Chlorofluorocarbons: CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31, HCFC-133a

Evaluation of health hazards and proposals of a health based quality criterion for air and groundwater

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Contents

Preface

This report has been prepared by Lea Bredsdorff and Elsa Nielsen, Division of Toxicology and Risk Assessment, National Food Institute (DTU Food), Technical University of Denmark.

Danish Regions have registered the chlorofluorocarbons CFC-11 (trichlorofluoromethane) and CFC-12 (dichlorodifluoromethane) in concentrations of up to 4 000 mg/m^3, as well as their degradation products, HCFC-21 (dichlorofluoromethane) and HCFC-31 (chlorofluoromethane) in concentrations of up to 120 µg/m^3 in porous air of soils in close proximity to residences. The contamination has been reported to stem from waste disposal on industrial sites and dry-cleaning facilities, disposal of rigid polyurethane products (isolation materials) at hazardous waste sites and waste dumps, and release from district heating pipes with polyurethane isolation. (Danske Regioner 2013)

The Danish EPA has set a C-value of 1 mg/m^3 for HCFC-141b (1,1-dichloro-1-fluoroethane) and for CFC-11 in order to protect the environment against their ozone depletion potential.

On this background the Danish EPA has requested documentation for health-based quality criteria in air and groundwater for the following six chlorofluorocarbons: CFC-11, CFC-12, HCFC-21, HCFC-31, CFC-113 (1,1,2-trichloro-1,2,2-trifluoroethane) and HCFC-133a (1-chloro-2,2,2-trifluoroethane). A concern for toxic effects of these chlorofluorocarbons, as well as of a carcinogenic potential of the degradation products of the chlorofluorocarbons has been expressed and therefore, this issue should be particularly addressed in the documentation.

The report has been elaborated according to the general practice laid down in the Danish EPA guidance document for the setting of health-based quality criteria for chemical substances in relation to soil, ambient air and drinking water (Vejledning fra Miljøstyrelsen 5/2006).

The report has been subjected to review and discussion and has been endorsed by a steering committee with representatives from the following Danish authorities / institutions:

The National Board of Health
The Danish Nature Agency
The Danish Veterinary and Food Administration
Danish Regions
Danish Environmental Protection Agency
Faculty of Agricultural Sciences, Aarhus University

1. General description

Fully halogenated chlorofluorocarbons (CFCs) are compounds derived by the complete substitution of the hydrogen atoms in methane and ethane with both fluorine and chlorine atoms. CFC-11 (trichlorofluoromethane) and CFC-12 (dichlorodifluoromethane) are both methane derivatives and CFC-113 (1,1,2-trichloro-1,2,2-trifluoroethane) is an ethane derivative.

Partially halogenated chlorofluorocarbons (HCFCs) are compounds derived by the partial substitution of the hydrogen atoms in methane and ethane with both fluorine and chlorine atoms. HCFC-21 (dichlorofluoromethane) and HCFC-31 (chlorofluoromethane) are both methane derivatives and HCFC-133a (1-chloro-2,2,2-trifluoroethane) is an ethane derivative.

1.1 Identity

The identity of the chlorofluorocarbons evaluated in this document is presented in Table 1.

1.2 Physical / chemical properties

Fully halogenated chlorofluorocarbons (e.g., CFC-11, CFC-12, CFC-113) are usually characterised by high vapour pressure and density and low viscosity, surface tension, refractive index, and solubility in water (EHC 1990).

The partially halogenated chlorofluorocarbons (HCFC-21, HCFC-31, HCFC-133a) are non-flammable gases at normal temperatures and pressures, colourless, and practically odourless. They are slightly or moderately soluble in water and miscible with many organic solvents. Generally, hydrochlorofluorocarbons of low relative molecular mass are characterised by high vapour pressure, density, and refractive index, and low viscosity and surface tension. (EHC 1991; EHC 1992)

The degree of fluorine substitution affects the physical properties of chlorofluorocarbons. In general, the vapour pressure increases as the number of fluorine atoms replacing chlorine increases, but the boiling point, density, and solubility in water decrease. Generally, the chlorofluorocarbons exhibit a high degree of chemical stability as a result of the strength of the carbon-fluorine bond, i.e. the carbon-fluorine bonds in the chlorofluorocarbon compounds are extremely resistant to almost all chemical reagents. Chlorofluorocarbons are generally also highly resistant towards oxidising agents at temperatures < 200°C, as well as to thermal degradation. (EHC 1990)

Selected physical / chemical properties of the chlorofluorocarbons evaluated in this document are presented in Table 2.

Substance	CAS-no.	Structural formula	Molecular weight (g/mol)	Synonyms include
Trichlorofluoromethane (CFC-11)	75-69-4	CCl_3F	137.37	Fluorochloroform; Fluorotrichloromethane; Trichlorofluorocarbon; Trichloromethyl fluoride; Freon 11; Propellant 11 and R 11
Dichlorodifluoromethane (CFC-12)	75-71-8	CCl_2F_2	120.92	Carbon dichloride difluoride; Chlorofluorocarbon 12; Difluorodichloromethane; Freon 12 and R 12
Trichlorotrifluoroethane (CFC-113)	76-13-1	$C_2Cl_3F_3$	187.38	1,1,2-Trichloro-1,2,2-trifluoroethane; 1,1,2-Trichlorotrifluoroethane; 1,1,2-Trifluoro-1,2,2-trichloroethane; 1,1,2-Trifluorotrichloroethane; 1,2,2-Trichlorotrifluoroethane; Chlorofluorocarbon 113; Freon 113 and R 113
Dichlorofluoromethane (HCFC-21)	75-43-4	$CHCl_2F$	102.92	Dichloromonofluoromethane; Fluorodichloromethane; Monofluorodichloromethane; Freon 21 and R 21
Chlorofluoromethane (HCFC-31)	593-70-4	CH_2ClF	68.48	Fluorochloromethane; Methylene chloride fluoride; Freon 31 and R 31
Chlorotrifluoroethane (HCFC-133a)	75-88-7	$C_2H_2ClF_3$	118.49	(Chloromethyl)trifluoromethane; 1,1,1-Trifluoro-2-chloroethane; 1,1,1-Trifluorochloroethane; 1,1,1-Trifluoroethyl chloride; 1-Chloro-2,2,2-trifluoroethane; 2,2,2-Trifluoro-1-chloroethane; 2,2,2-Trifluorochloroethane; 2,2,2-Trifluoroethyl chloride; 2-Chloro-1,1,1-trifluoroethane; Freon 133a; R 133a

TABLE 1
IDENTITY OF SELECTED CHLOROFLUOROCARBONS

Substance	Description	Melting point (°C)	Boiling point (°C)	Density of saturated vapour at boiling point (g/litre)	Vapour pressure (Torr at 25°C)	Conversion factor (1 mg/m³ = ppm) (25°c, 1 atm)	Conversion factor (1 ppm = mg/m³) (25°c, 1 atm)	Water solubility (mg/L at 25°C)	Flash point	logP octanol/water (25°C)	Henry's constant (atm m³/mol)
CFC-11	Liquid at temperatures < 23.7 °C. Colourless. Faint ethereal odour	-111	23.82	5.86	714	0.178	5.618	620	Nonflam-mable	2.44	0.11
CFC-12	Colourless and nearly odourless gas	-158	-29.79	6.33	4830	0.202	4.945	1 300	Nonflam-mable	2.05	0.009
CFC-113	Colourless and nearly odourless volatile liquid	-35	47.57	7.38	296	0.13	7.664	62	Nonflam-mable	3.2	0.53
HCFC-21	Volatile colourless, practically odourless gas at normal temperatures and pressures	-135	8.9	4.57	1340	0.038	4.209	3 300	Nonflam-mable	1.48	0.01
HCFC-31	Gas	-133	-10.8	_	2600	0.357	2.801	8 900	Nonflam-mable	0.97	0.007
HCFC-133a	Nearly odourless, colourless gas	-105.3-105.5	6.93	5.17	1430	0.206	4.846	1 100	Nonflam-mable	1.67	0.27

TABLE 2
PHYSICAL/CHEMICAL PROPERTIES OF SELECTED CHLOROFLUOROCARBONS.
REFERENCES: EHC 126, 1991; EHC 113, 1990; US EPA 113; EHC 139, 1992; SCIFINDER (HTTPS://SCIFINDER.CAS.ORG/SCIFINDER/LOGIN); HTTP://WWW.SKCINC.COM/CONVERTER/CONVERTER.ASP; IARC 1986; ECETOC 1990.

1.3 Production and use

CFCs and HCFCs, as well as several other halogenated substances are ozone-depleting chemicals. The protection of the ozone layer is coordinated internationally by regulations under the United Nations Environmental Program (UNEP). The UN Regulation consists of the 'Vienna Convention for the Protection of the Ozone Layer' and its 'Montreal Protocol on Substances that Deplete the Ozone Layer'. The Vienna Convention (agreed upon in 1985 and entered into force in 1988) acts as a framework for the international efforts to protect the ozone layer, but does not include legally binding reduction goals for the use of chemical agents causing ozone depletion. These are laid down in the accompanying Montreal Protocol (adopted on 16 September 1987 entered into force on 1 January 1989). Since its initial adoption, the Montreal Protocol has been adjusted and amended several times. The EU implements the UN regulation in 'Regulation (EC) No 1005/2009 of the European Parliament and of the Council of 16 September 2009 on substances that deplete the ozone layer'. (UNEP 2014; DEPA 2014a)

The production and use of CFCs are banned according to the Montreal Protocol and CFC-11, CFC-12 and CFC-113 are included in group I in Annex I (controlled substances) of Regulation 1005/2009. The HCFCs were introduced as substitutions for the CFCs because of lower ozone depletion potential. According to the Montreal Protocol the production and use of HCFCs are banned from 2020 in the industrial countries and from 2040 in the undeveloped countries. HCFC-21, HCFC-31 and HCFC-133 are included in group VIII in Annex I of Regulation 1005/2009. (DEPA 2014b)

Below the production and uses of the chlorofluorocarbons are summarised very briefly.

1.3.1 CFCs

The fully halogenated chlorofluorocarbons were traditionally manufactured by catalytic displacement of chlorine from chlorocarbons (normally carbon tetrachloride and hexachloroethane) with fluorine by reaction with anhydrous hydrofluoric acid. An alternative process for the production of the methane-based chlorofluorocarbons used the direct reaction of methane with a mixture of chlorine and hydrogen fluoride. (EHC 1990)

The main uses of CFCs (including CFC-11, CFC-12 and CFC-113) were as refrigerants, solvents, blowing agents, sterilants, aerosol propellants and as intermediates for plastics (EHC 1990).

1.3.2 HCFCs

HCFC-21 is primarily manufactured by reaction of chloroform with anhydrous hydrofluoric acid in the presence of a catalyst at various reaction temperatures and pressures.
HCFC-21 is used as a refrigerant for centrifugal machines, as a solvent in aerosol products, in fire extinguishers, as a propellant and as a heat exchange fluid in geothermal energy applications. (EHC 1991)

HCFC-31 is not produced in commercial or bulk quantities. It can be synthesised (laboratory scale) by treatment of dichloromethane with potassium fluoride, sodium fluoride and ethylene glycol at 180-200°C for 2 hours. HCFC-31 has been identified as an impurity (3.8 %) in commercial HCFC-21. (Ratcliffe & Target 1969 cited from IARC 1986).

HCFC-133a is synthesised by fluorination of trichloroethylene with hydrogen fluoride in the presence of a catalyst.
HCFC-133a is primarily used as intermediate in the synthesis of halothane (a commonly used general anaesthetic) and as a precursor for the production of trifluoroacetic acid.
HCFC-133a has been identified as an impurity in halothane and as a major mammalian metabolite of halothane. (IARC 1986)

1.4 Environmental occurrence and fate

The chlorofluorocarbons evaluated in this document are anthropogenic compounds with no known natural occurrence.

Chlorofluorocarbons can be released into the environment during manufacture, handling, use, or disposal of wastes. Because of the high vapour pressure of chlorofluorocarbons at ambient temperatures, the release from different sources will primarily be to the atmosphere (EHC 1990).

The following paragraph is an MST contribution provided in Danish and translated by the Contractor:
In Denmark, CFC's and HCFC's have been detected in the porous air of soils at former industrial sites at concentrations of up to a few thousands mg/m^3 for CFC's and of up to some hundreds mg/m^3 for HCFC-21. Concentrations of up to about 40 mg/m^3 of CFC-11 and of up to 0.2 mg/m^3 of HCFC's have been measured in the porous air of soils in close proximity to district heating pipes with polyurethane isolation. (DEPA 2014c)

1.4.1 Air

1.4.1.1 CFCs

Because of the high vapour pressure of the six chlorofluorocarbons evaluated in this document at ambient temperatures, the release from different sources will primarily be to the atmosphere. Once in the troposphere (the lowest layer of the atmosphere), CFC-11 and CFC-12 will eventually diffuse into the stratosphere (the second lowest layer of the atmosphere and includes the ozone layer) or be transported back to the earth through precipitation. (EHC 1990)

CFC-11 and CFC-12 are known to be relatively stable with respect to reaction with hydroxyl radicals present in the troposphere and they do not undergo photo-dissociation in the troposphere, since they do not absorb radiation at wavelengths greater than 200 nm. In the stratosphere CFC-11 and CFC-12 undergo photo-dissociation by higher energy, shorter wavelength ultraviolet radiation. The photo-dissociation of both CFC-11 and CFC-12 results in the release of two chlorine atoms since less energy is required to cleave the C-Cl bond than the C-F bond. The chlorine atoms released by the photo-dissociation are catalysts in the destruction of the stratospheric ozone layer. (EHC 1990)

The chlorofluorocarbons are relatively persistent in the environment because of their chemical stability. Average residence times in the atmosphere of 65, 110 and 90 years for CFC-11, CFC-12 and CFC-113, respectively, have been reported. Assuming a troposphere-to-stratosphere turnover time (the time taken for 63 % of troposphere air to diffuse into the stratosphere) of 30 years, tropospheric life-times of 65 and 110 years for CFC-11 and CFC-12, respectively, would result in about 86 % of tropospheric CFC-11 and CFC-12 eventually reaching the stratosphere. (EHC 1990)

1.4.1.2 HCFCs

The physical and chemical properties of the partially halogenated chlorofluorocarbons (HCFC-21, HCFC-31 and HCFC-133a) suggest that they will be rapidly mixed within the lower region of the troposphere. Reaction with naturally occurring hydroxyl radicals in the troposphere is thought to be the primary degradation route for the HCFCs. (EHC 1991; EHC 1992)

Based on the estimated trophospheric rate of the reaction of HCFCs with hydroxyl radicals, the average lifetime has been estimated to be about 2, 1.6 and 4.8 years for HCFC-21, HCFC-31 and HCFC-133a, respectively (EHC 1991; IARC 1986a; EHC 1992; IARC 1986b).

