level, dogs exhibited histopathological changes in the liver characterised by hypertrophy, clear cytoplasm and necrosis of liver cells with inflammatory infiltration and clinical chemistry changes. These changes included increased levels of serum and liver alkaline phosphatase, ALT and AST, indicative of slight liver damage. No compound-related effects were noted at the lower (1,000 ppm) exposure level (Rusch *et al*, 1994).

In another 90-day study, groups of 35 male and 25 female Sprague-Dawley rats were exposed to vapours of HCFC-123. Twenty-five male and 20 female rats in each group were sacrificed following the final exposure. The remaining 10 males and 5 females were held an additional 30 days and then sacrificed. The target levels for this study were 0 (control), 500, 1,000 or 5,000 ppm (0, 3,130, 6,250 or 31,300 mg/m^3). No treatment-related deaths occurred in this study and mean body weight reductions observed in high dosed males and the two highest dosed groups of females were significant only at the week 13 interval. Slight depressions were observed in heart weight in both male and female rats exposed to 1,000 ppm HCFC-123. While depressions in kidney weights and kidney/brain weight ratios, but not kidney/body weight ratios, were observed in male rats in all 3 exposure groups, these effects appeared to be biologically significant only in the 31,300 mg/m^3 exposure group. A depression in kidney weight and kidney/body weight ratio,

but not in kidney/brain weight ratio, occurred in the 10,000 ppm exposed females. Increased liver/body weight ratios, but not liver weight or liver/brain weight ratios, were observed in the 10,000 ppm exposed males and in all 3 female exposure groups. However, no significant differences were found for absolute or relative organ weights in animals sacrificed at the end of the 30-day recovery period. The absence of histopathological findings coupled with the absence of effects at the end of the recovery period suggest these effects to be of marginal significance, if at all, in relation to the HCFC-123 exposure (Rusch *et al,* 1994).

In a further study, groups of 10 Sprague-Dawley rats/sex/group were exposed (6 h/d, 5 d/wk) by inhalation to HCFC-123 at concentrations of 0, 300, 1,000, 5,000 ppm (1,880, 6,250 or 31,300 mg/m^3) for 90 days. Rats exposed at 31,300 mg/m^3 showed slight anaesthetic effects. At this same concentration, as well as at 1,000 ppm, decreased body weight gain was observed. Except for slightly elevated urinary fluoride levels in males at 5,000 ppm, and in all female groups, no other effects relating to haematology or urinary analysis were noted. Serum triglyceride and glucose levels were reduced in both sexes at all levels of exposure. Serum cholesterol was also reduced in female rats at 1,000 and 5,000 ppm. At the 90-day terminal sacrifice, slightly increased liver weights were observed at the two highest exposure concentrations. However, no histopathological effects were noted at any exposure level. Hepatic peroxisome β-oxidation activity to palmitoyl-CoA oxidase was increased in rats in all exposure groups. Comparison of liver sections from the control and high-exposure group by electron microscopy revealed a 2- to 3-fold increase in peroxisome number in the high dose animals (Rusch *et al,* 1994).

Two other subchronic studies were conducted with HCFC-123 in rats and/or guinea pigs (Lewis, 1990; Warheit, 1993). These studies were undertaken to clarify the findings of reduced serum triglycerides and cholesterol and the increase in benign adenomas of the liver, pancreas and testes observed in a 2-year inhalation study (Section 8.6). The study by Lewis is described in Section 8.7.3. In the Warheit study, 2 groups of male Crl:CD BR rats (17/group) were initially exposed (6 h/d, 5 d/wk) to 0 or 20,000 ppm HCFC-123 (0 or 125,000 mg/m^3). After 6 exposures and because of severe body weight losses, the HCFC-123 exposure concentration was reduced. The average concentration over the 4 weeks of exposure was 18,200 ppm (114,000 mg/m^3). Similarly, 2 groups of 15 male Hartley guinea pigs were exposed to either 0 or 20,000 ppm. After 6 exposures and because of severe body weight losses observed in the guinea pigs, the HCFC-123 exposure concentration was reduced, ultimately to 5,000 ppm (31,300 mg/m^3). The total exposure for these groups of animals was 23 days and the mean exposure level was 9,400 ppm (58,800 mg/m^3). One group each of 17 male rats and 15 male guinea pigs were fed diets containing 7,500 mg TFA/kg. Also, one group each of 17 male rats and 15 male guinea pigs were fed diets containing 100 mg/kg of Wyeth (WY)-14643, a compound known to induce peroxisomes in the liver (Section 8.7.3). These animals were treated with compound for 25 consecutive days. A decrease in body weight was observed in the HCFC-123, TFA and WY-

14643 exposed animals without concomitant changes in food consumption for rats, although there was a decrease in food consumption by guinea pigs exposed to HCFC-123 or TFA. Three guinea pigs exposed to HCFC-123 died during the study. These deaths were considered compound-related in particular to the initial high exposure concentration. The authors reported decreases in serum cholesterol, triglycerides, glucose and insulin levels were observed in rats exposed to either HCFC-123 or TFA (Table 7). An increase in serum glucose and cholesterol was observed with WY-14643, but a decrease was observed for triglycerides. In guinea pigs, decreases in triglycerides and glucose were observed with each treatment, although the changes were not as dramatic as those observed in rats. Furthermore, the decrease in these parameters in guinea pigs exposed to HCFC-123 may be related to the severe body weight effects of the compound. Alternatively, HCFC-123 may lower serum triglyceride levels via a mechanism unrelated to peroxisome induction.

Increases in mean absolute and relative liver weights were observed in rats exposed to HCFC-123, TFA and WY-14643. The increased liver weights correlated with diffuse hypertrophy observed microscopically in the treated rats. The weight changes and hypertrophy were most severe in the WY-14643 treated rats. In contrast, the liver weights of guinea pigs exposed to HCFC-123 were significantly reduced. Minimal to mild centrilobular fatty change was observed microscopically. In guinea pigs exposed to TFA or WY-14643 the liver weights were also reduced, although there were no significant changes observed microscopically.

Table 7: Clinical chemical results for rats and guinea pigs [a]

	Cholesterol (mg/100 ml)	**Triglycerides (mg/100 ml)**	**Glucose (mg/100 ml)**	**Insulin (ng/ml)**
Rat				
Control	51 ± 17 [b]	79 ± 30	105 ± 14	3.9 ± 1.9
HCFC-123 (113,750 mg/m^3)	33 ±10	31 ± 2.0	77 ± 12	1.9 ± 0.6
TFA (7,500 mg/kgbw)	43 ± 9	68 ± 18	87 ± 8	3.6 ± 1.4
WY-14643 (100 mg/kgbw)	70 ± 15	51 ± 9	121 ±10	3.7 ± 1.4
Guinea pig				
Control (0 ppm)	58 ± 13	94 ±15	155 ±13	ND [c]
HCFC-123 (58,750 mg/m^3)	36 ± 24	60 ± 24	134 ± 13	ND
TFA (7,500 mg/kgbw)	63 ± 31	92 ± 2	136 ± 10	ND
WY-14643 (100 mg/kgbw)	49 ± 13	87 ± 28	139 ± 12	ND

[a] Groups of rats and guinea pigs were exposed 6 h/d, 5d/wk for 28 days to either HCFC-123 or air (controls). For TFA and WY-14643, rats or guinea pigs were provided diets containing compound for 25 consecutive days (Warheit, 1993)

[b] Values are the mean ± standard deviation

[c] Not determined

In conclusion, there are several differences in the degree and type of changes observed within and between the two species. Guinea pigs were more sensitive to the systemic effects of HCFC-123 than rats based on body weight losses and mortality. Liver weights were decreased in guinea pigs, whereas liver weights were increased in the rat. These changes correlated with microscopic observations, e.g. the increased liver weights in rats correlated with hypertrophy whereas the decreased liver weights in guinea pigs correlated with cytotoxic fatty changes. In rats, repeated subchronic inhalation exposure to HCFC-123 at exposure levels of up to 5,000 ppm (31,300 mg/m^3) appears to be associated with decreased body weights, increased liver weights and effects on lipid metabolism, and reversible anaesthetic effects, without significant evidence of histopathological damage. The NOEL for anaesthetic effects was 1,000 ppm (6,250 mg/m^3). The NOEL for hypolipidemic effect was less than 300 ppm (1,880 mg/m^3).

8.4 Mutagenicity and cell transformation

8.4.1 *In vitro*

The data from *in vitro* genotoxicity studies and cell transformation test results are summarised in Table 8.

Table 8: Genotoxicity and cell transformation in vitro

Assay/ Endpoint	Strain or type	Metabolic activation	Result	Remark	Reference	CoR
Gene mutation - reverse						
Salmonella typhimurium	TA1535, TA1538, TA98, TA100	± S9	–ve	Tested as a gas up to 100,000 ppm (625,000 mg/m^3)	Longstaff *et al*, 1984	1b
Salmonella typhimurium	TA1535, TA1537, TA1538, TA98, TA100	± S9	–ve	Tested as a gas at a nominal concentration of 1000,000 ppm (6,250,000 mg/m^3) for up to 30 min	Brusick, 1976	1b
Salmonella typhimurium	TA1535, TA1537 TA1538, TA98 TA100	± S9	–ve	Tested as a liquid up to 0.5 ml per exposure	Callander, 1989	1a
Gene mutation - forward						
Saccharomyces cerevisiae	D4	± S9	–ve	Tested as a gas at a nominal concentration of 1000,000 ppm for up to 72 minutes	Brusick, 1976	2c
Chromosome aberration						
Structural (clastogenicity)	Human lymphocytes	– S9	+ve	Tested as a vapour at 25,000 and 100,000 ppm (156,000 or 625,000 mg/m^3)	Edwards, 1991	1a
		+ S9	+ve	Vapour at 300,000 ppm (1,880,000 mg/m^3)		
Structural (clastogenicity)	Human lymphocytes	– S9	+ve	Liquid at 0.005%	Dance, 1991	1a
		+ S9	–ve			
Structural (clastogenicity)	Human lymphocytes	– S9	+ve	Liquid at 50, 250, and 500 µg/ml	Mackay, 1992	1a
		+ S9	–ve	100, 500, 1,000 µg/ml		
Cell transformation						
	BHK21	+ S9	–ve	Tested as a liquid up to 250 µg	Longstaff *et al*, 1984; Styles, 1977	1d

Longstaff *et al* (1984) reported that HCFC-123 was not mutagenic when tested in several *Salmonella typhimurium* strains (Ames), both in the presence and absence of rat liver S9. In addition, these investigators found that HCFC-123 also gave negative results in a cell transformation (Styles, 1977) assay using a permanent cell line of baby hamster kidney fibroblasts (BHK21) in the presence of S9 mix.

In an earlier study, HCFC-123 was tested for mutagenicity in a series of suspension and plate assays using *Salmonella typhimurium* tester strains (Ames), as well as *Saccharomyces cerevisiae* strain D4 (forward mutation assay), in the presence and absence of S9. HCFC-123 was found to be negative in both of these assays (Brusick, 1976).

HCFC-123 was evaluated for clastogenic potential in an *in vitro* cytogenetic assay using human lymphocytes both in the presence and absence of rat liver-derived S9 mix. Cultures of these cells were exposed to HCFC-123 at dose levels of 50, 250 and 500 µg/ml in the absence of S9 mix and 100, 500 and 1,000 µg/ml in the presence of S9 mix. In the presence of S9 mix, no increases in the frequency of chromosomal aberrations were observed. In the absence of S9 mix, dose-related increases in the chromosomal aberration frequency were observed which were statistically and biologically significant at 500 µg/ml (Mackay, 1992). These results suggest that mammalian liver enzymes are capable of inactivating the mutagenic potential of HCFC-123.

The latter study was repeated at another laboratory, using both vapour phase and liquid exposure designs (Hodson-Walker *et al*, 1993). In the vapour phase study, cultured human lymphocytes were exposed to 25,000 ppm or 100,000 ppm HCFC-123 in the absence of S9, and to 300,000 ppm in the presence of S9. In both cases, biologically and statistically significant positive responses were produced (Edwards, 1991). When tested in the liquid phase at 0.005% (v/v), HCFC-123 gave a positive response in the absence of S9, but no significant evidence for a positive response in the presence of S9 (Dance, 1991).

8.4.2 *In vivo*

The available *in vivo* genotoxicity studies are summarised in Table 9.

Table 9: Genotoxicity in vivo

Assay/ Endpoint	Strain or type	Metabolic activation	Result	Remark	Reference	CoR
Micronucleus induction	Mouse polychromatic erythrocytes		–ve	2,000, 6,000 or 18,000 ppm (12,500, 37,500 and 112,500 mg/m^3) for 6 h	Müller and Hofmann, 1988	1a
Structural (clastogenicity)	Rat lymphocytes		–ve	0, 300, 1,000, 5,000 ppm (0, 1,880, 6,250 or 31,300 mg/m^3)	Marshall, 1992	1b
DNA repair						
Unscheduled DNA synthesis (UDS)	Rat hepatocytes		–ve	8,000, 12,500 or 20,000 ppm (50,000, 78,100, 125,000 mg/m^3)	Kennelly, 1993	1d

A micronucleus assay was conducted to further evaluate the genotoxic potential of HCFC-123 (Müller and Hofmann, 1988). NMRI mice were exposed to levels of 2,000, 6,000 or 18,000 ppm in air for 6 hours. Under the conditions of this assay, exposure to HCFC-123 did not result in an increased number of micronuclei.

HCFC-123 was further evaluated for genotoxic activity in an chromosome aberration study with peripheral blood lymphocytes from Sprague-Dawley rats (Marshall, 1992). The blood samples were taken from male rats that had been exposed (6 h/d, 7 d/wk) over a period of 14 weeks to HCFC-123 concentrations of 300, 1,000 or 5,000 ppm HCFC-123. Chromosome aberrations were determined only in the high dose group. The authors concluded that HCFC-123 was not genotoxic in this assay.

HCFC-123 was also tested for the ability to induce unscheduled DNA synthesis (UDS) in an rat hepatocyte assay incorporating an auto-radiographic technique. Male Alderley Park (Alpk:APfSD) rats were exposed by inhalation at 8,000, 12,500 or 20,000 ppm HCFC-123 for 6 hours. Hepatocytes from exposed rats were assessed for the induction of UDS at the two highest dose levels. At *in vivo* at exposure levels up to 20,000 ppm, HCFC-123 did not induce DNA repair in rat hepatocytes (Kennelly, 1993).

8.4.3 Conclusion

HCFC-123 was inactive in several *in vitro* studies including a series of *Salmonella typhimurium* assays, a *Saccharomyces cerevisiae* assay and a cell transformation assay. It was positive only in the human lymphocyte chromosome aberration assay. HCFC-123 was clearly negative in a series of *in vivo* studies, including mouse micronucleus, rat chromosome aberration and rat unscheduled DNA synthesis. In conclusion, HCFC-123 is not genotoxic *in vivo*.

8.5 Chronic toxicity and carcinogenicity

A 2-year inhalation toxicity (combined chronic toxicity and oncogenicity) study was conducted with HCFC-123 (Malley et al, 1995). Groups of 80 Crl:CD BR rats (41 days of age) were exposed (6 h/d, 5 d/wk) by whole-body inhalation to 0, 300, 1,000, or 5,000 ppm HCFC-123 (purity $\geq$ 99.8%) (0, 1,880, 6,250, 31,300 mg/m3) for approximately 104 weeks. Clinical pathology was evaluated at 6, 12, 18, and 24 months and an interim sacrifice of 10 animals per sex per group was conducted at 12 months. Clinical pathology data are summarised in Table 10.

Serum triglyceride concentrations were significantly decreased at all exposure concentrations for both sexes compared to controls. Serum glucose concentrations were significantly decreased at all

exposure concentrations at the 6- and 12-month evaluations. However, at the 18-month evaluation, only 1,000 and 5,000 ppm males and 5,000 ppm females had lower glucose concentrations. By the 24-month evaluation, glucose concentrations were similar to control at all exposure concentrations. Serum cholesterol was also lower in all treated females and in males in the 5,000 ppm group. Serum albumin was significantly higher in males in the 1,000 and 5,000 ppm groups, and serum globulin was significantly lower in the 1,000 and 5,000 ppm males and in all treated females. Urinary fluoride was generally higher in all treated animals. Urine volume was higher and urine osmolality lower in all treated males at the 6- and 12-month evaluations.