1.4.2 Water

Because of the high vapour pressure of the six chlorofluorocarbons evaluated in this document these chlorofluorocarbons will most likely volatilise to the atmosphere when released under ambient conditions into aquatic systems. (EHC 1990)

Chlorofluorocarbons generally exhibit a low rate of hydrolysis under ambient conditions and the rates of hydrolysis, which are greatly affected by temperature, pressure, and the presence of catalytic materials (such as metals) are considered to be negligible compared with the rate of volatilisation of the chlorofluorocarbons and subsequent photo-dissociation. No information was available concerning the oxidation of CFCs in the aquatic environment under ambient conditions. (EHC 1990)

Biodegradation of chlorofluorocarbons has been reported to occur under special circumstances, see section 1.4.4.

1.4.3 Soil

The octanol/water partition coefficients of the six chlorofluorocarbons evaluated in this document indicate that adsorption onto organic particulates may be possible. In cases of significant sorption to soils, the volatilisation of these compounds will be slower than in aquatic systems, though volatilisation may still be the major transport process from soils (EHC 1990).

Biodegradation of chlorofluorocarbons has been reported to occur under special circumstances, see section 1.4.4.

1.4.4 Biodegradation

Biodegradation of CFC-11, CFC-12, HCFC-21, HCFC-31 and CFC-113 has been reported to occur in various environmental media under special circumstances, predominantly under anaerobic conditions. No data on the biodegradation of HCFC-133a have been located.

The biodegradation of chlorofluorocarbons in general has only been reported to occur under co-metabolic conditions, either under anaerobic conditions with electron-donating compounds or under aerobic co-oxidation conditions with primary substrates that induce monooxygenase activity. Oxidation of chlorinated solvents by the methane monooxygenase expressed by methylotrophic organisms to oxidize methane is a classic example of co-metabolism. Under anaerobic conditions, a common form of co-metabolism is the reaction of reduced enzyme cofactors with chlorinated solvents, resulting in their reductive dehalogenation (Field & Sierra-Alvarez 2004).

1.4.4.1 CFCs

CFC-11 has been shown to be degraded in strongly reducing subsurface anoxic zones of the Black Sea and Saanich Inlet on the coast of British Columbia (Canada); no degradation occurred in aerobically incubated oxygenated water samples. CFC-11 and CFC-113 have been shown to be degraded by bay sediments. Both CFC-11 and CFC-12 were consumed in microcosms established with various anaerobic freshwater (river, pond, marsh, swamp) sediments. CFC-11 degradation was also observed in microcosms established with an anaerobic groundwater sample. CFC-11 and CFC-113 were significantly depleted in an anoxic groundwater leaching from a hazardous waste site. Biodegradation of CFC-113 was also observed in an aquifer contaminated by a hazardous waste dump and in landfill leachate. CFC-11 and to a lesser extent CFC-12 have been shown to be biodegraded in peat samples from swamp and bog sites; no degradation occurred in an aerobic soil microcosm. An un-adapted methanogenic municipal digester sludge significantly degraded CFC-11, CFC-12 and CFC-113 within 14 days. CFC-11 and to a lesser extent CFC-12 was degraded in anaerobically incubated municipal solid waste. (Field & Sierra-Alvarez 2004)

To compensate for the lack of actual data on fate and distribution of organic chemicals (including CFC-11, CFC-12 and CFC-113) in landfills a mathematical model for predicting these aspects has been proposed. The model simulate the distribution of organic chemicals between the leachate, the gas phase and the solid phase and predicts the relative fate routes of the chemicals in terms of gas and leachate emissions and degradation in the landfill body. The model is built on a series of assumptions (e.g. on the amount of organic chemicals entering a landfill and on the waste composition and state) but is founded on physical-chemical properties, a first order degradation term and average data for losses by leachate and gas. (Kjeldsen & Christensen 2001)

1.4.4.2 HCFCs

Anaerobic degradation of HCFC-21 has been observed in freshwater and salt marsh sediments. Aerobic degradation of HCFC-21 has been observed in aerobic soils supplied with methane. (Field & Sierra-Alvarez 2004)

HCFC-21 has been shown to be completely degraded by the bacterial strains *Methylosinus trichosporium* OB3b and *Mycobacterium vaccae* JOB5, as well as by the methanotrophs ENV2040 (a mixed methanotrophic culture with two members enriched from agricultural soil) and ENV2041 (an unidentified methanotroph obtained from local agricultural soil) under aerobic conditions (Streger et al. 1999). The bacteria *Methylosinus trichosporium* is commonly occurring in fresh water, and in marine and terrestrial environments (Sullivan et al. 1998).

Gas profiles of the upper oxic zone of waste, soil etc. suggests that HCFCs are rapidly degraded probably coupled to methane oxidation (e.g., via methanotrophic, aerobic co-metabolic biodegradation) (Scheutz et al. 2010; Scheutz & Kjeldsen 2005).

1.4.4.3 Biodegradation intermediates / products

Reported biodegradation intermediates/products of CFC-11, CFC-12, CFC-113, HCFC-21 and HCFC-31 are presented in Table 3. A more detailed description of the biodegradation of CFC-11 (including HCFC-21 and HCFC-31) and CFC-113 are presented in Figure 1 and 2, respectively.

Substance	Anaerobic	Aerobic	Matrix	References
CFC-11	HCFC-21		• Sewage sludge and aquifer sediment microcosm. • Simulated anaerobic landfill conditions. • Sulphate-reducing enrichment culture • Municipal solid waste • Digester sludge	Balsiger et al. 2005. Balsiger et al. 2005. Deipser & Stegmann 1997. Sonier et al. 1994. Deipser & Stegmann 1994. Olivas et al. 2002
CFC-11	HCFC-31		• Municipal solid waste	Ejlertsson et al. 1996
CFC-11	HCFC-21 and HCFC-31		• Anaerobic compost	Deipser 1998

CFC-11	HCFC-21; HCFC-31 and HFC-41		• Compost mixed with wood chips • Organic household waste inoculated with anaerobic digester sludge microcosm	Scheutz et al. 2009 Scheutz et al 2007
CFC-12	HCFC-22		• Sewage sludge and aquifer sediment microcosm. • Simulated anaerobic landfill conditions. • Anaerobic compost • Municipal solid waste	Balsiger et al. 2005 Deipser & Stegmann 1997 Deipser 1998 Ejlertsson et al. 1996
CFC-12	HCFC-22; HFC-32 and HFC-41		• Organic household waste inoculated with anaerobic digester sludge microcosm	Scheutz et al. 2007
CFC-113	HCFC-123a and CFC-1113		• Sewage sludge microcosm • Municipal landfill leachates • Contaminated groundwater from a landfill	Balsiger et al. 2005 Lesage et al. 1989 Lesage et al. 1990
CFC-113	HCFC-123a; HCFC-133; HCFC-133b and CFC-1113		• Landfill leachate	Lesage et al. 1992

Table 3 continued...

Substance	Anaerobic	Aerobic	Matrix	References
CFC-113	HCFC-123a; CFC-1113 and trifluoroethene		• Aquifer sediment microcosm	Balsiger et al. 2005
CFC-113	HCFC-123a; HCFC-122a and CFC-1113		• Contaminated aquifer	Lesage et al. 1990
HCFC-21	HCFC-31		• Sewage sludge and aquifer sediment microcosm. • Compost mixed with wood chips	Balsiger et al. 2005 Scheutz et al. 2009
HCFC-21		*Aerobic	• Compost mixed with	Scheutz et al. 2009

	oxidation in parallel with oxidation of CH_4	• wood chips • Supermuld®	Scheutz et al. 2009
HCFC-31	*Aerobic oxidation in parallel with oxidation of CH_4	• Compost mixed with wood chips • Supermuld®	Scheutz et al. 2009 Scheutz et al. 2009

TABLE 3
BIODEGRADATION INTERMEDIATES/PRODUCTS OF SELECTED CHLOROFLUOROCARBONS

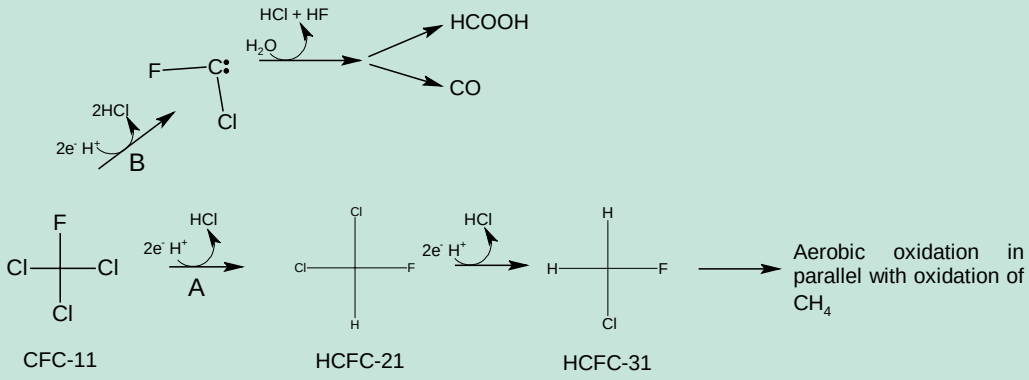

FIGURE 1
BIODEGRADATION OF CFC-11, HCFC-21 AND HCFC-31.
A: *IN VIVO* BIODEGRADATION PATHWAYS
B: THIS DEGRADATION PATHWAY HAS ONLY BEEN SHOWN *IN VITRO*.
REFERENCES: FIELD & SIERRA-ALVAREZ 2004; ARCHBOLD ET AL. 2012

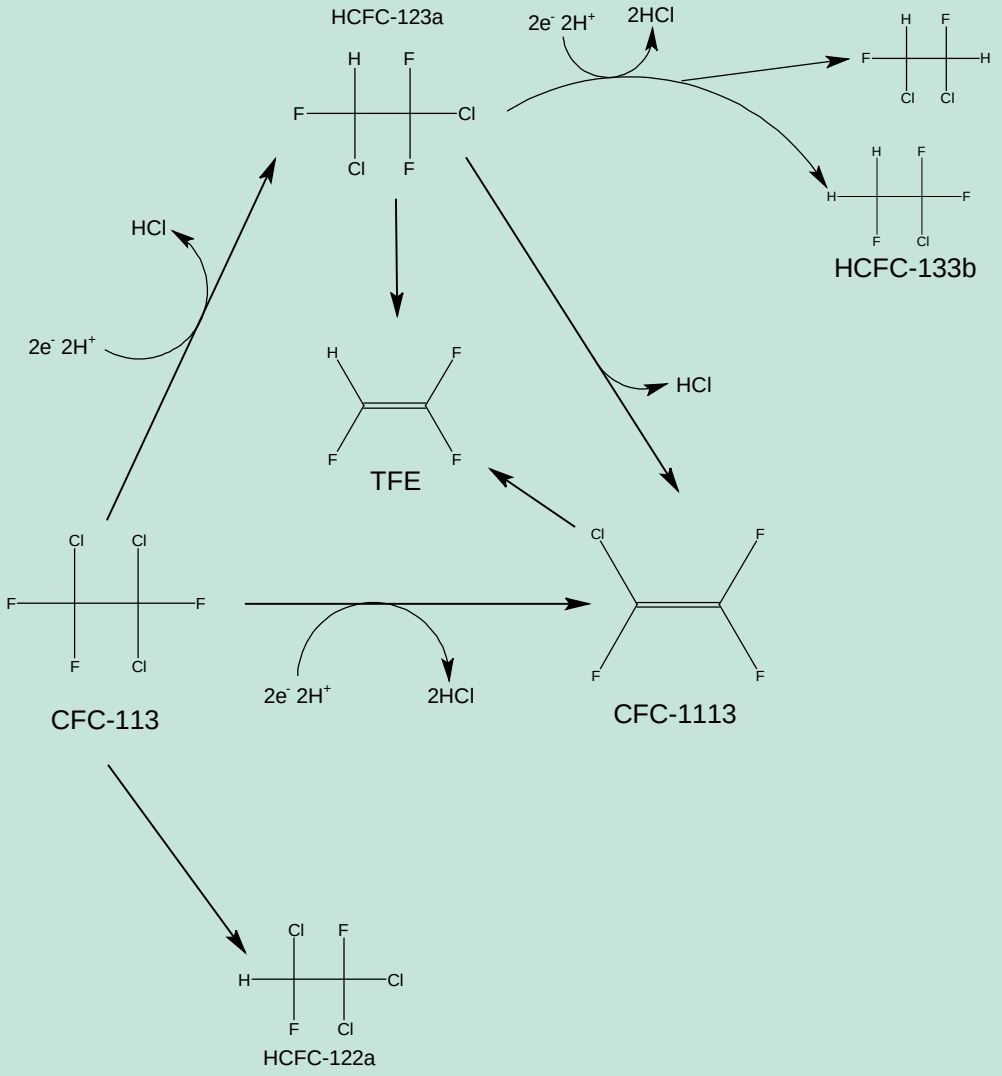

FIGURE 1
BIODEGRADATION OF CFC-113. TFE: TRIFLOUROETHENE.
REFERENCES: FIELD & SIERRA-ALVAREZ 2004; BALSIGER ET AL. 2005; ARCHBOLD ET AL. 2012.

The reductive dehalogenation of CFC-11 and CFC-12 may lead to accumulation of the lower chlorinated compounds HCFC-21 and HCFC-22, respectively. The lower halogenated compounds might then be rapidly degraded in the oxidative zone in the surrounding soil by methane oxidising bacteria (Scheutz & Kjeldsen 2005).
Based on conducted experiments, Scheutz et al. (2007) concluded that CFC-11 was only partly dechlorinated to HCFC-21, HCFC-31 and HFC-41 under methanogenic conditions, and that it is likely that CFC-11 is degraded into non-volatile compounds, not further specified.

An additional possibility for the biodegradation of CFC-11 is via the formation of a dihalocarbene radical resulting in carbon monoxide, hydrogen fluoride and formate, see Figure 1. The formation of formate, however, has only been shown to occur in *in vitro* experiments with corrinoids. CFC-41 and CFC-1112 have also been reported to be products after degradation of CFC-11 by corrinoids. (Field & Sierra-Alvarez 2004).

CFC-11 has been reported to be degraded to HCFC-21 (28 %), HCFC-31 (trace), carbon monoxide (6 %) and fluoride (1 %) in a pure culture of *Methanosarcina barkeri* (Krone & Thauer 1992).

1.4.5 Foodstuffs

No data regarding the occurrence of chlorofluorocarbons in foodstuffs have been located.

1.4.6 Bioaccumulation

The low octanol/water partition coefficients of the six chlorofluorocarbons evaluated in this document indicate a low potential for bioaccumulation (EHC 1990; EHC 1991).

1.5 Human exposure

Human exposure to chlorofluorocarbons can result from inhalation of air, consumption of drinking water, or incidental ingestion of soil or dust contaminated with these compounds. Inhalation of contaminated air is considered as the predominant source of exposure to the chlorofluorocarbons.

As the production and use of the CFCs have been banned and thus phased out, the human exposure to these compounds is considered to be low, although long average residence times in the atmosphere of 65, 110 and 90 years for CFC-11, CFC-12 and CFC-113, respectively, have been reported.

As HCFC-21 is still produced and used in a number of products, there is a potential for release to the environment. No data are, however, available regarding human exposure.

As HCFC-31 is not produced in commercial or bulk quantities, the human exposure to this compound is considered to be unlikely, although HCFC-31 has been identified as an impurity (3.8 %) in commercial HCFC-21.

As HCFC-133a is used as a chemical intermediate in the production of the anaesthetic halothane, the human exposure to this compound is considered to be unlikely, although HCFC-133a has been identified as an impurity in halothane, as well as a major mammalian metabolite of halothane.

2. Toxicokinetics

2.1 Absorption and Distribution

2.1.1 CFC-11

A retention of inhaled CFC-11 of 23 % was measured in humans in a breath-holding study with the radioisotopically marked substance by subtracting the radioactivity exhaled 30 min after inhalation from the amount of radioactivity inhaled with a single breath (Paulet & Chevrier 1969; Morgan et al. 1972, both cited from EHC 1990)

In human volunteers exposed to CFC-11 by inhalation at a concentration of 5 710 mg/m^3 (1 000 ppm) for 8 hours, the blood level was reported to be 4.69 µg/ml. According to a mathematical model developed for the description of the pharmacokinetics, 77 % of the dose applied was absorbed. (Aviado & Micozzi 1981 cited from EHC 1990)

In human volunteers (3 individuals) exposed to CFC-11 by inhalation at a concentration of 3 750 mg/m^3 (657 ppm), the average pulmonary retention was reported to be 19 %. The CFC-11 levels in alveolar air and blood were 3 066 mg/m^3 (537 ppm) and 2.8 µg/ml, respectively. The initial and second phase venous blood half-lives were measured to be 11 min and 1 hour, respectively. Half-lives for the initial and second phases of CFC-11 elimination in alveolar air were 7 min and 1.8 hours, respectively. (Angerer et al. 1985 cited from EHC 1990)

In dogs exposed to CFC-11 by inhalation at a concentration of 5 710 mg/m^3 (1 000 ppm) for 10 min, the blood level was reported to be 6.5-10 µg/ml. According to a mathematical model developed for the description of the pharmacokinetics, 77 % of the dose applied was absorbed. (Azar et al. 1973 cited from EHC 1990)

In mice CFC-11 was distributed to the heart, fat, and adrenal tissue after inhalation for 5 min with the highest concentration in the adrenals followed by the fat and then the heart (Allen & Hanburys 1971 cited from EHC 1990)

In dogs CFC-11 was distributed to the cerebrospinal fluid after inhalation exposure (Paulet et al. 1975 cited from EHC 1990)

2.1.2 CFC-12

A retention of inhaled CFC-12 of 10% was measured in humans in a breath-holding study with the radioisotopically marked substance by subtracting the radioactivity exhaled 30 min after inhalation from the amount of radioactivity inhaled with a single breath (Paulet & Chevrier 1969; Morgan et al. 1972, both cited from EHC 1990)

In dogs exposed to CFC-12 by inhalation at a concentration of 5 030 mg/m^3 (1 000 ppm) for 10 min, the arterial blood level was reported to be 1.1 µg/ml and the venous blood level to be 0.4 µg/ml. Similar concentrations were reported at higher concentrations. (Azar et al. 1973 cited from EHC 1990)

In mice CFC-12 was distributed to the heart, fat, and adrenal tissue after inhalation for 5 min with the highest concentration in the adrenals followed by the fat and then the heart (Allen & Hanburys 1971 cited from EHC 1990)

In dogs CFC-12 was distributed to the cerebrospinal fluid after inhalation exposure (Paulet et al. 1975 cited from EHC 1990)

In dogs CFC-12 was distributed to the fatty tissue after oral administration of CFC-12 at 80 mg/kg bw/day for 2 years (Sherman et al. 1966 cited from JECFA 1975).

2.1.3 CFC-113

A retention of inhaled CFC-113 of 20 % was measured in humans in a breath-holding study with the radioisotopically marked substance by subtracting the radioactivity exhaled 30 min after inhalation from the amount of radioactivity inhaled with a single breath (Paulet & Chevrier 1969; Morgan et al. 1972, both cited from EHC 1990)

Retention studies on CFC-113 were conducted in human volunteers over occupationally relevant periods. The chlorofluorocarbon concentration was measured in the expired air of volunteers exposed to 3 835 mg/m^3 or 7 670 mg/m^3 for 3 hours in the morning and for 3 hours in the afternoon. Detectable levels were retained overnight in four cases at 3 835 mg/m^3 and in 14 cases at 7 670 mg/m^3. In one case, there was a detectable level on a Monday morning following a final exposure to 7 670 mg/m^3 on the previous Friday. There was no indication of chlorofluorocarbon accumulation. (Reinhardt et al. 1971 cited from EHC 1990)

In humans exposed dermally to CFC-113, the concentration in expired air declined from a peak of 97 mg/m^3 (12.7 ppm) to 4 mg/m^3 (0.5 ppm) within 90 min (US EPA 1994).

In dogs exposed to CFC-113 by inhalation at a concentration of 7 664 mg/m^3 (1 000 ppm) for 1 min, the arterial blood level was reported to be 2.7 µg/ml and the venous blood level to be 1.9 µg/ml (Trochimowicz et al. 1974 cited from EHC 1990)

In rats CFC-113 was distributed to the heart, fat, and adrenal tissue after inhalation for 7-14 days with the highest concentration in the fat and the adrenal levels relatively low (Carter 1970 cited from EHC 1990)

Shortly after exposure of rats and guinea pigs to CFC-113, the following tissue distribution in decreasing order was noted: fat, brain, liver, kidney, heart, lung, muscle, and blood (Furuya 1979 cited from EHC 1990)

2.1.4 HCFC-21

No data have been located regarding absorption and distribution of HCFC-21. However, it may be inferred from toxicity studies that absorption occurs.

2.1.5 HCFC-31

No data have been located regarding absorption and distribution of HCFC-31. However, it may be inferred from toxicity studies that absorption occurs.

2.1.6 HCFC-133a

No data have been located regarding absorption and distribution of HCFC-133a. However, it may be inferred from toxicity studies and studies of the metabolism of HCFC-133a that absorption occurs.

2.2 Elimination

2.2.1 CFC-11

In human volunteers (one female and one male) that inhaled radiolabelled CFC-11 (560 mg/m^3; 100 ppm) for 7-17 min, total metabolites were equal to or less than 0.2 % of the administered dose (Mergner et al. 1975 cited from EHC 1990).

In Beagle dogs exposed to CFC-11 (containing up to 180 μCi of ^{14}C-chlorofluorocarbon) at concentrations of up to 28 100 mg/m^3 (5 000 ppm) for 6-20 min virtually all the administered CFC-11 was recovered in exhaled air within one hour. Only traces of radioactivity were found in urine or exhaled carbon dioxide. The authors concluded that less than 1 % of CFC-11 is metabolised after inhalation. (Blake & Mergner 1974 cited from EHC 1990).

No evidence of reductive dehalogenation of CFC-11 in microsomal preparations from rats, chickens, or other species was found (Cox et al. 1972 cited from EHC 1990) whereas reductive dechlorination of CFC-11 to HCFC-21 was reported in rat liver microsomes *in vitro* (Wolf et al. 1978 cited from EHC 1990).

2.2.2 CFC-12

In human volunteers (one female and one male) that inhaled radiolabelled CFC-12 (500 mg/m^3; 100 ppm) for 7-17 min, total metabolites were equal to or less than 0.2 % of the administered dose (Mergner et al. 1975 cited from EHC 1990).

In Beagle dogs exposed to CFC-12 (containing up to 180 μCi of ^{14}C-chlorofluorocarbon) at concentrations of up to 59 300 mg/m^3 (12 000 ppm) for 6-20 min virtually all the administered CFC-12 was recovered in exhaled air within one hour. Only traces of radioactivity were found in urine or exhaled carbon dioxide. The authors concluded that less than 1 % of CFC-12 is metabolised after inhalation. (Blake & Mergner 1974 cited from EHC 1990 and JECFA 1975).

About 2 % of an oral dose of ^{14}C-labelled CFC-12 given to rats was exhaled as $^{14}CO_2$ and 0.5 % was excreted in urine. Most of the CFC-12 was excreted as such through the lungs with a half-life of 15 minutes. CFC-12 and/or its metabolites were no longer detectable in the body 30 hours after administration (Eddy & Griffith 1971 cited from EHC 1990 and JECFA 1975).

2.2.3 CFC-113

In human volunteers exposed to CFC-113 at concentrations of 1 900 mg/m^3 (247 ppm) or 3 800 mg/m^3 (494 ppm), only 2.6-4.3 % of the dose was recovered in expired air after termination of exposure (US EPA 1994).

2.2.4 HCFC-21

No data have been located regarding metabolism of HCFC-21. However, an increase in the urinary fluoride level observed in a 90-day inhalation toxicity study with rats indicates that metabolism may occur.

2.2.5 HCFC-31

No *in vivo* data have been located regarding metabolism of HCFC-31.

HCFC-31 was reported to be metabolised *in vitro* to carbon monoxide by Aroclor-induced rat hepatic microsomes and to formaldehyde by rat hepatic cytosolic fractions in the presence of glutathione (Green 1983 cited from IARC 1986a).

2.2.6 HCFC-133a

Male Fischer 344 rats (250-275 g) were exposed by inhalation to 48 500 mg/m^3 (10 000 ppm) HCFC-133a (v/v) for 2 hours and then urine was collected for 24 hours. Urinary metabolites were identified by ^{19}F nuclear magnetic resonance (NMR). A trifluoroacetaldehyde urea adduct (40 %) and trifluoroacetaldehyde hydrate (26 %) were the major metabolites; 2,2,2-trifluoroethyl glucuronide (16 %), trifluoroacetic acid (14 %) and inorganic fluoride (3 %) were also detected. No covalent binding of fluorine-containing metabolites was detected in the liver and kidney from the exposed rats. (Yin et al. 1995)

Based on the available data on partially halogenated chlorofluorocarbons – ethane derivatives, it is expected that HCFC-133a would be metabolised by a cytochrome P-450-dependent monooxygenase liver enzyme to give reactive metabolic products including 1,1,1-trihaloacetic acid and 1,1,1-trihaloethanol (EHC 1992)

Male Alpk:APfSD Wistar-derived rats (3 animals, 350-400 g) were exposed to HCFC-133a at 242 000 mg/kg (50 000 ppm) for 6 hours/day for 2 days. Urine was collected during and after the exposure in 24 hours intervals up to 48 hours. Identification and quantification of urinary metabolites were performed by NMR. Five major metabolites were identified: trifluoroacetaldehyde hydrate (TFAA-hydrate) (34 %), trifluoroacetic acid (TFA) (29 %), trifluoroacetaldehyde urea adduct (TFAA-urea) (23 %), 2,2,2-trifluoroethyl glucuronide (TFE-glu) (14 %) and 2,2,2-trifluoroethanol (TFE) (not quantified). Following exposure, the elimination of metabolites into urine was rapid, with 83 % of the total recovered metabolites being excreted within 24 hours. (Ellis et al. 1995)
The proposed oxidative metabolism of HCFC-133a is illustrated in Figure 3.

Dechlorination of HCFC-133a has been observed in an *in vitro* study with incubation in rat liver microsomes and an NADPH-generating system (Salmon et al. 1981 cited from IARC 1999 and EHC 1992). Trifluoroacetaldehyde hydrate was identified as the only metabolite (Yin et al. 1995).

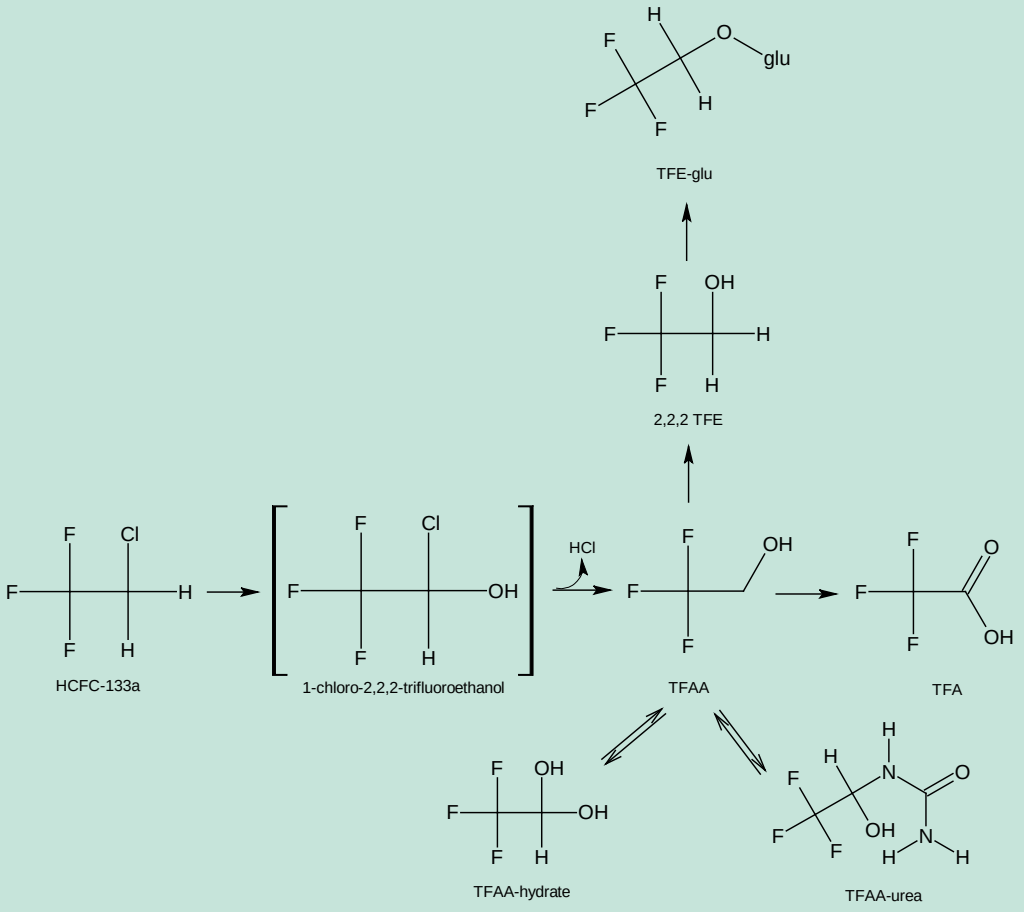

FIGURE 2
PROPOSED OXIDATIVE METABOLISM OF HCFC-133A.
BASED ON ELLIS ET AL. 1995. TFA, TRIFLUOROACETIC ACID; TFAA, TRIFLUOROACETALDEHYDE; TFAA-UREA, TRIFLUOROACETALDEHYDE UREA ADDUCT; TFAA-HYDRATE, TRIFLUOROACETALDEHYDE HYDRATE; 2,2,2 TFE, 2,2,2-TRIFLUOROETHANOL AND TFE-GLU, 2,2,2-TRIFLUOROETHYL GLUCURONIDE.