Table 10: Chronic toxicity-oncogenicity in rats: clinical chemical findings (after Malley *et al*, 1995)

Test	Concentration		Sampling time (month)			
	(ppm)	(mg/m^3)	6	12	18	24
Male rats			**Concentration (mg/dl) in blood [a]**			
Triglyceride	0	(0	96 (55)	201 (133)	183 (117)	176 (70)
	300	1,880	45 (23) [b]	49 (22) [b]	87 (70) [b]	95 (30) [b]
	1,000	6,300	20 (1 0) [b]	35 (34) [b]	66 (29) [b]	85 (24) [b]
	5,000	31,300)	8 (9) [b]	4 (8) [b]	34 (1 0) [b]	44 (12) [b]
Glucose	0	(0	117 (11)	109 (9)	93 (13)	74 (22)
	300	1,880	94 (12) [c]	93(12) [c]	84 (15)	73 (10)
	1,000	6,250	85 (7) [c]	92 (11) [c]	71 (10) [c]	69 (9)
	5,000	31,300)	78 (9) [c]	81 (5) [c]	73 (9) [c]	76 (14)
Cholesterol	0	(0	63 (21)	120 (61)	121 (49)	131 (48)
	300	1,880	69 (22)	101 (24)	85 (39)	100 (48)
	1,000	6,250	63 (9)	94 (19)	84 (25)	115 (26)
	5,000	31,300)	54 (16)	68 (22) [b]	76 (24) [c]	78 (32) [c]
Female rats			**Concentration (mg/dl) in blood [a]**			
Triglyceride	0	(0	104 (70)	207 (173)	148 (46)	122 (87)
	300	1,880	42 (18) [b]	72 (54) [b]	68 (11) [b]	70 (35)
	1,000	6,250	25 (7) [b]	5 (14) [b]	66 (30) [b]	59 (18) [b]
	5,000	31,300)	15 (2) [b]	0 (1) [b]	37 (5) [b]	40 (15) [b]
Glucose	0	(0	110 (12)	97 (9)	85 (10)	77 (17)
	300	1,880	93 (8) [c]	78 (11) [c]	81 (9)	63 (18)
	1,000	6,250	77 (11) [c]	66 (12) [c]	75 (10)	69 (19)
	5,000	31,300)	78 (7) [c]	67 (5) [c]	69 (9) [c]	79 (18)
Cholesterol	0	(0	73 (18)	76 (12)	100 (31)	110 (27)
	300	1,880	57 (9) [c]	56 (7)	78 (11)	76 (16) [c]
	1,000	6,250	52 (12) [c]	52 (8) [c]	79 (25)	94 (36)
	5,000	31,300)	54 (11) [c]	52 (10) [c]	58 (12) [c]	57 (21) [c]

[a] Group mean and standards deviation

[b] Statistically different from control ($p < 0.05$) by Mann-Whitney U criteria

[c] Statistically different from control ($p < 0.05$) by Dunnett criteria

Ophthalmologic evaluations did not reveal any observable gross abnormalities at any time point evaluated.

All rats exposed to 5,000 ppm and females exposed to 1,000 ppm had lower body weight and body weight gain. Females exposed to 300 ppm also had lower body weight over a period of several months. Food consumption was slightly higher and food efficiency slightly lower in males and females exposed to 5,000 ppm. During exposures, rats exposed to 5,000 ppm were less responsive to auditory stimuli compared to controls. However, by the time residual test material had exhausted from the chamber and the rats returned to the animal room, the responsiveness of rats in that group was similar to that of the control animals. Males and females exposed to 1,000 or 5,000 ppm had higher incidences of 1 or more observed gross clinical observations, which included stained fur, wet perineum and wet inguen[a]. In addition, 5,000 ppm females had a decreased incidence of coloured discharge from the eye, and 1,000 and 5,000 ppm females had a decreased incidence of skin sores. Males at 5,000 ppm had a significantly higher incidence of observed gross inguinal masses; however, females at 1,000 and 5,000 ppm had a significantly lower incidence of inguinal masses and total masses.

At the 12-month sacrifice, a compound-related increase in mean relative liver weight was observed for 5,000 ppm males and females; however, no compound-related gross or microscopic morphological changes were seen.

At the 24-month sacrifice, increased liver and kidney weights were noted in 5,000 ppm in males and females. There were also compound-related increases in the incidences of grossly observed large and discoloured livers in 5,000 ppm males and liver masses in 5,000 ppm females. Mean absolute kidney weights were lower in 5,000 ppm males and in 1,000 and 5,000 ppm females. The decrease in kidney weights was attributed to the reduction in the incidence and severity of spontaneously occurring glomerulo-nephropathy.

The observed decreased incidence of several spontaneous lesions was attributable to the beneficial effects of reduced body weight and/or lower serum lipid levels. As shown in Table 11, males and females exposed to 1,000 ppm or 5,000 ppm had also significantly greater survival than controls at year 2. The increased survival was correlated with the decreased incidence of some spontaneous lesions in aged rats.

[a] Synonym groin, a fold between the belly and the thigh

Table 11: Chronic toxicity-oncogenicity in rats: survival at 2 years (after Malley *et al*, 1995)

Concentration		Survival (%)	
(ppm)	**(mg/m^3)**	**M**	**F**
0	0	26	23
300	1,880	31	36
1,000	6,250	40 [a]	47 [a]
5,000	31,200	43 [a]	59 [a]

[a] Statistically significant increase ($p < 0.05$)

All treated males and females exposed to 1,000 or 5,000 ppm of HCFC-123 had higher hepatic β-oxidation activity compared to controls, indicating an induction of hepatic peroxisome proliferation. Compound-related differences in the rate of hepatic cell proliferation were not seen at any exposure level at the 12-month sacrifice. This indicates that HCFC-123 did not induce an increase in regenerative repair of the liver.

Diffuse retinal atrophy, a common age-related finding in rats, was increased in all test groups of males and females. However, incidences of retinal atrophy were not dose related in females, were within historical incidences in most treated groups, and similar changes were not seen in other studies at higher concentrations of HCFC-123. Therefore retinal atrophy was considered to be secondary to increased survival and nutritional effects and not a primary effect of exposure to HCFC-123.

Data for tumour incidences at the 24-month kill are summarised in Table 12.

Table 12: Combined chronic toxicity-oncogenicity study with HCFC-123 in the rat: tumour findings (after Malley *et al*, 1995)

	Concentrations			
Sex/ Parameters	**0** (0)	**300** (1,880)	**1,000** (6,250)	**5,000 ppm** (31,300 mg/m^3)
Males (80/group)	**Number of animals**			
Survival at 24 months [a]	26	31	40 [b]	43 [b]
Testes, interstitial cell adenoma	4	12 [c]	9	14 [c]
Pancreas, acinar cell adenoma	1	4	12 [c]	14 [c]
Liver, hepatocellular adenoma	3	2	2	8 [c]
Total animals with primary tumours	58	55	56	60
Total animals with benign tumours	55	48	49	53
Total animals with malignant tumours	12	13	21	18
Females (80/group)	**Number of animals**			
Survival at 24 months [a]	23	36	47 [b]	59 [b]
Liver, hepatocellular adenoma	0	5 [c]	2	6 [c]
Liver, cholangio-fibroma	0	0	0	6 [c]
Pancreas, acinar cell adenoma	0	2	0	2
Total animals with primary tumours	60	65	61	62
Total animals with benign tumours	57	63	56	61
Total animals with malignant tumours	19	14	17	16

[a] Out of 70 animals
[b] Statistically significant increase ($p < 0.05$)
[c] Statistically different from control ($p < 0.05$)

The following observations were noted:

- The incidence of cellular alteration (basophilic) in the male and female liver was increased in all test groups. The increase in benign hepatocellular adenomas was statistically significant in males exposed to 5,000 ppm and in all test groups of females. Furthermore, hepatic cholangio-fibroma incidence increased in 5,000 ppm exposed females, and males had a compound-related increased incidence of hepatic focal necrosis. Females exposed to 5,000 ppm had an increased incidence of sinusoidal ectasia. In addition, 1,000 and 5,000 ppm males and 5,000 ppm females had an increased incidence of hepatic cystic degeneration. Males exposed to 5,000 ppm also had a compound-related increased incidence of hepatic focal necrosis. The incidence of hepatic centrilobular fatty change was also increased in the 5,000 ppm males and females.