2.3 Mode of action

Simple dissolution of CFC-12 in the lipid layer of biological membranes with alteration of membrane configuration may account for its anaesthetic effect and some of its cardiac effects (Lessard & Paulet 1985 cited from EHC 1990).

It has been suggested that CFC-12 is bound to the hydrophilic areas of various phospholipids and that potassium chloride may stop adrenaline-induced arrhythmia in hearts sensitised by CFC-12 by displacing the CFC-12 molecule held by the phospholipid (Young & Parker 1972 cited from EHC 1990).

CFC-11 has been shown to bind *in vitro* to liver microsomal protein and lipid and to cytochrome P-450. CFC-113 can also bind to P-450. In view of the very low liver toxicity potential of CFC-11 and CFC-113 the toxicological significance of the P-450 binding is unknown (EHC 1990).

3. Human toxicity

3.1 Single dose toxicity

3.1.1 Inhalation

3.1.1.1 CFC-11

Single exposures of human volunteers to CFC-11 at concentrations of 1 400 mg/m^3, 2 800 mg/m^3 or 5 600 mg/m^3 for 1 min to 8 hours, induced no observable effects on clinical haematology and chemistry, electrocardiography (ECG), electroencephalography (EEG), pulmonary function, neurological parameters or cognitive tests (Stewart et al. 1978 cited from EHC 1990).

In human volunteers exposed to CFC-11, CFC-12, or two mixtures of CFC-11 and CFC-12 (breathing concentrations between 16 000 and 150 000 mg/m^3) for 15, 45, or 60 seconds, significant acute reduction of ventilatory lung capacity (FEF50, FEF25), bradycardia and increased variability in heart rate, and negative T-waves were reported. Mixtures exerted stronger respiratory effects than individual chlorofluorocarbons at the same level of exposure. (Valic et al. 1977 cited from EHC 1990)

3.1.1.2 CFC-12

Single exposures of human volunteers to CFC-12 at concentrations of 1 200 mg/m^3, 2 500 mg/m^3 or 5 000 mg/m^3, for 1 min to 8 hours, induced no observable effects on clinical haematology and chemistry, ECG, EEG, pulmonary function, neurological parameters or cognitive tests (Stewart et al. 1978 cited from EHC 1990).

In human volunteers exposed to CFC-11, CFC-12, or two mixtures of CFC-11 and CFC-12 (breathing concentrations between 16 000 and 150 000 mg/m^3) for 15, 45, or 60 seconds, significant acute reduction of ventilatory lung capacity (FEF50, FEF25), bradycardia and increased variability in heart rate, and negative T-waves were reported. Mixtures exerted stronger respiratory effects than individual chlorofluorocarbons at the same level of exposure. (Valic et al. 1977 cited from EHC 1990)

When 11 subjects (7 being maintenance technicians of large cooling and refrigerating systems) were exposed for 130 min to CFC-12 (weighted exposure 460, 49 900, and 87 700 mg/m^3), acute reduction of ventilatory lung capacity and a significant decrease in the heart frequency were reported at the two highest concentrations (Valic et al. 1982 cited from EHC 1990).

3.1.1.3 CFC-113

Psychomotor performance was evaluated in humans exposed to 12 000 mg/m^3 (1 500 ppm), 19 000 mg/m^3 (2 500 ppm), 27 000 mg/m^3 (3 500 ppm), or 35 000 mg/m^3 (4 500 ppm) for 165 min. No effect was noted at the lowest level. At 19 000 mg/m^3 there was difficulty in concentrating and some decrease in test scores, which were more pronounced at 27 000 mg/m^3, and at 35 000 mg/m^3 performance in various tasks was decreased by between 10 and 30 %. These decreases were reported to coincide with sensations of 'heaviness' in the head, drowsiness, and a slight loss of orientation after shaking the head from left to right. (Stopps & McLaughlin 1967 cited from EHC 1990 and US EPA 1994)
Based on these data a NOAEL for short-term exposure to CFC-113 in the range of 12 000 to 15 000 mg/m^3 was considered (US EPA 1994).

Three cases of accidental death attributed to occupational exposure to CFC-113 have been reported. In each case, the individuals succumbed to high concentrations of CFC-113 vapour. A level of 997 000 mg/m^3 (128 000 ppm) was estimated in one case and in another case death occurred within 15 min after exposure to an estimated concentrations of 47 000 – 288 000 mg/m^3 (6 000 – 37 000 ppm). (May & Blotzer 1984 cited from EHC 1990)

An industrial accidental death due to inhalation of vapour of CFC-113 used as a solvent for cleaning a washer tub filter has been reported. The concentration of CFC-113 was estimated to be in the range of 935 000 to 1 091 000 mg/m^3 (120 000 – 140 000 ppm). (Yonemitsu et al. 1983 cited from EHC 1990)

3.1.1.4 HCFC-21

No human data have been located regarding acute inhalation toxicity of HCFC-21.

3.1.1.5 HCFC-31

No human data have been located regarding acute inhalation toxicity of HCFC-31.

3.1.1.6 HCFC-133a

No human data have been located regarding acute inhalation toxicity of HCFC-133a.

3.1.2 Oral intake

One litre of CFC-113 accidentally released into the stomach of an anaesthetized patient caused transient cyanosis and for the next 3 days, the patient experienced severe rectal irritation and diarrhoea (Clayton 1966 cited from EHC 1990 and US EPA 1994)

No human data have been located regarding acute oral toxicity of CFC-11, CFC-12, HCFC-21, HCFC-31 and HCFC-133a.

3.1.3 Dermal contact

No human data have been located regarding acute dermal toxicity of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.2 Irritation

3.2.1 Skin irritation

3.2.1.1 CFC-113

No adverse toxicity or dermal irritation resulted from application of CFC-113 to the scalp and forehead for up to 30 days (US EPA 1994).

No human data have been located regarding skin irritation of CFC-11, CFC-12, HCFC-21, HCFC-31 and HCFC-133a.

3.2.2 Eye irritation

No human data have been located regarding eye irritation of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.2.3 Respiratory irritation

No human data have been located regarding respiratory irritation of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.3 Sensitisation

3.3.1 Skin sensitisation

Allergic contact eczema was reported in patch tests performed on three patients that had a prior history of skin reactions to deodorant sprays. All three patients showed strong positive reactions to 11 deodorant sprays and mild to strong reactions to CFC-11 and one patient showed a mild reaction to CFC-12. Fifteen controls (without prior history of allergy to deodorants) showed no response to either CFC-11 or CFC-12. (Van Ketel 1976 cited from EHC 1990)

No human data have been located regarding skin sensitisation of CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.3.2 Respiratory sensitisation

No human data have been located regarding respiratory sensitisation of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.4 Repeated dose toxicity

3.4.1 Inhalation

3.4.1.1 CFC-11

There was a statistically significant decrease in cognitive test performance in subjects exposed to CFC-11 at 5 600 mg/m^3, 8 hours/day, 5 days/week, for 2-4 weeks (Stewart et al. 1978 cited from EHC 1990).

3.4.1.2 CFC-12

No effects in cognitive test performance were seen in subjects exposed to CFC-12 at 5 000 mg/m^3 8 hours/day, 5 days/week, for 2-4 weeks (Stewart et al. 1978 cited from EHC 1990).

3.4.1.3 CFC-113

Four human subjects were exposure to CFC-113 at concentrations of 8 000 mg/m^3 (1 000 ppm) and 4 000 mg/m^3 (500 ppm) for 180-min periods in the morning and afternoon on 5 days. No decreases in psychomotor ability and no abnormal findings during post-exposure physical examination, haematological and blood chemistry tests (conducted 3 days after final exposure), and steady-state measurements of diffusing capacity of lungs and fractional uptake of carbon monoxide were reported. (Reinhardt et al. 1971 cited from EHC 1990)

No effects have been reported for workers occupationally exposed to CFC-113 at 500 mg/m^3 for 11 years or 5 400 mg/m^3 for 2.77 years (Imbus & Adkins 1972 cited from US EPA 1994 and EHC 1990).

Epidemiological studies of men and women with greater than 1 year of occupational exposure to CFC-113 showed no alterations in blood chemistry or urinalyses; one case of dermatitis was reported among males (US EPA 1994).

3.4.1.4 HCFC-21

No human data have been located regarding repeated dose inhalation toxicity of HCFC-21.

3.4.1.5 HCFC-31

No human data have been located regarding repeated dose inhalation toxicity of HCFC-31.

3.4.1.6 HCFC-133a

No human data have been located regarding repeated dose inhalation toxicity of HCFC-133a.

3.4.2 Oral intake

No human data have been located regarding repeated dose oral toxicity of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.4.3 Dermal contact

No human data have been located regarding repeated dose dermal toxicity of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.5 Toxicity to reproduction

No human data have been located regarding toxicity to reproduction of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.6 Mutagenic and genotoxic effects

No human data have been located regarding mutagenic and genotoxic effects of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

3.7 Carcinogenic effects

No human data have been located regarding carcinogenic effects of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

4. Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

4.1.1.1 CFC-11

LC_{50} values for CFC-11 in mouse, rat, hamster and guinea-pig are presented in Table 4.

Mice

Mice exposed to CFC-11 at 57 000 mg/m^3 for 24 hours showed no clinical signs of exposure (Quevauviller et al. 1963 cited from EHC 1990).

Rats

Rats were exposed to CFC-11 at 285 000 (120 min) or 514 000 (30 min) mg/m^3. Incipient narcosis and deep narcosis occurred at the low and high concentration, respectively (Scholz 1961; Lester & Greenberg 1950, both cited from EHC 1990).

Guinea pigs

Guinea pigs exposed to CFC-11 at 125 000 – 143 000 mg/m^3 or 257 000 – 291 000 mg /m^3 for 120 min displayed tremor and dyspnoea and tremor and incipient narcosis, respectively (Nuckolls 1933 cited from EHC 1990).

When guinea pigs were exposed to CFC-11 at 571 000 mg/m^3 for 50 min deep narcosis was observed (Scholz 1961 cited from EHC 1990).

4.1.1.2 CFC-12

LC_{50} values for CFC-12 in mouse, rat, guinea-pig, dog and monkey are presented in Table 4.

Mice

Mice were exposed to CFC-12 at 1 610 000 mg/m^3 for 30 min. Unspecified initial effects on the CNS were reported (Paulet 1969 cited from EHC 1990).

Rats

Rats were exposed to CFC-12 at 3 521 000 – 4 024 000 mg/m^3 for 30 min or 4 024 000 mg/m^3 for 360 min. No mortalities were observed but deep narcosis was reported after exposure for 30 min (Lester & Greenberg 1950 cited from EHC 1990).

Rats exposed to CFC-12 at 1 006 000; 1 509 000 – 2 012 000 or 2 515 000 mg/m^3 for 30 min showed no effects; tremor or reduced reflexes, respectively (Lester & Greenberg 1950 cited from EHC 1990).

Guinea pigs

Guinea pigs were exposed to CFC-12 at 2 716 000 or 4 527 000 mg/m^3 for 30 min. Initial effects on CNS narcosis but no mortalities were reported after both doses (Paulet 1969 cited from EHC 1990).

Dogs

Dogs exposed to CFC-12 at 1 006 000 mg/m^3 for 420-480 min showed incoordination (Sayers et al. 1930 cited from EHC 1990).

Monkeys
Monkeys exposed to CFC-12 at 1 006 000 mg/m^3 for 420-480 min showed incoordination (Sayers et al. 1930 cited from EHC 1990).

4.1.1.3 CFC-113
LC_{50} values for CFC-113 in mouse, rat, guinea-pig and rabbit are presented in Table 4.

4.1.1.4 HCFC-21
An LC_{50} value for HCFC-21 in rat is presented in Table 4.

Mice
Mice exposed to 42 700 mg HCFC-21/m^3 for 30 to 100 min became hyperactive (Booth & Bixby 1932 cited from EHC 1991).

Rats
Rats exposed to HCFC-21 at 213 070 mg/m^3 for 4 hours showed CNS depression, lacrimation, piloerection and mydriasis (Tappan & Waritz 1964 cited from EHC 1991).

Rats were exposed to a range of high concentrations of HCFC-21. No changes were observed after 10 000 mg/m^3 (2 hours); loss of balance, tremors and excitation was observed after 106 750 mg/m^3 (2 hours); loss of balance and narcosis was observed after 213 500 mg/m^3 (2 hours) and deep narcosis and death was observed after 427 000 mg/m^3 (15-50 min) (Weigand 1971 cited from EHC 1991).

Guinea pigs
Guinea pigs were exposed to a range of high concentrations of HCFC-21. No changes were observed after 10 000 mg/m^3 (2 hours); loss of balance, tremors and excitation was observed after 106 750 mg/m^3 (2 hours); loss of balance and narcosis was observed after 213 500 mg/m^3 (2 hours) and deep narcosis and death was observed after 427 000 mg/m^3 (15-50 min) (Weigand 1971 cited from EHC 1991).

Guinea pigs were exposed to concentrations of HCFC-21 ranging from 51 240 (2 hours) to 1 708 000 mg/m^3 (6 min). Various effects on the CNS including loss of balance, dyspnoea, stupor and seizures at the lower concentrations and deep narcosis, tremors and death at the higher concentrations were reported. The animals stated to die at 213 500 mg/m^3 (2 hours) (Booth & Bixby 1932; Nuckolls 1935 and Caujolle 1964, all cited from EHC 1991).

4.1.1.5 HCFC-31

Rats
Rats (number of animals unspecified) were exposed to HCFC-31 at 56 000 mg/m^3 (2 % v/v) for 4 hours. CNS depression was observed (Coate et al. 1979 cited from IARC 1986a).

Monkeys
Cynomolgus monkeys (2 animals) were exposed to HCFC-31 at 28 000 mg/m^3 (1 %) for 4 hours. CNS depression was observed and one monkey died 4 days after the exposure (Coate et al. 1979 cited from IARC 1986a).

4.1.1.6 HCFC-133a
LC_{50} values for HCFC-133a in mice are presented in Table 4.

Mice
Mice were exposed to an unspecified range of concentrations of HCFC-133a for 10 to 30 min. Anaesthesia, convulsions and death was observed. The calculated concentrations expected to produce anaesthesia in 50 % of the animals (AC_{50}) were HCFC-133a concentrations of 394 000 and 208 000 mg/m^3 (4.3 % v/v) after 10 and 30 min exposure, respectively (Robbins 1946; Raventos & Lemon 1965, both cited from EHC 1992).

Mice were exposed to HCFC-133a at 123 000 – 1 230 000 mg/m^3 for 10 min. Rapid onset of anaesthesia was followed by rapid recovery after cessation of exposure. The calculated concentration expected to produce anaesthesia in 50 % of the animals was 397 000 mg/m^3 (Shulman & Sadove 1965 cited from EHC 1992).

Rats
Female rats were exposed to HCFC-133a at 2 500 000 mg/m^3. Lack of muscular coordination occurred after 3 min; anaesthesia after 4 min and death within 8 min (Diggle & Gage 1956 cited from EHC 1992).

Dogs
Dogs were exposed to a range of concentrations of HCFC-133a. Anaesthesia occurred at 492 000 mg/m^3; respiratory depression at 1 131 000 mg/m^3; respiratory arrest at 1 427 000 mg/m^3 and circulatory arrest at 2 902 000 mg/m^3 (Shulman & Sadove 1965 cited from EHC 1992).

4.1.2 Oral intake

4.1.2.1 CFC-11
An approximate lethal oral dose of 3 725 mg/kg bw was reported for CFC-11 in rats (Slater 1965 cited from EHC 1990).

4.1.2.2 CFC-12
An approximate lethal oral dose of > 1 000 mg/kg bw was reported for CFC-12 in rats (EHC 1990).

4.1.2.3 CFC-113
An LD_{50} value of 43 000 mg/kg bw was reported for CFC-113 in rats (EHC 1990).

4.1.2.4 HCFC-21
No data have been located regarding acute oral toxicity of HCFC-21.

4.1.2.5 HCFC-31
No data have been located regarding acute oral toxicity of HCFC-31.

4.1.2.6 HCFC-133a
No data have been located regarding acute oral toxicity of HCFC-133a.

4.1.3 Dermal contact
No data have been located regarding acute dermal toxicity of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

Substance	Species	Exposure period (min)	LC_{50} (mg/m^3)
CFC-11	Guinea-pig	30	1 427 000
	Mouse	30	571 000
	Rat	30	856 000
	Hamster	240	571 000
CFC-12	Guinea-pig	30	> 4 527 000
	Mouse	30	> 1 610 000
	Rat	360	> 4 024 000
	Monkey, dog	420-480	> 1 006 000
CFC-113	Guinea-pig	60	935 000
	Mouse	120	701 000
	Rat	120	857 000
	Rat	240	409 000
	Rabbit	120	463 000
HCFC-21	Rat	240	213 000
HCFC-133a	Mouse (male)	10	1 230 000
HCFC-133a	Mouse	30	727 000
HCFC-133a	Mouse	10	1 033 000

TABLE 4
ACUTE INHALATION TOXICITY FOR SELECTED CHLOROFLUOROCARBONS.
REFERENCES: EHC 1990; EHC 1991; EHC 1992.

4.2 Irritation

4.2.1 Skin irritation

4.2.1.1 CFC-11

CFC-11 caused slight skin irritation in rats following dermal contact 1-2 times/day, 5 days/week for 5-6 weeks) (Quevauviller et al. 1964 and 1965, both cited from EHC 1990).

4.2.1.2 CFC-12

CFC-12 caused slight skin irritation in rats following dermal contact 1-2 times/day, 5 days/week for 5-6 weeks) (Quevauviller et al. 1964 and 1965, both cited from EHC 1990).

4.2.1.3 CFC-113

CFC-113 caused severe local irritation on shaved rabbit skin when kept occluded in liquefied form at 5 000 mg/kg/day for 5 days (Waritz 1971 cited from EHC 1990).

In another study CFC-113 caused local irritation when applied to the skin of rabbits at 11 000 mg/kg (Clayton 1966 cited from EHC 1990).

4.2.1.4 HCFC-21

HCFC-21 produced mild irritation when applied at concentrations higher than 25 % (in propylene glycol) to the shaved, intact skin of guinea pigs; no irritation was observed at concentrations of 2.5 % (Goodman 1985 cited from EHC 1991).

4.2.1.5 HCFC-31

No data have been located regarding skin irritation of HCFC-31.

4.2.1.6 HCFC-133a

No data have been located regarding skin irritation of HCFC-133a.

4.2.2 Eye irritation

4.2.2.1 CFC-11

CFC-11 caused slight irritation in the eye of rabbits following instillation once a day, 5 days/week for 1 month) (Quevauviller et al. 1964 and 1965, both cited from EHC 1990).

4.2.2.2 CFC-12

CFC-12 caused slight irritation in the eye of rabbits following instillation once a day, 5 days/week for 1 month) (Quevauviller et al. 1964 and 1965, both cited from EHC 1990).

4.2.2.3 CFC-113

No data have been located regarding eye irritation of CFC-113.

4.2.2.4 HCFC-21

Undiluted liquid HCFC-21, chilled to the temperature of dry ice produced slight corneal opacity, transient congestion of the iris and moderate conjunctival irritation in the eyes of rabbits. The effects were reversed within 5 days after treatment (Brittelli 1975 cited from EHC 1991). According to EHC 1991, this report did not distinguish between the effects of cold, including that caused by evaporation, and the intrinsic properties of HCFC-21.

Mild lacrimation was seen in rabbits up to 4 hours after HCFC-21 was sprayed directly into the eyes from a distance of 5 cm (Hood 1964 cited from EHC 1991).

Varying degrees of injuries to the cornea, iris and conjunctivae were observed in rabbits exposed to 0.1 ml solution with 50 % HCFC-21 in one eye. Milder irritant effects were seen with a 15 % solution. The effects were reversed within 7-10 days after treatment (Hood 1964 and Eddy 1970, both cited from EHC 1991).

4.2.2.5 HCFC-31

No data have been located regarding eye irritation of HCFC-31.

4.2.2.6 HCFC-133a

No data have been located regarding eye irritation of HCFC-133a.

4.2.3 Respiratory irritation

No data have been located regarding respiratory irritation of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

4.3 Sensitisation

4.3.1 Skin sensitisation

4.3.1.1 HCFC-21

No evidence of skin sensitisation with HCFC-21 was found in guinea-pigs (Hood 1964b; Goodman 1975, both cited from EHC 1991).

No data have been located regarding skin sensitisation of CFC-11, CFC-12, CFC-113, HCFC-31 and HCFC-133a.

4.3.2 Respiratory sensitisation

No data have been located regarding respiratory sensitisation of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

4.3.3 Cardiac sensitisation

A variety of hydrocarbons, with and without halogen substitution, have long been known to sensitise the heart to adrenaline-induced arrhythmias (EHC 1990, 1991, 1992).
Several special studies have been performed with CFC-12, HCFC-21 and HCFC-22 in a number of animal species. The dog turned out to be the most sensitive animal species to this effect (EHC 1990, 1991).
For CFC-12 it has been shown that a minimum concentration in air of 250 000 mg/m^3 was necessary to sensitise the heart in dogs to an intravenous dose of adrenaline (Reinhardt et al. 1971 cited from EHC 1990).
For HCFC-21 and HCFC-22 the lowest concentration causing cardiac sensitisation in dogs to an intravenous dose of adrenaline was 43 000 and 175 000 mg/m^3, respectively (Mullin 1975 cited from EHC 1991).

Special studies performed with CFCs in a number of animal species have also shown cardiac sensitisation to asphyxia-induced arrhythmias at very high concentrations (> 100 000 mg/m^3) (EHC 1990).

Some chlorofluorocarbons have been found to affect cardiac function under conditions of adequate oxygenation or in the absence of elevated adrenaline levels following exposure to very high concentrations (> 100 000 mg/m^3) (EHC 1990).

4.4 Repeated dose toxicity

4.4.1 Inhalation

4.4.1.1 CFC-11

Rats
The lowest reported effect level for CFC-11 was 68 500 mg/m^3 (4 hours/day for 10 days) in rats, at which pathological changes in the brain, liver, lung and spleen were observed (Clayton 1966 cited from EHC 1990).

No adverse effects were reported in rats exposed to CFC-11 at 143 000 mg/m^3 (3.5 hours/day, 5 days/week for 4 weeks) (Scholz 1962 cited from EHC 1990).

Rats exposed to CFC-11 at 58 000 mg/m^3 (8 hours/day, 5 days/week for 6 weeks) or at 57 000 mg/m^3 (continuous exposure for 90 days) did not show any treatment related effects (Jenkins et al. 1970 cited from EHC 1990).

In rats exposed to CFC-11 at 57 100 mg/m^3 (6 hours/day for 90 days) no treatment-related changes were reported (Leuschner et al. 1983 cited from EHC 1990).

Guinea pigs
No adverse effects were reported in guinea-pigs exposed to CFC-11 at 143 000 mg/m^3 (3.5 hours/day, 5 days/week for 4 weeks) (Scholz 1962 cited from EHC 1990).

Guinea-pigs exposed to CFC-11 at 58 000 mg/m^3 (8 hours/day, 5 days/week for 6 weeks) or at 57 000 mg/m^3 (continuous exposure for 90 days) did not show any treatment related effects (Jenkins et al. 1970 cited from EHC 1990).

Dogs
No adverse effects were reported in dogs exposed to CFC-11 at 71 000 mg/m^3 (3.5 hours/day, 5 days/week for 4 weeks) (Scholz 1962 cited from EHC 1990).

Dogs exposed to CFC-11 at 58 000 mg/m^3 (8 hours/day, 5 days/week for 6 weeks) or at 57 000 mg/m^3 (continuous exposure for 90 days) did not show any treatment related effects (Jenkins et al. 1970 cited from EHC 1990).

In dogs exposed to CFC-11 at 28 500 mg/m^3 (6 hours/day for 90 days) no treatment-related changes were reported (Leuschner et al. 1983 cited from EHC 1990).

Monkeys
Monkeys exposed to CFC-11 at 58 000 mg/m^3 (8 hours/day, 5 days/week for 6 weeks) or 57 000 mg/m^3 (continuous exposure for 90 days) did not show any treatment related effects (Jenkins et al. 1970 cited from EHC 1990)

4.4.1.2 CFC-12

Rats
No adverse effects were reported in rats exposed to CFC-12 at 503 000 mg/m^3 (3.5 hours/day, 5 days/week for 4 weeks) (Scholz 1962 cited from EHC 1990).

In rats exposed to CFC-12 at 50 000 mg/m^3 (6 hours/day for 90 days) no adverse effects were reported (Leuschner et al. 1983 cited from EHC 1990).

No effects were reported in rats exposed to CFC-12 at 4 100 mg/m^3 (8 hours/day, 5 days/week for 90 days or continuously for 90 days) (Prendergast et al. 1967 cited from EHC 1990).

Guinea pigs
No adverse effects were reported in guinea-pigs exposed to CFC-12 at 503 000 mg/m^3 (3.5 hours/day, 5 days/week for 4 weeks) (Scholz 1962 cited from EHC 1990).

Fatty infiltration and necrosis in the liver was observed after exposure of guinea-pigs to CFC-12 at 4 100 mg/m^3 8 hours/day, 5 days/week or continuously for 90 days (Prendergast et al. 1967 cited from EHC 1990).

Rabbits
No effects were reported in rabbits exposed to CFC-12 at 4 100 mg/m^3 (800 ppm) 8 hours/day, 5 days/week for 90 days (Prendergast et al. 1967 cited from EHC 1990).

Dogs
No adverse effects were reported in dogs exposed to CFC-12 at 503 000 mg/m^3 (3.5 hours/day, 5 days/week for 4 weeks) (Scholz 1962 cited from EHC 1990).

In dogs exposed to CFC-12 at 25 000 mg/m^3 (6 hours/day for 90 days) no adverse effects were reported (Leuschner et al. 1983 cited from EHC 1990).

No effects were reported in dogs exposed to CFC-12 at 4 100 mg/m^3 (8 hours/day, 5 days/week for 90 days or continuously for 90 days) (Prendergast et al. 1967 cited from EHC 1990).

Tremor, ataxia, dyspnoea, salivation and lacrimation were observed in dogs exposed to CFC-12 at 1 006 000 mg/m^3 7-8 hours/day; no histological changes were reported (Sayers 1930 cited from EHC 1990).

Monkeys
No adverse effects were reported in monkeys exposed to CFC-12 at 4 100 mg/m^3 (800 ppm) 8 hours/day, 5 days/week or continuously for 90 days (Prendergast et al. 1967 cited from EHC 1990).

Tremor, ataxia, dyspnoea, salivation and lacrimation were observed in monkeys exposed to CFC-12 at 1 006 000 mg/m^3 7-8 hours/day; no histological changes were reported (Sayers 1930 cited from EHC 1990)

4.4.1.3 CFC-113

Mice
No adverse effects were reported in mice exposed to CFC-113 at 16 000 mg/m^3 (24 hours/day for 14 days) (Trochimowicz 1984 cited from EHC 1990).

No adverse effects were reported in mice after continuous exposure to CFC-113 at 16 000 mg/m^3 for 14 days (Carter et al. 1970 cited from EHC 1990).

Rats
Rats exposed to CFC-113 at a concentration of 15 300 mg/m^3 6 hours/day, 5 days/week, for 2 weeks had decreased cerebral glutathione and glutathione peroxidase levels as well as decreased hepatic cytochrome P-450; CFC-113 appeared to bind to microsomal cytochrome P-450 (US EPA 1994).

Changes in liver enzyme activities and proliferation of the smooth endoplasmic reticulum were reported in rats exposed to CFC-113 at 16 000-31 000 mg/m^3 (6 hours/day for 7-14 days) (Vainio et al. 1980 cited from EHC 1990).

Increased kidney weights were observed in rats after continuous exposure to CFC-113 at 16 000 mg/m^3 for 14 days (Carter et al. 1970 cited from EHC 1990).

Reduced rate of body weight gain and pale discolouration of the liver, but no adverse effects were observed in rats exposed to CFC-113 at 16 000-22 000 mg/m^3 (7 hours/day, 30 exposures) (Clayton 1966 cited from EHC 1990).

No adverse effects were reported in rats exposed to CFC-113 at 16 000 mg/m^3 (24 hours/day for 14 days), 40 000 mg/m^3 (6 hours/day, 20 exposures), 195 000 mg/m^3 (3.5 hours/day, 20 exposures), or up to 156 000 mg/m^3 (6 hours/day 5 days/week for 90 days) (Trochimowicz 1984 cited from EHC 1990).

In rats exposed to CFC-113 at 78 000 mg/m^3 (6 hours/day for 90 days) no adverse effects were reported (Leuschner et al. 1983 cited from EHC 1990).