- The 1,000 and 5,000 ppm males and 5,000 ppm females had an increased incidence of hepatic cystic degeneration
- Males exposed to 5,000 ppm had an increased incidence of focal degeneration of the adrenal cortex; however, it was minimal to mild in severity and was considered to be a compound-related effect of minimal or no biological significance.
- Benign pancreatic acinar cell adenomas were seen in all male rat test groups. Acinar cell hyperplasia of the pancreas was increased in the 1,000 and 5,000 ppm in males and females.
- In the testes, benign interstitial cell adenomas and focal interstitial cell hyperplasia were increased in all male test groups.
- The incidence of ovarian cysts in the 5,000 ppm females was significantly increased; however, since they were minimal to mild in severity these cysts were considered to be of minimal or no biological significance.

8.5.1 Discussion and assessment

The study described above shows some notable effects of HCFC-123 in the rat: an increase in survival rate, particularly at 5,000 ppm HCFC-123 (Table 10); a decrease in body weight, particularly at 5,000 ppm HCFC-123 (although this group of rats had the same rate of food consumption). There was also a dose-related, strong and persistent decrease in serum triglyceride concentration present at all exposure levels. When considered together these data suggest that improved rat survival at the high exposure level was possibly due to lower body weights which itself was probably associated with the reduction of plasma triglycerides.

Also, the study identified some statistically significant increases in tumour incidence in the liver, testis and pancreas (Table 12). These tumours were all benign, were all a continuum from hyperplasia, and all occurred late in life. Age adjustment of tumour rates to correct for the higher mortality in controls compared to HCFC-123 exposed rats tended to reduce the actual observed tumour rates. However, these changes did not affect the overall conclusion of the significance of the tumours.

A NOEL was not achieved in this study, based on effects in clinical chemistry parameters at all concentrations tested, and lower body weight and body weight gains at 300, 1,000 and 5,000 ppm. There were also higher liver weights at 5,000 ppm; and increased incidence of neoplastic and non-neoplastic morphological changes and higher hepatic peroxisomal β-oxidation activity at all concentrations.

Assessment of benign liver adenomas

In the liver there were increased numbers of hepatocellular adenoma in male rats exposed to 5,000 ppm HCFC-123, although after application of age adjustment statistics the trend was not statistically significant. Incidence was also increased in female rats, and although the dose response relationship was not good, the increase at 300 and 5,000 ppm and the overall trend were statistically significant.

HCFC-123 is a moderate peroxisome proliferator (Section 8.7.3), probably due to its metabolism to TFA (Section 7.1.3), a known rat hepatic peroxisome proliferator (Just *et al*, 1989; Lock *et al*, 1989; Warheit, 1993). Peroxisome proliferation has been identified as a rodent-specific phenomenon, and is causally linked to hepatic tumours in rats and mice (ECETOC, 1992). This is supported by the fact that peroxisome proliferation is not seen in rhesus monkeys (Cappon *et al*, 2002). The finding of a small increase in the incidence of benign hepatic adenoma in rats, following lifetime exposure to HCFC-123, is considered to be associated with its moderate peroxisome proliferating activity, and should not represent a hazard to man.

Female rats exposed to 5,000 ppm HCFC-123 had a small increase in incidence of benign hepatocholangio-fibroma. This was not seen at lower exposure concentrations or in males. Also seen in this group of females was a marked increase in the incidence of biliary hyperplasia, and to a lesser degree, cholangio-fibrosis. Although hepatocholangio-fibromas were also increased, together with hepatocellular tumours, by peroxisome proliferators such as thioacetamide (Becker, 1983) and ethionine (Hiruma *et al*, 1993), most peroxisome proliferations do not give rise to this tumour type. Peroxisome proliferation does not appear as an obvious hypothesis for the increase of cholangio-fibroma.

Assessment of benign testicular adenomas

The incidence of benign testicular interstitial cell adenomas was increased in HCFC-123 treated groups compared to controls, and the difference was statistically significant for the 300 ppm and the 5,000 ppm groups. Although adjusting for the increased survival of treated animals showed equivocal significance for a dose-related trend, if only animals surviving to the study end at 2 years are considered, there is clearly a dose-related increase in testicular Leydig cell adenoma in all treated groups.

Tumours of the testis are known to make up approximately 1% of all human male neoplasms and of this actually palpable Leydig cell tumours are rare, accounting as they do for some 1 to 3% of testicular tumours. When Leydig cell tumours do occur the vast majority (80 - 90%) are benign adenomas. This low level of tumour incidence in man would appear to be in marked contrast to

that which is observed in rats. Leydig cell tumours are frequently increased in rat bioassays following treatment with approved pharmaceutical agents or dietary materials yet is rarely reported in man, even after long-term exposure to the same substances (Bär, 1992; Prentice and Meikle, 1995).

Biegel *et al* (1992) have hypothesised that peroxisome proliferators may increase Leydig cell tumour incidence in rats. This can be seen only if a strain with low spontaneous Leydig cell tumours is used in the bioassay. Most recent carcinogenicity studies were performed on Fisher 344 rats and this may have precluded detecting substances that would have increased Leydig cell adenoma incidences. Substances with rodent hepatic peroxisome proliferation potential that increased Leydig adenoma incidences in non Fisher 344 rat strains were: Gemfibrozil (Fitzgerald *et al*, 1981), trichloroethylene (Maltoni *et al*, 1986) and ammonium perfluoro-octanoate (Sibinski, 1987). Biegel *et al* (1992) were able to demonstrate an increased formation of Leydig cell adenomas in Sprague-Dawley CRL:CD rats but not in Fisher 344 rats, when treated with the potent hepatic peroxisome proliferator WY-14643. Peroxisome induction was not seen in the testes. At present, therefore, it is not possible to clearly establish causal links between peroxisome proliferation and Leydig cell adenoma, although results from the afore-mentioned study suggest that Leydig cell tumours may represent a class effect of peroxisome proliferators.

A more direct hypothesis for the increased incidence of rodent Leydig cell tumours suggests that hormonal imbalance may be associated with Leydig cell tumour induction. Cook *et al* (1999) provided an extensive review of the non-genotoxic basis of rodent Leydig cell tumour induction and its relevance to man. In their assessment, the authors gave a brief summary of the toxicity of HCFC-123. The plausible mechanisms for chemical induction of these tumours involve elevation of serum luteinising hormone (LH) or Leydig cell responsiveness to LH. Several lines of evidence were presented that suggest that human Leydig cells are quantitatively less sensitive than those of rats in their proliferative response to LH and thereby in their sensitivity to chemically-induced Leydig cell tumours. The authors noted that several human epidemiology studies on a number of rodent Leydig cell tumour inducers do not demonstrate an association between human exposure and induction of Leydig cell adenomas or hyperplasia.

The benign tumours of the testicular interstitial cells are common in the aging rat. The spontaneous incidence of this tumour type is variable from one strain to another, ranging from a few percent in Sprague-Dawley rats up to 100% in some Wistar derived strains and in Fisher 344 rats (Bär, 1992). These tumours do not usually progress to malignancy in the rat, as is shown by the absence of malignant Leydig cell tumours. Benign Leydig cell tumours typically appear late in life and are not life-threatening to rats. They are associated with the senescence process. The high incidence of hyperplasia and tumours of these testicular cells in old rats is thought to be related to senile endocrine disturbance (Mostofi and Price, 1973).

In conclusion, the rarity of Leydig cell tumours in human as compared to the high spontaneous incidence in the rat make the relevance of the rat findings to man highly questionable. Consequently, the increased frequency of benign Leydig cell tumours in rats exposed to HCFC-123 is not likely to be indicative of a tumourigenic hazard to humans (Klaunig *et al*, 2003).