Rats were exposed to CFC-113 at 0 (control) or 93 000 mg/m^3 for 2 hours/day, 5 days/week for 2 years. Three out of six rats died in the treatment group and three rats died in the control group (total number of control animals not specified). Slight dizziness was observed in the exposed animals. No compound related effects were observed on body-weight, growth, haematology values or morphology. (Desoille et al. 1986 cited from EHC 1990)

Crl:CD(SD)BR rats (100 animals/sex/group, 5 weeks old) were exposed to CFC-113 at approximately 0, 15 300, 76 600 or 153 000 mg/m^3 6 hours/day, 5 days/week for up to 2 years (Trochimowicz et al. 1988). Body weight, appearance and behaviour were monitored regularly. Urine and blood for haematology, clinical chemistry, and urinalysis was collected from subgroups of 10 animals/sex/group after 3, 6, 12, 18 and 24 months. Animals subjected to the 3, 6 and 12 month clinical laboratory measurements were sacrificed after 12 months. At the end of the study all animals were necropsied and had their tissues collected and weighed. Tissues from the control and high dose animals and the tissues from rats (from all dose groups) that were found dead or terminated *in extremis* were investigated microscopically. Mean body weights of male rats in the high dose group and female rats in the intermediate and the high dose group were lower than those of the control group at the end of the study. Approximately 18-35 % of the male rats and 5-8 % of the female rats in the exposed groups died as a consequence of unintentional infections with *Corynebacterium kutscheri*. The infections appeared to affect all groups equally including the control group. No adverse treatment related effects were seen in haematological, serum chemistry or urinalysis values. After the 6 months sampling the male control rats were misplaced into the low dose group and the low dose males were misplaced into the control group. The mistake was discovered and corrected after 11 exposures and the misplaced low dose group animals were included in the 12 months sampling. According to the authors there were no effects of the misplacement on their body weight, physical appearance or behaviour. The mean total fluoride content of urine from high dose males was higher compared to control ($p \leq 0.05$) during the length of the study while it was only higher in the intermediate and the high dose females after 3 and 6 months, respectively ($p \leq 0.05$). No treatment related non-neoplastic changes or evidence of hepatotoxicity were reported. A no-observed-effect level of 15 300 mg/m^3 was established by the authors based on the lower weight gain seen at higher doses. The carcinogenic effects investigated in this study are described in section 4.7.1.3.

Guinea pigs
No adverse effects were reported in guinea-pigs exposed to CFC-113 at 40 000 mg/m^3 (6 hours/day, 20 exposures) or 195 000 mg/m^3 (3.5 hours/day, 20 exposures) (Trochimowicz 1984 cited from EHC 1990).

Dogs
No adverse effects were reported in dogs after continuous exposure to CFC-113 at 16 000 mg/m^3 for 14 days (Carter et al. 1970 cited from EHC 1990).

No adverse effects were reported in dogs exposed to CFC-113 at 16 000 mg/m^3 (24 hours/day for 14 days), 40 000 mg/m^3 (6 hours/day, 20 exposures), or 97 000 mg/m^3 (3.5 hours/day, 20 exposures) (Trochimowicz 1984 cited from EHC 1990).

In dogs exposed to CFC-113 at 39 000 mg/m^3 (6 hours/day for 90 days) no adverse effects were reported (Leuschner et al. 1983 cited from EHC 1990).

Monkeys
CFC-113 caused no adverse effects in monkeys exposed continuously to 16 000 mg/m^3 for 14 days (Trochimowicz, 1984 cited from EHC 1990).

Enlarged thyroids were observed in monkeys after continuous exposure to CFC-113 at 16 000 mg/m^3 for 14 days (Carter et al. 1970 cited from EHC 1990).

4.4.1.4 HCFC-21

Rats
Rats (5 animals) were exposed 3.5 hours/day, 5 days/week for 4 weeks to 42 700 mg/m^3 of HCFC-21. The increase of body weight was somewhat retarded. Histopathological examination showed hepatic single cell necrosis and fatty degeneration (Weigand 1971 cited from EHC 1991).

Male rats (10 animals) were exposed 6 hours/day, 5 days/week for 2 weeks to 42 700 mg/m^3 of HCFC-21. The rats lost weight and exhibited marked anaemia and increased serum transaminase levels, indicating liver damage. Pathological examination immediately after the last exposure indicated liver necrosis, which had not recovered after 14-days post-exposure (Kelly 1976, 1977; Trochimowicz et al. 1977, all cited from EHC 1991 and ECETOC 1990a).

Charles River albino rats (27 animals/sex/group) were exposed to HCFC-21 at 4 270 mg/m^3 or 21 350 mg/m^3 6 hours/day, 5 days/week for 90 days. Between days 59 and 90, 37 % of the rats exposed to the low concentration and 28-29 % exposed to the high concentration died. Extensive liver cirrhosis was observed in both groups. Neither the mortality nor the histopathological damage was related to the dosage. (Trochimowicz et al. 1977 cited from ECETOC 1990a; Kelly 1977 cited from EHC 1991)

Charles River albino rats (35 animals/sex/group) were exposed to HCFC-21 at 213, 640 or 2 130 mg/m^3 6 hours/day, 5 days/week for 90 days. At 2 130 mg/m^3 the body weight gain was lower than in controls during the early phase of the experiment. Leucocyte counts were higher in animals exposed to 2 130 mg/m^3 as were serum alkaline phosphatase and alanine amino transferase. Histopathological evaluation of tissues revealed portal cirrhosis of the liver, interstitial oedema of the pancreas and degeneration of the seminiferous epithelium in all treatments groups. (Lindberg 1979 cited from ECETOC 1990a and EHC 1991)

Guinea-pigs
Guinea-pigs (5 animals) were exposed 3.5 hours/day, 5 days/week for 4 weeks to 42 700 mg/m^3 of HCFC-21. The animals lost weight. Histopathological examination showed hepatic single cell necrosis and fatty degeneration (Weigand 1971 cited from EHC 1991).

Dogs
Beagle dogs (2 animals) were exposed 3.5 hours/day, 5 day/week for 4 weeks to 42 700 mg/m^3 of HCFC-21. Histopathological examination showed hepatic single cell necrosis and fatty degeneration. (Weigand 1971 cited from EHC 1991)

Beagle dogs (4 males/group) were exposed 6 hours/day, 5 days/week for 90 days to 4 270 mg/m^3 or 21 350 mg/m^3 of HCFC-21. Dogs in the high dose group showed slight weight loss and minimal unspecified morphological changes in the liver. (Trochimowicz et al. 1977 cited from ECETOC 1990a; Kelly 1977 cited from EHC 1991)

4.4.1.5 HCFC-31

Rats
Rats exposed to HCFC-31 at 28 000 mg/m^3 6 hours/day on 5 days/week for 2 weeks showed moderate damage to the kidneys, adrenal glands, testes, epididymis and haematopoietic tissues (Trochimowicz et al. 1977).

Monkeys
Monkeys (8 animals) were exposed to HCFC-31 at 11 000 (0.4 %) or 14 000 mg/m^3 (0.5 %) for 19-20 days. Five animals died with severe epistaxis and 5 animals had centrolobular to diffuse hepatocytic swelling in the high dose group. (Coate et al. 1979)

4.4.1.6 HCFC-133a

Mice
Mice were exposed to anaesthetic concentrations (the actual concentration was not specified) of HCFC-133a for 30 min/day for 12 days. The animals were killed after the last exposure by over-dosage of HCFC-133a. No adverse treatment related effects were observed in the investigated organs (heart, lung, liver, kidney, adrenal gland, spleen and pancreas). (Shulman & Sadove 1965 cited from EHC 1992 and ECETOC 1990b)

Rats
Female rats (2-3 animals/group) were exposed to HCFC-133a at 50 000-500 000 mg/m^3 for up to 8 days. Incoordination and lethargy were caused by concentrations between 50 000 and 125 000 mg/m^3 while at 250 000 or 500 000 mg/m^3 rats became comatose. They recovered between each exposure and no dose-related pathological changes were found on histological examination. No effect was seen at 25 000 mg/m^3 during 7 exposures lasting 6 hours/day. (Diggle & Gage 1956 cited from EHC 1992 and ECETOC 1990b)

Sprague-Dawley rats (20 animals/sex/group) were exposed to HCFC-133a at 0 or 49 000 mg/m^3 6 hours/day for 90 days. Observations for overt clinical signs of toxicity and investigations on body weight, food consumption, haematology, blood and urine biochemistry, urine sediments, ophthalmology, auditory reflex, organ weights, and histopathology were performed. There were no treatment-related deaths. The rats were sedated during each exposure but appeared normal before and after. Seventeen out of 40 rats developed bloody and inflamed noses; this was associated with histological evidence of inflammatory changes of the mucosa. Body weight gain was reduced, so that the terminal average body weights were approximately 28 and 17 % lower than those of male and female controls, respectively. Food consumption in the treated groups was also lower than in the controls. Haemoglobin concentration, haematocrit, red blood cell counts and platelet counts were all slightly reduced. Reduction in leucocyte counts of approximately 30 % and increase in reticulocyte counts of approximately 40 % were seen. There were reductions in plasma glucose levels of approximately 15 % and in protein levels of approximately 10 %. Bromosulfophthalein retention time was increased by approximately 35 % and 62 % in males and females, respectively. The relative thymus, testis and ovary weight was reduced by approximately 50, 60 and 35 %, respectively. Histologically, these organs showed atrophy. The relative thyroid weight was increased by approximately 45 % in males only. Atrophy of the spleen was also observed. The exposure induced emphysema and oedema of the lungs as well as bronchitis and pneumonia. (Leuschner et al. 1977 cited from EHC 1992 and ECETOC 1990b)

Dogs
Beagle dogs (6 animals/group) were exposed to HCFC-133a at 0 or 24 000 mg/m^3 6 hours/day for 3 months. No adverse treatment related effects were seen on external appearance, faeces, food and water consumption, body weight gain, haematology, blood and urine biochemistry, urine sediments, electrocardiography, blood pressure, ophthalmology, hearing or dentition. There was no effect on organ weight at autopsy. No treatment-related histopathological changes were seen on microscopic examination of a standard range of 24 tissues. (Leuschner 1977 cited from EHC 1992)

4.4.2 Oral intake

4.4.2.1 CFC-11

Mice

B6C3F$_1$ mice (50 animals/sex/treatment group and 20 animals/sex/control group) were given CFC-11 by gavage (in corn oil) 5 days/week for 78 weeks and observed untreated for an additional 13 weeks. Time-weighted average doses were 1 962 and 3 925 mg/kg bw per day for male and female mice, respectively. Chronic murine pneumonia occurred in control and treated animals at incidences of almost 90 %. No statistically significant compound-related effects were noted on weight gain, clinical signs, or non-tumour pathology. In female mice, a significant ($p=0.009$) dose-related increase in mortality was noted compared with the vehicle controls. (NCI 1978 cited in IRIS 2012a and EHC 1990)

Rats

Osborne-Mendel rats (50 animals/sex/treatment group and 20 animals/sex/control group) were given CFC-11 by gavage (in corn oil) 5 days/week for 78 weeks and observed untreated for an additional 28-33 weeks. Time-weighted average doses were 488 and 977 mg/kg bw per day for male rats, 538 and 1 077 mg/kg bw per day for female rats. In both male and female rats, a significant ($p < 0.001$) dose-related acceleration of mortality was noted compared with the vehicle control. This increase in mortality occurred as early as 4 weeks in high-dose females. The early mortality could not be related to changes in body weights, clinical signs, or non-tumour pathology. Low incidences (2-6%) of pleuritis and pericarditis were seen in the treated rats of both sexes at both dose levels but not in the control animals. Chronic murine pneumonia occurred in control and treated animals at incidences of almost 90 %. (NCI 1978 cited in IRIS 2012a and EHC 1990)

Based on the mortality in rats a LOAEL of 349 mg/kg bw/day ((488 mg/kg/day * 5 days)/7 days) on a 7-day exposure basis was established by the US-EPA (IRIS 2012a).

4.4.2.2 CFC-12

Rats

Adult rats (15 animals/group) were given 4 ml sesame oil containing CFC-12 at 5.1 %, 6.5 % or 8.3 % (equivalent to 395, 527 and 667 mg/kg bw/day, respectively) once a day for 14 days. The rats developed diarrhea and did not gain weight. No adverse effects were reported on organ weights or histopathological findings in stomach, liver, kidney, spleen or adrenals. (Imamichi 1973 cited from JECFA 1975)

Male rats (10 animals/group) were intragastrically given corn oil, corn oil with 56 mg or corn oil with 112 mg CFC-12 (equivalent to 280 or 560 mg/kg bw assuming an average body weight of 20 g) 5 times/week for a total of 43 doses. Weight gain was slightly lower and plasma alkaline phosphatase was higher in the high dose group compared to control. Plasma alkaline phosphatase was slightly higher in the low dose group. (Barnes & Sherman 1966 cited from JECFA 1975)

Rats were orally administered dose levels of CFC-12 ranging from 160-379 mg/kg bw per day for approximately 12 weeks. No significant adverse effects related to nutritional, clinical, laboratory, or histopathological indices were reported. (Clayton 1967a cited from EHC 1990)

Charles River F$_{1a}$ rats (50 animals/sex/group, 6 weeks old) of the three-generation reproduction study described in section 4.5.2 were given CFC-12 at 0, 15 or 150 mg/kg bw/day by oral gavage for 2 years. An interim kill (6 animals/group) was made after 1 year. The animals were dosed daily the first 6 weeks of the study and 5 times/week hereafter. Over the course of the study, actual daily doses of CFC-12 for low-dose males and females declined from 27 to 11 and 25 to 11 mg/kg bw per day, respectively, and, for the high-dose males and females, declined from 273 to 130 and 242 to 128 mg/kg bw per day, respectively. Average doses were 15 mg/kg per day for the low dose group

and 150 mg/kg bw per day for the high dose group. Body weight gain was depressed in the high dose group, particularly among the females, and a slight decline in food efficiency was noted in high dose females, relative to controls. No overt signs of toxicity were seen, and there were no significant differences between treated and control groups in survival, periodic measurements of haematological, clinical chemistry, and urinalysis values, or in organ weights and histopathological findings. There was no increase in fluoride excretion in dosed animals but higher fluoride content of bone was seen at one year but not at two years. No evidence of carcinogenicity was seen. (Sherman 1974 cited from EHC 1990; IRIS 2012b and JECFA 1975)
The high dose (150 mg/kg bw/day) caused decreased body weights and was therefore considered a LOAEL by US-EPA (IRIS 2012b), whereas the low dose (15 mg/kg bw/day) produced no treatment related adverse effects and is the NOAEL by US-EPA (IRIS 2012b).