Assessment of benign pancreatic acinar cell adenomas

The incidence of benign pancreatic acinar cell adenoma was increased in a dose-dependent pattern in all male groups exposed to HCFC-123. Although not statistically significant, increased incidence of this tumour was also seen in females exposed at 300 and 5,000 ppm, but not at 1,000 ppm. The incidence was lower in females compared to males. Also increased was the incidence of acinar cell hyperplasia, which is considered the precursor to the adenoma.

It has been noted that treatment with a number of hypolipidemic agents has resulted in pancreatic acinar cell tumours in experimental studies. These have included hepatic peroxisome proliferators such as clofibrate and nafenopin (Svoboda and Azarnof, 1979; Reddy and Rao, 1977; Longnecker, 1983) and gemfibrozil (Fitzgerald *et al*, 1981), which also induced rat hepatocellular and Leydig cell adenomas. However, not all peroxisome proliferators have been shown to cause pancreatic acinar cell tumours and a direct link between peroxisome proliferation and the occurrence of pancreatic tumours is not established, for example for di(2-ethylhexyl) phthalate (US-NTP, 1982).

In view of the marked perturbation of lipid metabolism by HCFC-123, as evidenced by the depression of triglycerides (and cholesterol), it is possible that an endocrine mechanism may lead to stimulation of the exocrine pancreas, and this, over a lifetime, may lead to the increase in pancreatic hyperplasia and adenoma. Alternatively, it may be a consequence of altered bile acid synthesis and/or composition (Klaunig *et al*, 2003).

In conclusion, the above 2-year combined chronic toxicity/carcinogenicity study with HCFC-123 in rats has shown increased incidences of liver, pancreatic and testis tumours. It is noted that these tumours were all benign, appeared late in life (primarily in males) and were not life threatening to the animals. In fact, animals in the high-exposure groups had a statistically significant increase in survival at 2 years compared to controls (Table 11). Because HCFC-123 was assessed as non-genotoxic (Section 8.4), the tumours appear to be epigenetic in origin. The formation of hepatic tumours can be linked with the rodent-specific peroxisome proliferation potential of HCFC-123, while the testicular tumours may have resulted from enhanced hormonal disturbances in senescent rats. Thus, the hepatic and testicular tumours are not relevant for

human health hazard assessment. The mechanism of pancreatic acinar cell tumour formation is not understood, and the significance of these tumours for humans remains uncertain.

8.6 Embryotoxicity, teratology and reproductive performance

The major inhalation studies conducted on HCFC-123 described below have been published in the peer-reviewed literature by Malinverno *et al* (1996).

8.6.1 Embryotoxicity and teratology

An inhalation developmental toxicity study was conducted with vapours of HCFC-123 (Rusch *et al,* 1994). For this study, 2 groups of 20 pregnant female rats were exposed to 0 or 5,000 ppm HCFC-123 (0 or 31,300 mg/m^3) for 6 hours from days 6 to 15 of gestation. The animals were sacrificed on day 20 and all dams and foetuses examined. Maternal mean body weights in the exposed groups were significantly depressed on days 12 and 15 of the gestation period (20 and 40 grams, respectively). At termination, maternal mean body weights were still depressed (21 grams), but not to a statistically significant degree. The numbers of corpora lutea, implantation sites, resorption sites and foetuses were similar among control dams and those exposed to HCFC-123. In summary, exposure of pregnant rats to a concentration of 5,000 ppm of HCFC-123, a level that produced a response in the dams (depressed weight gain), did not result in developmental toxicity.

HCFC-123 did not induce embryotoxicity or teratogenic effects in an inhalation study in which 25 pregnant Charles River-CD Albino rats were exposed to HCFC-123 at a concentration of 10,000 ppm (62,500 mg/m^3) 6 hours per day on days 6 to 15 of gestation. Dams and foetuses were sacrificed on day 21 and examined for gross changes (Kelly *et al,* 1978).

A study was conducted to evaluate the teratogenic potential of HCFC-123 when administered to pregnant rabbits by inhalation. Initially, in the range-finding study, groups of 6 pregnant rabbits were exposed (6 h/d) to concentrations of 1,000, 5,000, 10,000 or 20,000 ppm (6,250, 31,300, 62,500 and 125,000 mg/m^3) during days 6 to 18 of gestation. An air exposed control group was included. All rabbits exposed to HCFC-123 lost weight during the study and food consumption was markedly reduced, especially at 10,000 and 20,000 ppm. Based on marked decreased food consumption, decreased body weights, and an increased number of resorptions seen at 10,000 and 20,000 ppm, all indicating maternal toxicity and possibly embryotoxicity, exposure levels of 500, 1,500 or 5,000 ppm (3,125, 9,380 or 31,300 mg/m^3) were selected for the main study. This study consisted of 6 h/day exposures of 24 mated females per exposed group during days 6 to 18 of gestation. No compound-related mortality was observed in any of the exposure groups. Evidence

of maternal toxicity occurred during day 6 to 18 of gestation at all exposure levels and included body weight loss as well as reduced food consumption. No other signs of maternal toxicity were observed. In conclusion, there was no evidence of embryotoxic, foetotoxic or teratogenic effects (Trochimowicz, 1989).

8.6.2 Reproductive performance

A one-generation reproduction study (Hughes *et al*, 1994) was performed to aid in establishing experimental parameters for the conduct of an inhalation 2-generation reproduction study on HCFC-123. Male and female Crl:CD(SD)BR rats and their offspring were exposed (6 h/d, 7 d/wk) by whole-body inhalation to concentrations of 0 (control), 300, 1,000 or 5,000 ppm (0, 1,880, 6,250 or 31,300 mg/m^3). Parental animals (12 males and 12 females per group) were exposed for 4 weeks prior to pairing, through mating, gestation, lactation and weaning of their offspring and were sacrificed after about 17 weeks of exposure. Exposure to HCFC-123 caused a dose-related increase in water consumption and decrease in food consumption. Also, a slight dose-related retardation in body weight gain was seen in the adults of all treatment groups as well as a reduced rate of growth in the pups. As in other repeated-exposure studies in the rat (Section 8.3) reduction in triglycerides was seen at all exposure levels. The administration of HCFC-123 did not affect the reproductive ability of the animals. There were no effects on implantations, litter size, or pup survival at any exposure level. Sexual maturation was delayed slightly in males in the 1,000 and 5,000 ppm groups. This was probably due to lower body weight gain seen in these groups compared to controls.

The effect of HCFC-123 on the reproductive performance and growth was evaluated in a 2-generation reproduction study conducted in male and female rats exposed (6 h/d, 7 d/wk; whole-body) to the test material at concentrations of 0 (control), 30, 100, 300 or 1,000 ppm HCFC-123 (188, 625, 1,880 or 6,250 mg/m^3). There were no clinical signs attributable to the exposure. Retarded body weight was observed among F_0 and F_1 males and females of the 1,000 ppm exposure group. At 100 and 300 ppm, a slight retardation of body weight gain was observed only in F_0 males, while there were no effects at 30 ppm. For both generations, weight gain at 1,000 ppm was lower than controls throughout pregnancy. For both generations during lactation, the overall pattern of weight change was considered comparable among the groups and not obviously affected by exposure. The food consumption was increased only in both F_0 male and female animals at 300 and 1,000 ppm. During lactation, food consumption was lower at 300 and 1,000 ppm in both generations. Food utilisation was impaired in F_0 animals at 300 and 1,000 ppm (only females) and F_1 animals only at 1,000 ppm. Increased water consumption was observed at 100, 300 or 1,000 ppm (only F_0 animals). Decrease of cholesterol and triglycerides, and VLDL values were observed in the animals of both generations at 100, 300 or 1,000 ppm. As discussed in Section 8.7.2, basal levels of oestradiol, testosterone, LH, 4-androstenedione,

progesterone and FSH were unaffected by treatment. Increased liver weights of F_0 and F_1 animals, macroscopic changes in the liver with associated microscopic changes of centrilobular hepatocyte enlargement and vacuolation were observed at 100, 300 or 1,000 ppm. At 30 ppm, a slight increase of liver weight was observed in the F_0 animals. Decreased litter weight and mean pup weight in F_0 offspring from day 14 post-partum to weaning and F_1 offspring from day 7 post-partum to weaning was observed at 100 ppm and above. At 1,000 ppm a reduction of implantation counts in F_1 females was observed. Male sexual maturation was slightly delayed at 300 and 1,000 ppm. The difference in growth rate may have been a factor in the delay of sexual maturation. No effects were seen at 30 and 100 ppm and in the female sexual maturation. At 30 ppm a decreased mean pup weight was observed only in the F_1 generation. The fat content in the milk of both F_0 and F_1 lactating dams was highly variable and did not yield useful data (Hughes, 1994).

Buschmann *et al* (2001) performed a study in Sprague-Dawley rats (Crl:CD BR) to differentiate between effects of HCFC-123 (1,000 ppm) on the lactating dam and on the foetus using fostering and cross-fostering of the offspring. Pregnant and/or lactating dams without the pups present were exposed (6 h/d) to HCFC-123 or clean air by whole-body inhalation from day 6 to 19 post-conception and from day 5 to 21 post-partum. Pups were cross-fostered on new dams within the first 2 days after birth. In mothers, HCFC-123 treatment caused decreased serum glucose, cholesterol and triglycerides and increased absolute and relative liver weights. There was no effect on milk production or composition. The effects on offspring due to HCFC-123 treatment consisted of decreased litter weight and individual pup weight and decreased serum triglycerides at weaning. All effects were due to treatment of the lactating dams as no pre-natally induced effects were obtained. The authors concluded that the presence of TFA in maternal milk was the possible cause of the effects seen in the pup (HCFC-123 was too volatile to allow measurement of concentrations in milk).

Summary and evaluation

In conclusion, exposure to HCFC-123 was principally associated with effects on growth, lipid metabolism and on the liver as has been seen in the subchronic studies. For both generations there were no treatment-related effects on mating performance. Reduced weight gains were observed among directly exposed adults as well as among offspring during the pre-weaning period when exposure was confined to the lactating dam. Effects on weight gains were observed at 100 ppm in adult animals and at the lowest exposure level employed (30 ppm) in offspring during the pre-weaning phase. During the post-weaning phase, the body weight gain was comparable to the controls at all dose levels except at 1,000 ppm. Liver weights were increased at 100 ppm but only among F_1 pups. Histopathological changes appeared confined to exposure of 100 ppm and above. In terms of reproductive performance, the only adverse finding was a decrease in implantation

counts among F_1 females at 1,000 ppm. As this effect was not seen in the 1-generation study, even with exposures up to 5,000 ppm, it is considered to be of marginal significance at most.

Regarding development, all exposure levels of HCFC-123 were associated with impaired pup growth in the offspring of F_1 generation. This was seen only during the pre-weaning phase. Although effects on fertility were not observed, it is not possible to identify a clear NOEL as effects were seen in some parameters at the lowest exposure level (30 ppm).

8.7 Special studies

8.7.1 Neurotoxicity

The potential for neurotoxic effects of HCFC-123 was investigated in a 13-week inhalation neurotoxicity study in rats (Coombs, 1994). Groups of 10 male and 10 female Sprague-Dawley rats were exposed (whole-body; 6 h/d, 5 d/wk), to vapour of HCFC-123 at concentrations of 0, 300, 1,000 or 5,000 ppm (0, 1,880, 6,250 and 31,300 mg/m^3).

The behaviour was assessed on several occasions: on 2 consecutive days before starting exposures; then at the end of weeks 4, 8 and 13 (on the day following the last 6-h exposure of the week concerned); then at the end of a 4-week recovery period. The Irwin behavioural screen methodology (Irwin, 1968) as indicated by WHO (1986) was used. It comprised a series of standardised observations in the home cage, on the bench, in the hand and in a few selected situations, including testing for grip strength, landing foot splay, startle response, tail pinch and righting reflex. In addition, whole-body perfusion/fixation was performed on 5 males and 5 females of each group at the end of the exposure and recovery periods. The brain was weighed and the following nerve tissues were examined histologically by light microscopy after haematoxylin-eosin staining: brain, medulla/pons, cerebellar cortex, spinal cord, ganglia, dorsal and ventral root fibres (C3-C6 and L1-L4), and peripheral nerves (sciatic, sural and tibial).

There were no treatment-related effects at any time or exposure level on the brain weight or on any of the nerve tissues. There was no apparent specific clinical sign although the body weight gain was slightly reduced in the high concentration group. The Irwin behavioural screen showed no treatment-related change, except for an apparent tendency to a reduction in arousal in male rats, which attained statistical significance at 1,000 and 5,000 ppm on week 13.

It should be noted that the behavioural assessment was performed on the day after the last 6-h exposure. By that time, the rats should normally have recovered from the anaesthesia-like effects that occurred during the inhalation exposure of HCFC-123 at concentrations of 5,000 ppm and above (Sections 8.1.3 and 8.3). However, the arousal reduction might be interpreted as a residual

effect in animals that may have not fully recovered from the anaesthesia-like effects of the previous day.

The lack of neurotoxicity of HCFC-123 in this study is consistent with the lack of any adverse clinical signs in medium and long-term exposed animals (Sections 8.3 and 8.5) at similar concentrations.

8.7.2 Endocrine evaluations

An evaluation performed by Sandow *et al* (1994) designed to investigate the mechanism of testicular changes (Leydig cell hyperplasia) observed in aging Sprague-Dawley rats after long-term treatment with HCFC-123 was conducted as an addendum to a 2-generation reproduction study (Hughes, 1994; also Section 8.6.2.). Near the end of the study, the pituitary-gonadal function was evaluated by a dynamic stimulation test using luteinising hormone-releasing hormone (LHRH) injection. At final necropsy, the capacity for androgen biosynthesis was evaluated by incubation of the testes *in vitro* with human chorionic gonadotropin (HCG).

Serum levels of several steroids (testosterone, progesterone, oestradiol, 17a-OH progesterone, and d4-androstenedione) were measured using male rats that were exposed (6 h/d, 7 d/wk) to HCFC-123 at levels up to 1,000 ppm (6,250 mg/m^3) for 22 weeks. In addition, testicular levels of luteinising hormone (LH) and testosterone were determined under both normal and stimulated conditions, with LHRH or HCG, respectively. No effects were observed on serum steroid levels. Basal levels of LH and testosterone were unaffected by the HCFC-123 exposures. With stimulation, the levels of LH in the 300 and 1,000 ppm exposure level groups were significantly lower than in the control and 100 ppm exposure level group. Moreover, a slight reduction in testosterone level was seen in all treatment groups compared to the control.

Warheit (1993) also evaluated serum hormone levels in male rats exposed to 18,200 ppm HCFC-123 (113,800 mg/m^3) and in guinea pigs exposed to 9,400 ppm (58,800 mg/m^3). Levels of testosterone, oestradiol and LH were measured in rats following 3 and 21 exposures. In addition, levels of cholecystokinin (CCK) were measured after 21 exposures. In the guinea pigs, levels of testosterone were measured after 3 and 21 exposures and CCK levels were determined after 21 exposures. No significant differences were seen in the HCFC-123 exposed rats compared to controls. In guinea pigs, testosterone levels may have appeared lower in HCFC-123 exposed animals compared to controls. CCK levels were unaffected by treatment.

The above studies indicate that exposure to HCFC-123 may have a minimal effect on the rat endocrine system. These endocrine effects are consistent with the testicular findings in the chronic inhalation study with rats.

8.7.3 Peroxisome proliferation and hypolipidemia

HCFC-123 induced hypolipidemia and hepatic proliferation of peroxisomes in rats in several studies. These effects suggest that HCFC-123 belongs to a particular class of chemicals, commonly referred to as peroxisome proliferators or hypolipidemic agents, whose effects are mediated through a disruption of lipid metabolism (Reddy and Lalwani, 1983). A thorough review of hepatic peroxisome proliferation has been published (ECETOC, 1992). As part of some of the studies conducted with HCFC-123, measurement of certain clinical chemical parameters was included, e.g. triglycerides and cholesterol. In addition, peroxisome proliferation was measured through measurement of β-oxidation of ^{14}C-palmitoyl-CoA, and actual changes in the density and numbers of peroxisomes were measured with electron microscopy.