Dogs
Dogs were orally administered dose levels of CFC-12 ranging from 84-95 mg/kg bw per day for approximately 12 weeks. No significant adverse effects related to nutritional, clinical, laboratory, or histopathological indices were reported. (Clayton 1967a cited from EHC 1990)

Beagle dogs (4 animals/sex/group) were given CFC-12 in concentrations of 0, 300 or 3 000 mg/kg in the diet for 2 years (equivalent to 0, 8 and 80 mg/kg bw/day using a conversion factor of 0.025 for dogs (IPCS 2009)). None of the dogs died or showed signs of toxicity. No significant differences between treated and control groups were found in food consumption, body weight, periodic haematology, clinical chemistry, urinalysis, organ weights, or histopathological findings. An adrenal function test (urinary 17-ketosteroid excretion) also revealed no effects. CFC-12 was found in the fatty tissue of 2 dogs at the high dose level. (Sherman 1966 cited from JECFA 1975; Sherman 1974 cited from EHC 1990)

4.4.2.3 CFC-113
No data have been located regarding repeated dose oral toxicity of CFC-113.

4.4.2.4 HCFC-21
No data have been located regarding repeated dose oral toxicity of HCFC-21.

4.4.2.5 HCFC-31
No data have been located regarding repeated dose oral toxicity of HCFC-31, except for the study described in section 4.7.2.5 in which no general toxic effects were described.

4.4.2.6 HCFC-133a
Alpk/Ap rats (36 animals/sex/group) were given 0 or 300 mg/kg bw HCFC-133a by gavage on 5 days/week for 1 year. Reduced growth and increased aggressive behaviour, arrest of spermatogenesis and seminiferous tubular atrophy were observed in males. (Longstaff et al. 1984 cited from IARC 1986)

4.4.3 Dermal contact
4.4.3.1 CFC-11
CFC-11 at 40 % in sesame oil was sprayed onto shaved rabbit skin for 12 exposures with no effect (Scholz 1962 cited from EHC 1990).

4.4.3.2 CFC-12
CFC-12 at 40 % in sesame oil was sprayed onto shaved rabbit skin for 12 exposures with no effect (Scholz 1962 cited from EHC 1990).

4.4.3.3 CFC-113

A pad saturated with CFC-113 was applied to an area corresponding to 10 % of the body surface of hairless mice for 5 min, twice daily, for 10, 20, or 40 days. No changes occurred in the group exposed for 10 days. Increased vacuolization of liver endoplasmic reticulum was seen after 20 days exposure, which was less pronounced after 40 days, whereas swollen mitochondria were only found after 20 days exposure. (McNight & McGraw 1983 cited from EHC 1990)

CFC-113 applied to rabbit skin at 5 000 mg/kg per day for 5 days caused gross and histological damage to the skin as well as slight changes in the liver (Clayton 1966 cited from EHC 1990).

CFC-113 at 40 % in sesame oil was sprayed onto shaved rabbit skin for 12 exposures with no effect (Scholz 1962 cited from EHC 1990).

4.4.3.4 HCFC-21

No data have been located regarding repeated dose dermal toxicity of HCFC-21.

4.4.3.5 HCFC-31

No data have been located regarding repeated dose dermal toxicity of HCFC-31.

4.4.3.6 HCFC-133a

No data have been located regarding repeated dose dermal toxicity of HCFC-133a.

4.5 Toxicity to reproduction

4.5.1 Inhalation

4.5.1.1 CFC-11

No data have been located regarding reproductive toxicity of CFC-11 as such. Two studies have been located in which rats and rabbits were exposed to a mixture of CFC-11 and CFC-12.

Rats and rabbits were exposed to a mixture of CFC-11 (10 %) and CFC-12 (90 %) on gestation day (GD) 4-16 (rats) or 5-20 (rabbits) for 2 hours/day at a concentration of 1 558 000 mg/m^3. No evidence of embryotoxicity, foetotoxicity or teratogenicity was reported in rats sacrificed on GD 20 or rabbits sacrificed on GD 30. Offspring of the dams allowed to deliver showed no evidence of toxicity relative to survival or growth. (US EPA 1983 cited from EHC 1990)

4.5.1.2 CFC-12

No data have been located regarding reproductive toxicity of CFC-11 as such. Two studies have been located in which rats and rabbits were exposed to a mixture of CFC-11 and CFC-12.

Rats and rabbits were exposed to a mixture of CFC-11 (10 %) and CFC-12 (90 %) on GD 4-16 (rats) or 5-20 (rabbits) for 2 hours/day at a concentration of 1 558 000 mg/m^3 (200 000 ppm). No evidence of embryotoxicity, foetotoxicity or teratogenicity was reported in rats sacrificed on GD 20 or rabbits sacrificed on GD 30. Offspring of the dams allowed to deliver showed no evidence of toxicity relative to survival or growth. (US EPA 1983 cited from EHC 1990)

4.5.1.3 CFC-113

Rats

Rats were exposed by inhalation 6 hours/day, 5 days per week, for 10 weeks (males) or 3 weeks (females) to CFC-113 at either 39 000 or 97 000 mg/m^3. Each male rat was then paired with two females for 2 weeks during which time exposure was 6 hours/day, 7 days/week. Females that showed positive signs of mating continued to be exposed 6 hours/day until day 20 of gestation

when they were allowed to give birth. The development of their offspring was followed for up to 4 weeks. There were no adverse effects on any of the standard reproductive indices. (US EPA 1983 cited from EHC 1990)

Pregnant rats (24 animals/group) were exposed to CFC-113 6 hours/day on GD 6-15 to either 39 000, 97 000, or 195 000 mg/m^3. Some evidence of maternal toxicity (reduced weight gain, decreased food intake) was seen at the highest exposure level. However, there was no evidence of embryotoxicity, foetotoxicity, or teratogenicity at any exposure level. (US EPA 1983 cited from EHC 1990)

Rabbits
Pregnant rabbits (8 animals/group) were given CFC-113 at 0, 1 000 or 5 000 mg/kg/day by gavage on GD 8-11. Low pregnancy rates and foetal deaths were observed in both control and test groups. No unusual skeletal or visceral abnormalities were observed at any dose level. (Hazleton Laboratories 1967a cited from EHC 1990)

Pregnant rabbits (12 animals/group) were exposed to CFC-113 at 15 600 or 156 000 mg/m^3 (2 000 and 20 000 ppm) 2 hours/day on GD 8-16. Unspecified signs of maternal toxicity were observed in the high dose group but no evidence of treatment related embryotoxicity or teratogenicity. (Hazleton Laboratories 1967a cited from EHC 1990)

Both studies were considered to be inadequate by US-EPA (US EPA 1983 cited from EHC 1990) due to the small number of dams and foetuses evaluated, the limited exposure time each day, and excessive maternal toxicity.

4.5.1.4 HCFC-21

Pregnant rats (25 animals) were exposed to HCFC-21 at 42 700 mg/m^3 6 hours/day on GD 6 to 15. The rats gained substantially less weight than the control animals. Out of the 25 mated rats 15 had no implants or viable foetuses. No other effects on pregnancy or foetal development were observed. (Kelly et al. 1978 cited from ECETOC 1990a)

Pregnant rats were exposed for the whole gestation period to 153 mg/m^3 or 303 mg/m^3 to HCFC-21. Decreased levels of DNA and total nucleic acids in the liver, brain, ovaries and placenta were observed. (Aranjina 1972 cited from ECETOC 1990a)

4.5.1.5 HCFC-31

Pregnant rats were exposed to HCFC-31 at 2 800 mg/m^3 6 hours/day on days 6-15 of gestation. Cervical ribs were found in 8/208 treated foetuses. The number of cervical ribs in the control group was not reported. (Coate et al. 1976 cited from IARC 1986a)

Rats were exposed to HCFC-31 at 2 800 or 14 000 mg/m^3 for 6 hours/day for 20 days. Minimal to slight hypospermatogenesis was observed in the high dose group. (Coate et al. 1976 cited from IARC 1986a)

Rats were exposed to HCFC-31 at 2 800 for 6 hours/day for 13 weeks (65 exposures). Hypospermatogenesis was observed which was not reversed after a 4 week recovery period. (Coate et al. 1976 cited from IARC 1986a)

Male rats exposed to HCFC-31 at 2 800 mg/m^3 for 10 weeks were mated weekly with unexposed females over a 16 week period. Pregnancy rate was reduced throughout this period. (Coate et al. 1976 cited from IARC 1986a)

4.5.1.6 HCFC-133a

Mice

Mice were exposed to HCFC-133a at 12 000 or 48 000 mg/m^3 6 hours/day for 5 days. The mice were subdued and 17/60 died in the low dose group and while 27/80 died in the high dose group. Body weight gain was lower in treated animals. Lower testis and epididymis weights were observed in mice killed at weekly intervals up to 9 weeks after treatment and higher incidences of abnormal sperm in the treated groups were reported. Damage to the germinal epithelium affecting spermatogonia and spermatocytes were found during histological examination of the testis. Recovery was observed after 5 weeks particularly in the low dose group. (Hodge et al. 1980 cited from ECETOC 1990b)

Mice were exposed to HCFC-133a at 0, 485, 2 500, 4 800 or 12 000 mg/m^3 6 hours/day for 5 days. At 485 mg/m^3 1/59 died; at 4 800 mg/m^3 mice were subdued and 4/60 died and at 12 000 mg/m^3 mice were subdued and 18/60 died. Lower testis and epididymis weights were observed in mice killed at weekly intervals up to 9 weeks after treatment at exposure levels of 2 400 mg/m^3 and above, while it was observed only in week 7 in the lowest dose group. A higher incidence proportion of abnormal sperm was observed in all treated groups although minimal in the lowest dose group. Damage to the germinal epithelium which affected the normal production of sperm was found during microscopic examination of the testes. (Kilmartin et al. 1980 cited from ECETOC 1990b)

Male mice (15 animals/group (30 controls)) were exposed to concentrations of HCFC-133a between 0 and 98 000 mg/m^3, 6 hours/day, for 5 consecutive days. At the end of exposure the treated mice were serially mated two virgin females for four consecutive nights. This four-nightly mating procedure was continued for 8-9 consecutive weeks. The females were sacrificed 15 days later and their uteri examined for numbers of live implantations, early deaths and late deaths. The proportion of pregnant females was 0-60 % in the treated groups and 90-100 % in the control group. Lower fertility was observed at exposure concentrations of 2 500 mg/m^3 and above. No effect on male fertility was seen at 485 mg/m^3. (Hodge et al. 1979, 1980 and Kilmartin 1980, all cited from EHC 1992 and ECETOC 1990b)

Rats

Pregnant Charles River-CD rats were exposed to HCFC-133a at 0 (control), 2 500, 10 000, 25 000 or 98 000 mg/m^3 6 hours/day on GD 6 to 15 and were sacrificed on GD 21. No clear evidence of maternal toxicity was reported. Foetal weights and crown-rump length were lower in all treatment groups compared to control group. Foetal deaths and total litter resorption was seen in the three highest doses. At 10 000 mg/m^3 4/21 pregnant rats had total resorption and 67 foetuses were alive in the remaining 17 rats. At 25 000 mg/m^3 37/41 pregnant rats had total resorption and 7 foetuses were alive in the remaining 4 rats. At 98 000 mg/m^3 22/23 pregnant rats had total resorption and 1 foetus was alive in the remaining rat. Treatment related higher numbers of runts and delayed ossifications in several bone structures were observed at all dose levels. A higher incidence of hydronephrosis was reported in all treated groups, which, according to the authors, were an indication of interferences by HCFC-133a with timely organ development. A no-effect level for embryo-lethality was established at 2 500 mg/m^3 but a no-effect level for embryotoxicity could not be established due to the effects on foetal weights and crown-rump length in the lowest dose group. (Culik & Kelly 1979 cited from ECETOC 1990b and EHC 1992)

Pregnant Wistar rats (12 animals) were exposed to HCFC-133a at 25 000 mg/m^3 6 hours/day on GDs 7 to 16. All animals were autopsied at GD 21. Data from the study was compared to historical control data. Mild transient sedation and piloerection was observed and body weight gain and food consumption was lower in treated animals. The prenatal mortality was 77 %. Placental weight, foetal weight and crown-rump length were lower and some foetuses showed generalised oedema

and external anomalies of the limbs and tail. (Weigand et al. 1977 cited from ECETOC 1990b and EHC 1992)

Rabbits
Pregnant Himalayan rabbits (12 animals) were exposed to HCFC-133a at 25 000 mg/m^3 6 hours/day on GDs 7 to 19. Data from the study was compared to historical control data. Body weight gain and food consumption was lower in treated animals. All animals showed vaginal bleeding during the last three days of exposure and 4/12 animals aborted. All foetuses had died on GD 29. (Weigand et al. 1977 cited from ECETOC 1990b and EHC 1992)

4.5.2 Oral intake

4.5.2.1 CFC-11

No oral data have been located regarding reproductive toxicity of CFC-11.

4.5.2.2 CFC-12

Weanling rats (48 females and 44 males) were given CFC-12 at 0, 0.2 or 2 % (according to EHC 1990 equivalent to average doses of 0, 15 and 150 mg/kg bw/day) in corn oil by gavage for 3 months. After 3 months the animals were mated. The dosage continued for the males but ceased during gestation day 18 to lactation day 5 for the females. The F_{1a} generation was used for long-term studies described in section 4.4.2.2. The F_0 rats were mated a second time to initiate an F_{1b} litter. F_{2a} and F_{3a} litters were also produced. No adverse effects were reported on reproductive capability as measured by the fertility index (percentage of matings resulting in pregnancy), gestation index (percentage of pregnancies resulting in birth of live litters), viability index (percentage of rats born that survived four days), and lactation index (percentage of rats alive at 4 days that survived to be weaned at 21 days). (Sherman et al. 1974 cited from EHC 1990 and JECFA 1975)

Pregnant Charles River rats (25-27 animals/group) were given CFC-12 by gavage at doses of 16.6 or 179 mg/kg per day on days 6-15 of gestation. Neither dose induced any evidence of embryotoxicity or teratogenicity. (Sherman 1974 cited from EHC 1990)

Rats (total of 78 animals) were given 0, 0.2 or 2 % CFC-12 by gavage from gestation day (GD) 6 to 16 and were sacrificed on GD 21. No effects on parents or offspring were reported. (Culik et al. 1973 cited from JECFA 1975)

4.5.2.3 CFC-113

No oral data have been located regarding reproductive toxicity of CFC-113.

4.5.2.4 HCFC-21

No oral data have been located regarding reproductive toxicity of HCFC-21.

4.5.2.5 HCFC-31

No oral data have been located regarding reproductive toxicity of HCFC-31.