In 90-day inhalation studies (Section 8.3), decreases in serum cholesterol, triglycerides or glucose were observed in rats at HCFC-123 concentrations of 300 ppm and greater. Likewise, in the chronic / oncogenicity study, decreases in these parameters were observed throughout the 2-year study at concentrations of 300 ppm and greater (Section 8.5).

In a 28-day inhalation study to assess the effects of HCFC-123 on rat liver, microsomal cytochrome P450 plasma and associated enzymes, male CD rats (6/group) were exposed to HCFC-123 concentrations of 0, 1,000, 5,000 or 20,000 ppm (0, 6,250, 31,300 or 125,000 mg/m^3) resulting in elevated liver and testes weights (Lewis, 1990). A dose-related reduction in plasma cholesterol levels was noted in the HCFC-123 exposed rats, with about a 50% reduction observed at the high concentration. Likewise, a reduction of about 60 to 70% in triglyceride levels was observed in the exposed rats (Table 13). An increase in alkaline phosphatase activity was also observed. In this study, an increase in β-oxidation activity measured by palmitoyl-CoA oxidase activity was observed at 20,000 ppm (229%), with increases also occurring at 1,000 and 5,000 ppm. Similar results were observed in the 90-day and 2-year inhalation studies at HCFC-123 concentrations of 300, 1,000 and 5,000 ppm. Cytochrome P450 or cytochrome b5 activities were unchanged.

Consistent with the increased β-oxidation levels was an increase in peroxisome numbers detected by electron microscopy (Table 13). Peroxisome numbers were 126% and 242% higher in the 5,000 and 20,000 ppm groups, respectively. Mitochondria levels were also increased. Taken together, these data indicate that HCFC-123 is a mild peroxisome proliferating compound. Liver hypertrophy was observed by light microscopy at all concentrations, although the severity of the response was much less at 1,000 ppm.

Table 13: Clinical chemical and liver biochemical measurements [a]

	HCFC-123 inhalation concentration			
Parameter	**0 (0)**	**1,000 (6,250)**	**5,000 (31,200)**	**20,000 ppm (125,000 mg/m^3)**
Plasma cholesterol (mg/100 ml)	71 ± 14[b]	55 ± 10	40 ± 3	35 ± 5
Plasma triglycerides (mg/100 ml)	82 ± 26	30 ± 14	21 ± 8	25 ± 8
Cytochrome P450 (nmol/mg protein)	0.73 ± 0.17	0.76 ± 0.13	0.81 ± 0.14	0.78 ± 0.11
β-Oxidation (nmol/min/mg protein) [c]	2.8 ± 0.56	5.3 ± 0.58	5.7 ± 1.6	9.2 ± 1.8
Peroxisome density [d]	1.9 ± 0.7	2.7 ± 0.7	4.3 ± 1.2	6.5 ± 1.1

[a] Groups of rats were exposed (6 h/d, 5 d/wk) for 28 days. From Lewis (1990)
[b] Values are the mean ± standard deviation
[c] β-Oxidation activity was measured as ^{14}C-palmitoyl-CoA oxidase activity
[d] Morphometric analysis of liver samples with electron microscopy

A 'mechanistic study' was conducted by Warheit (1993) using rats and guinea pigs in order to identify a potential mechanism for HCFC-123 induced tumours in the liver, pancreas and testes (Section 8.5). The study also included the use of Wyeth (WY)-14643, a compound known to induce peroxisomes, and TFA the primary metabolite of HCFC-123 (for details, see Section 8.3).

At the end of the exposure phase, the animals were subjected to cell turnover and histopathology evaluations, serum hormonal determinations, β-oxidation and clinical chemistry studies. The rate of hepatic peroxisomal β-oxidation was increased in rats exposed to HCFC-123, TFA or WY-14643 (Table 14). These data correlate with the observed increase in liver weights seen in this study, as well as with the microscopic findings of hypertrophy and the increased peroxisome number. In contrast, no increases in peroxisomal proliferation were observed in the pancreas. In guinea pigs exposed to any of these compounds, the rate of hepatic peroxisomal β-oxidation was unchanged. The species differences in the response to HCFC-123 exposure is associated with the sensitivity of the rat for the induction of peroxisome proliferation, and WY-14643 was clearly the more potent agent causing a greater degree of peroxisome induction and liver hypertrophy.

Table 14: Hepatic peroxisomal β-oxidation activity in rat and guinea pig

Rat	β-oxidation [a,b]
Control (0 ppm) [c]	10.9 ± 1.4 (n = 5)
HCFC-123 (18,200 ppm) [c]	51.2 ± 1.9 (n = 5)
TFA (7,500 ppm) [d]	45.8 ± 13.3 (n = 5)
WY-14643[d]	81.2 ± 8.5 (n = 5)
Guinea pig	
Control (0 ppm) [c]	9.3 ± 1.4 (n = 3)
HCFC-123 (18,200 ppm) [c]	7.1 ± 1.1(n = 4)
TFA (7,500 ppm) [d]	8.8 ± 1.4 (n = 3)
WY-14643 [d]	7.1 ± 1.7(n=3)

[a] β-Oxidation activity was measured as ^{14}C-palmitoyl CoA oxidase activity
[b] Values are mean ± standard deviation
[c] Exposures were 6 h/d, 5d/wk
[d] Administered in the diet

An evaluation of the human relevance of the rodent liver tumours induced by HCFC-123 is best considered within the context of peroxisome proliferator activated receptor (PPAR) or the pharmacological activity associated with this class of compounds. TFA, the principal metabolite of HCFC-123, has also been shown to act as a peroxisomal proliferator in the liver (Just *et al*, 1989 and Warheit, 1993). The nature of the chronic tumourigenic response to HCFC-123 in rats and the short-term peroxisomal responses to both HCFC-123 and TFA are consistent with expectations based on other peroxisomal proliferators. For all three tissues in which tumours occurred, the cell type associated with the lesion contained peroxisomes, and/or had been a site of tumourigenic activity for other peroxisomal proliferators (Fitzgerald *et al*, 1981; Mennear, 1988; Sibinski, 1987; Svoboda and Azarnof, 1979; Reddy and Rao, 1977; Cook *et al*, 1994). However, peroxisome proliferation with HCFC-123 has only been demonstrated in the liver.

Male Crl:CD BR rats were exposed (6 h/d) to 5,000 ppm (31,300 mg/m^3) HCFC-123 for 5 consecutive days. Liver weights were slightly decreased compared to controls. The serum triglycerides and cholesterol levels were decreased to approximately 20% and to less than 80% of the controls, respectively. HCFC-123 increased hepatic β-oxidation by approximately 3-fold over control and caused a significant increase in hepatic cytochrome P450 content (Keller *et al*, 1998).

In conclusion, the above results provide good evidence that HCFC-123 is a rat liver peroxisome proliferator, although the proliferating activity is weak. The peroxisome proliferating activity is very likely due to its metabolism to TFA.

8.7.4 *In vitro* studies in testicular cell cultures

An investigation was made of the ability of several fluorocarbons, including HCFC-123 and postulated metabolites of HCFC-134a (including TFA), to perturb key types of cultured testicular cells (*in vitro*) obtained from Sprague-Dawley rats. Chemical effects on isolated Leydig cell cultures, Sertoli cell only cultures and Sertoli germ cell co-cultures were investigated. HCFC-123 at atmospheric concentrations in the range of 2.5 to 10% was cytotoxic. In Sertoli germ cell co-cultures, HCFC-123 caused altered morphology, increased cell loss and lactate dehydrogenase-X (LDHX) leakage, and in Sertoli cell only cultures, HCFC-123 also altered cell morphology and increased lactate and pyruvate production. HCFC-123 had no effect on Leydig cell cultures. The author concluded that the study provided evidence that HCFC-123 could cause effects on testicular cells *in vitro* (Williams, 1997). However, the *in vitro* systems used do not allow the establishment of neither the relative roles of the fluorocarbon versus metabolites nor the extrapolation of the *in vitro* findings to the whole animal *in vivo*.

8.7.5 Other investigations

A study in male Hartley guinea pigs investigated the effects of HCFC-123 alone or in a blend containing non-hepatotoxic HCFC-124. Animals were exposed for 4 hours to 5,000 ppm HCFC-123 alone (31,300 mg/m^3) or in combination with 5,000 ppm HCFC-124 (27,900 mg/m^3) [a] for 1 (single exposure) or for 5 consecutive (repeated exposure) days. Animals were killed 24 or 48 hours after the end of the respective exposure. HCFC-123 caused increased mean serum levels of alanine aminotransferase at 24 hours and isocitrate dehydrogenase at 24 and 48 hours after either single or repeated exposure. Assessment of liver tissue revealed mild (foci of necrotic hepatocytes) to moderate (multifocal random degeneration and necrosis) damage. Steatosis was also seen and found to be more pronounced with repeated exposure. With few exceptions, there were no significant differences between animals treated with HCFC-123 alone or with the blend. One animal out of 6 (blend, repeated exposure, 24-h kill) showed symptoms similar to halothane-induced hepatitis. HCFC-124 had no effect on the urinary excretion of metabolites (TFA and chlorodifluororacetic acid) or on the HCFC-123 induced depletion of hepatic glutathione. The study concluded that there was very limited indication of a potentiation by HCFC-124 of the hepatotoxicity induced by HCFC-123 (Hoet *et al*, 2001).

Hoet *et al* (2002) investigated liver effects of multiple exposures to HCFC-123 and whether ethanol potentiates the hepatotoxicity of HCFC-123 in male Hartley guinea pigs. In one set of experiments, animals were exposed (2 x 4 h/wk) to 5,000 ppm HCFC-123 (31,300 mg/m^3) for 3 weeks, followed by a 2-week recovery period after which some animals were exposed (single 4 h) again to 5,000 ppm HCFC-123. Multiple exposures did not enhance liver toxicity seen with

[a] Calculated according to Appendix C; molecular mass: 136.5

single exposure to HCFC-123. In the ethanol-effect study, animals received ethanol (5 or 10% in drinking water) for 12 days before a single 4-hour exposure to 5,000 ppm HCFC-123. In addition to control animals, one group received only 10% ethanol and another was administered a single 4-hour HCFC-123 exposure (5,000 ppm). Liver toxicity was assessed 24 hours post-exposure by measuring serum alanine aminotransferase and isocitrate dehydrogenase and also histopathologically. The urinary levels of the metabolites TFA and chlorodifluoroacetic acid were measured. CYP2E1 activity was also determined, as ethanol is a potent inducer of CYP2E1. Ethanol consumption induced CYP2E1, increased urinary output of HCFC-123 metabolites and markedly potentiated liver toxicity. The effects associated with 10% ethanol were less pronounced than those with 5% ethanol. The authors suggested that remaining (un-metabolised) ethanol in the 10% exposed animals might have inhibited the biotransformation of HCFC-123 to TFA.

9. EFFECTS ON HUMANS

9.1 General population exposure

HCFC-123 is not used in consumer products. Indirect exposure of the general population would be minimal as the concentration in ambient air is less than 0.01 ppt and because it is unlikely for HCFC-123 to persist in other media because of its limited solubility and high volatility (IPCS, 2000).

9.2 Occupational exposure

Hoet *et al* (1997) reported the occurrence of liver disease in workers exposed to HCFC-123 and HCFC-124 (1-chloro-1,2,2,2-tetrafluoroethane). Workers were exposed when the refrigerant permeated the tubing and leaked into the cab of an overhead crane. Six workers were affected to various degrees. Liver biopsy in 1 employee showed hepatocellular necrosis that was prominent in pre-venular zone 3 and extended focally from portal tracts and centrilobular areas. Trifluoroacetyl-adducted proteins were detected in surviving hepatocytes. Auto-antibodies previously associated with halothane-induced hepatitis were detected in the serum of 5 of the workers. The workers recovered when exposure was discontinued. No estimate of exposure levels was provided.

Takebayashi *et al* (1998) also reported liver dysfunction among workers exposed to HCFC-123 for 2 months. Four out of 14 workers developed severe liver damage as determined by liver function tests. Other symptoms included poor appetite and abdominal pain. Five workers were reported to have slight increases in serum aspartate transaminase (AST) and serum alanine transferase (ALT) with normal bilirubin levels. Viral and other causes of hepatitis were ruled out. All workers recovered quickly when removed from exposure. No estimate of exposure levels was provided.

A case of acute and recurrent hepatitis was reported in a 49-year old female dry-cleaning worker. The dry-cleaning solvent used was a mixture of HCFC-123 (23.7% w/w) and HCFC-141b (29.7%) in *n*-heptane (46.4%). Subsequently, simulated exposure concentrations were measured to be as high as 1,370 and 1,590 ppm HCFC-123 (8,560 and 9,940 mg/m^3) (2 personal samples) for 10 minutes. The corresponding mean area concentrations were 1,360 and 1,990 ppm HCFC-123 (8,500 and 12,440 mg/m^3) (2 points at the work place). Upon the actual exposure, the patient showed acute hepatitis as demonstrated by high hepatic function parameters, including serum AST, ALT, alkali phosphatase (ALP), γ-glutamyl transpeptidase (GGT), LDH and total bilirubin, without viral infection. Serum parameters returned to normal within a few weeks without specific treatment. Upon return to her dry-cleaning job, after 1 day, the patient relapsed into the same

symptoms and clinical signs and was diagnosed with chronic hepatitis. As before, serum parameters of liver dysfunction returned to normal within about 1 month. The authors concluded that the hepatitis was induced by HCFC-123, although urinary metabolites were not determined (Omae *et al*, 2000).

Boucher *et al* (2003) indicated that when HCFC-123 was introduced as a precision cleaning agent in a controlled operation, marked elevations in ALT and AST were seen in exposed workers. Industrial hygiene sampling collected at that location during the start-up period indicated personal samples ranging from 24 to 480 ppm (150 - 3,000 mg/m^3) for 375 and 21 minutes, respectively. Personal and area samples collected at the site after the liver abnormalities had been observed were 5 to 12 ppm (31 - 75 mg/m^3), but exposure data were not available during the time when abnormalities were suspected to have developed. The authors describe two models developed to estimate exposure during the monitored period. One model treated the plant as one homogeneous box whereas the other divided the plant into smaller work zones. The one homogeneous box model estimated 8-h TWA exposures ranging from 10 to 35 ppm (63 - 219 mg/m^3). Modelling using estimates of work area and air exchange rates indicate that individuals working with the degreaser could have been exposed to peak levels from 280 to 2,100 ppm (8-h TWA 252 - 1,630 ppm) (1,750 - 13,100; 1,580 - 10,200 mg/m^3). Modelling of the work environment estimated to be one-third of the volume of the entire open building indicated that employees in the area could have been exposed to peak levels from 28 to 210 ppm (8-h TWA 25 - 163 ppm) (175 - 1,310; 156 - 1,020 mg/m^3). The investigators' estimates using 12 air changes per day suggest that peak levels around the degreaser could have been from 635 to 2,100 ppm (8-h TWA 499 - 1,630 ppm) (3,970 - 13,100; 3,120 - 10,200 mg/m^3) and in the work area 63 - 207 ppm (8-h TWAs 50 - 163 ppm) (394 - 1,290; 313 - 1,020 mg/m^3). All liver function parameters returned to normal upon termination of the use of HCFC-123.

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APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

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

APPENDIX B: NAMING AND NUMBERING SYSTEM FOR FLUOROCARBON COMPOUNDS

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

B.1 Prefixes

These prefixes are generally applicable:

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

B.2 Numbering code

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

The number of chlorine atoms in the compound is calculated by subtracting the sum of fluorine and hydrogen atoms from the total atoms which can be connected to the carbon atoms. If some of the chlorine has been replaced by bromine, then the number is followed by a ‘B’ 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-$CF_3$

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
- CF3-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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[b] Part-time (ECETOC, 1996)

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Monographs

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