4.5.2.6 HCFC-133a

SPF Alpk/Ap (Wistar-derived) rats (36 animals/sex/group, 6 weeks old) were given HCFC-133a at 300 mg/kg bw in corn oil by gavage on 5 days/week for 52 weeks. An undosed (32 animals/sex) and a dosed control group (40 animals/sex) was included and the study was terminated at week 125. Animals were observed for clinical abnormalities daily throughout the study. Histopathological examinations on the major organs together with any tissue observed to be grossly abnormal were conducted on all animals. Animals, particularly males, became very aggressive and a distinct reduction in testicular size was observed during the study. The testes of all dosed male animals were abnormal. The changes seen were arrest of spermatogenesis and seminiferous tubular atrophy. (Longstaff et al. 1984 cited from IARC 1986b)

These results are part of a carcinogenicity study described in more detail in section 4.7.2.5.

4.5.3 Dermal contact

No data have been located regarding reproductive toxicity of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a following dermal contact.

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

Results from *in vitro* mutagenic and genotoxic studies for CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a are reported in Table 5.

No evidence of *in vitro* mutagenic activity was observed for CFC-11, CFC-12, CFC-113, HCFC-21 or HCFC-133a.

HCFC-31 was reported to be mutagenic in *Salmonella typhimurium* strains TA 100 and TA 1535 at high vapour concentrations (2.5-10 %) and induced concentration- and time-dependent increases in 6-thioguanine-resistant mutants in Chinese hamster ovary cells at high vapour concentrations (10-40 %) (IARC 1986a).

4.6.2 *In vivo* studies

Results from *in vivo* mutagenic and genotoxic studies on CFC-12, CFC-113, HCFC-31 and HCFC-133a are reported in Table 6. No data have been located for CFC-11 and HCFC-21.

No evidence of *in vivo* mutagenic activity was reported for CFC-12, CFC-113 or HCFC-31.

CFC-12 was tested for mutagenicity in a dominant lethal assay performed in F_{1b} litter rats from the three-generation reproduction study described in section 4.5.2.1 (Scherman et al. 1974 cited from JECFA 1975).

HCFC-31 was tested for dominant lethal effects and cytogenetic effects on bone marrow cells in a reproductive toxicity study described in section 4.5.1.6 (Coate et al. 1976 cited from IARC 1986a).

Three dominant lethal studies with HCFC-133a were performed in male mice (Hodge et al. 1979, 1980; Kilmartin et al. 1980, all cited from EHC 1992 and ECETOC 1990b).
HCFC-133a at 48 000 or 96 000 mg/m^3 (the high dose level was reduced to 24 000 mg/m^3 after 2 days) caused a statistically significant increase in the incidence of early deaths in animals mated in weeks 6-8. In week 6, however, the number of males mating was low and in weeks 7 and 8 the incidence of early foetal deaths was particularly low in the controls (Hodge et al. 1979 cited from EHC 1992 and ECETOC 1990b).
HCFC-133a at 12 000 and 48 000 mg/m^3 caused a statistically significant increase in the incidence of early foetal deaths in week 7 but without dose-response relationship (Hodge et al. 1980 cited from EHC 1992 and ECETOC 1990b).
HCFC-133a at 485, 2 400, 4 800 or 12 000 mg/m^3 did not cause any incidence of early death (Kilmartin et al. 1980 cited from EHC 1992 and ECETOC 1990b).

Substance	*Salmonella typhimurium* TA98	*Salmonella typhimurium* TA100	*Salmonella typhimurium* TA1535	*Salmonella typhimurium* TA1537	*Salmonella typhimurium* TA1538	CHO cells	BHK21 cells	*S. cerevisiae* D4	Use of metabolic activating system	Ref
CFC-11			NEG		NEG				yes	A
CFC-11	NEG	NEG	NEG		NEG				no/yes	B
CFC-11						NEG			no/yes	C
CFC-11							NEG		yes	B
CFC-12		NEG	NEG						no/yes	B
CFC-12						NEG			no/yes	C
CFC-12							NEG		yes	B
CFC-113		NEG	NEG						no/yes	B
HCFC-21	NEG	NEG	NEG	NEG	NEG					D
HCFC-21								NEG		D
HCFC-31		POS							no/yes	E
HCFC-31		POS	POS						no/yes	F
HCFC-31						POS			no/yes	G
HCFC-133a	NEG	NEG	NEG		NEG				no/yes	H
HCFC-133a	NEG	NEG							no/yes	I
HCFC-133a	NEG	NEG							no/yes	J
HCFC-133a							NEG		no/yes	K

TABLE 5
IN VITRO MUTAGENIC AND GENOTOXIC STUDIES.
NEG: NEGATIVE, POS: POSITIVE.
REFERENCES: A: UEHLEKE ET AL. 1977 (EHC 1990); B: LONGSTAFF ET AL 1984 (EHC 1990); C: KRAHN ET AL 1982 (EHC 1990); D: BRUSICK 1976 (EHC 1992); E: GREEN 1983 (CITED FROM IARC 1986A); F: LONGSTAFF ET AL 1984 (CITED FROM IARC 1986A); G: KRAHN ET AL 1982 (CITED FROM IARC 1986A); H: MCGREGOR 1976 (EHC 1992); I: WASKELL 1979 (EHC 1992); J: EDMUNDS ET AL 1979 (EHC 1992); K: LONGSTAFF ET AL 1984 (EHC 1992).

Substrate (exposure)	Dominant lethal assay (mice)	Dominant lethal assay (rat)	Rat bone marrow test	Trandescantia hybrid	Dose	Remarks	Ref
CFC-12 (p.o)		negative			15 and 150 mg/kg bw/d		A
CFC-12				negative	-		B
CFC-113 (i.p)	negative				-		C
HCFC-31			negative		2 800 mg/m^3 (0.1 % v/v) 6 hours/day, 5 days/week, 13 weeks		D
HCFC-31		negative			2 800 mg/m^3 (0.1 %) 10 weeks		D
HCFC-133a			negative		Up to 98 000 mg/m^3, 6 hours		E
HCFC-133a			negative		Up to 98 000 mg/m^3, 6 hours/day, 5 days/week		E
HCFC-133a	positive				48 000 mg/m^3, 6 hours/day, 5 days/week	Early deaths increased in mating weeks 6-8	F
HCFC-133a	positive				12 000 mg/m^3, 6 hours/day, 5 days/week	Early deaths increased in mating week 7, no dose response	G
HCFC-133a	negative				12 000 mg/m^3, 6 hours/day, 5 days/week		H

TABLE 6
IN VIVO MUTAGENIC AND GENOTOXIC STUDIES.
O: PER ORAL, I.P: INTRAPERITONEAL.
REFERENCES: A: SHERMAN 1974 CITED FROM EHC 1990 AND JECFA 1975; B: VAN'T HOF & SCHAIRER 1982 CITED FROM EHC 1990; C: EPSTEIN ET AL 1972 CITED FROM EHC 1990; D: COATE ET AL. 1979 CITED FROM IARC 1986A; E: ANDERSON & RICHARD 1979 CITED FROM EHC 1992 AND ECETOC 1990B; F: HODGE ET AL. 1979 CITED FROM EHC 1992 AND ECETOC 1990B; G: HODGE ET AL. 1980 CITED FROM EHC 1992 AND ECETOC 1990B; H: KILMARTIN ET AL. 1980 CITED FROM EHC 1992 AND ECETOC 1990B.

4.7 Carcinogenic effects

4.7.1 Inhalation

4.7.1.1 CFC-11

Mice

Swiss mice (60 animals/sex/treatment group, 90 animals/sex in the control group, 8 weeks old) were exposed to CFC-11 at 0, 5 600 or 28 000 4 hours/day, 5 days/week for 78 weeks. Histopathological examinations were performed on each animal on the subcutaneous lymph nodes, brain and cerebellum, Zymbal glands, interscapular brown fat, salivary glands, Harderian glands, tongue, thymus and mediastinal lymph nodes, lungs diaphragm, liver, kidneys, adrenals, spleen, mesenteric lymph nodes, stomach, various segments of the intestine, bladder, uterus, gonads, bone marrow smear and any other organs with pathological lesions. The survival rate was generally lower in the control group than in the treated groups and showed statistically significant differences after various periods. A higher number of mammary tumours (high dose females), lung adenomas (females, dose related), leukemias (females, dose related) and a higher total number of tumours (females) were observed, but according to the authors these tumours were generally age-related. Only a statistically significant difference in incidence of mammary tumours were observed after adjustment for the differences in survival but according to the authors the incidence of mammary tumours in the strain of mice used was comparable to those observed in controls of recently conducted experiments. (Maltoni et al. 1988)

Rats

Sprague-Dawley rats (90 animals/sex/treatment group, 150 animals/sex in the control group, 9 or 13 weeks old) were exposed to CFC-11 at 0, 5 600 or 28 000 mg/m^3 4 hours/day, 5 days/week for 104 weeks. Histopathological examinations were performed on each animal on the subcutaneous lymph nodes, brain and cerebellum, Zymbal glands, interscapular brown fat, salivary glands, Harderian glands, tongue, thymus and mediastinal lymph nodes, lungs diaphragm, liver, kidneys, adrenals, spleen, mesenteric lymph nodes, stomach, various segments of the intestine, bladder, uterus, gonads, bone marrow smear and any other organs with pathological lesions. No treatment related differences in the incidence of total benign or malignant tumours when compared with groups of unexposed rats were observed. (Maltoni et al. 1988)

4.7.1.2 CFC-12

Mice

Swiss mice (60 animals/sex/treatment group, 90 animals/sex in the control group, 8 weeks old) were exposed to CFC-12 at 0, 5 000 or 25 000 4 hours/day, 5 days/week for 78 weeks. Histopathological examinations were performed on each animal on the subcutaneous lymph nodes, brain and cerebellum, Zymbal glands, interscapular brown fat, salivary glands, Harderian glands, tongue, thymus and mediastinal lymph nodes, lungs diaphragm, liver, kidneys, adrenals, spleen, mesenteric lymph nodes, stomach, various segments of the intestine, bladder, uterus, gonads, bone marrow smear and any other organs with pathological lesions. The survival rate was generally lower in the control group than in the treated groups and showed statistically significant differences after various periods. A higher number of pulmonary adenomas (high dose males and females), leukemias (low and high dose males and low dose females) and a higher total number of tumours (females and males (dose-related in males)) were observed, but according to the authors these tumours were generally age-related. After adjustment for the differences in survival no statistically significant increases in these types of tumours or total number of tumours were observed in treated animals compared to control animals. (Maltoni et al. 1988)

Rats

Sprague-Dawley rats (90 animals/sex/treatment group, 150 animals/sex in the control group, 9 or 13 weeks old) were exposed to CFC-12 at 0, 5 000 or 25 000 mg/m^3 4 hours/day, 5 days/week for

104 weeks. Histopathological examinations were performed on each animal on the subcutaneous lymph nodes, brain and cerebellum, Zymbal glands, interscapular brown fat, salivary glands, Harderian glands, tongue, thymus and mediastinal lymph nodes, lungs diaphragm, liver, kidneys, adrenals, spleen, mesenteric lymph nodes, stomach, various segments of the intestine, bladder, uterus, gonads, bone marrow smear and any other organs with pathological lesions. No treatment related differences in the incidence of total benign or malignant tumours when compared with groups of unexposed rats were observed. (Maltoni et al. 1988)

4.7.1.3 CFC-113

Crl:CD(SD)BR rats (100 animals/sex/group, 5 weeks old) were exposed to CFC-113 at approximately 0, 15 300, 76 600 or 153 000 mg/m^3 6 hours/day, 5 days/week for up to 2 years. Body weight, appearance and behaviour were monitored regularly. At the end of the study all animals were necropsied and the following tissues collected: adrenal glands, brain, heart, kidneys, liver, lungs, pituitary, spleen, testes, thymus, adipose tissue, aorta, bone (sternum), bone marrow, cervix, epididymides, oesophagus, eyes, exorbital lacrimal glands, Harderian gland, lymph nodes, mammary glands, nasal turbinates, ovaries, pancreas, parathyroids, pinna, prostate, salivary glands, thyroid gland, trachea, urinary bladder, uterus, vagina, Zymbal's gland and any gross lesions and/or tissue masses. Tissues from the control and high dose animals and the tissues from rats (from all dose groups) that were found dead or terminated *in extremis* were investigated microscopically. Approximately 18-35 % of the male rats and 5-8 % of the female rats in the exposed groups died as a consequence of unintentional infections with *Corynebacterium kutscheri*. The infections appeared to affect all groups equally including the control group. No treatment related effects were observed on tumour incidence, as all incidences of tumours were reported by the authors to be within normal historical background levels for their laboratory. (Trochimowicz et al. 1988)

4.7.1.4 HCFC-21

No data were located on the carcinogenicity of HCFC-21.

4.7.1.5 HCFC-31

No data were located on the carcinogenicity of HCFC-31.

4.7.1.6 HCFC-133a

No data were located on the carcinogenicity of HCFC-133a.

4.7.2 Oral intake

4.7.2.1 CFC-11

Mice

When administered by gavage to groups of 50 male and 50 female B6C3F1 mice (see section 4.4.2.1), CFC-11 at 1 962 or 3 952 mg/kg bw per day, 5 days/week, for 78 weeks, followed by 13 weeks of observation, produced no evidence of carcinogenicity (NCI 1978 cited from EHC 1990).

Rats

Gavage administration of CFC-11 to groups of 50 male and 50 female Osborne-Mendel rats in the also produced no evidence of carcinogenicity (see section 4.4.2.1), but the results were considered to be inconclusive by the NCI (1978) because the numbers of rats surviving long enough to be at risk from late-developing tumours were insufficient. In this study, time-weighted average doses of CFC-11 (488 and 977 mg/kg bw per day for male rats and 538 and 1 077 mg/kg bw per day for female rats) were administered 5 days/week for 78 weeks, followed by 28-33 weeks of observation. (NCI 1978 cited from EHC 1990)

4.7.2.2 CFC-12

CFC-12 administered by gavage at doses of 15 or 150 mg/kg per day for 2 years to groups of 50 male and 50 female Charles River rats of the F1a generation in a multi-generation study (see section 4.4.2.2) produced no evidence of carcinogenicity (Sherman 1974 cited from EHC 1990).

CFC-12 administered in the diet in concentrations of 0, 300 or 3 000 mg/kg in the diet for 2 years (equivalent to 0, 8 and 80 mg/kg bw/day using a conversion factor of 0.025 for dogs (IPCS 2009)) to groups of 4 male and 4 female Beagle dogs produced no evidence of carcinogenicity (Sherman 1966 cited from JECFA 1975; Sherman 1974 cited from EHC 1990).

4.7.2.3 CFC-113

No data were located on the carcinogenicity of CFC-113.

4.7.2.4 HCFC-21

No data were located on the carcinogenicity of HCFC-21.

4.7.2.5 HCFC-31

SPF Alpk/Ap (Wistar-derived) rats (36 animals/sex/group, 6 weeks old) were given HCFC-31 at 300 mg/kg bw in corn oil by gavage on 5 days/week for 52 weeks. An undosed (32 animals/sex) and a dosed control group (40 animals/sex) was included and the study was terminated at week 125. Animals were observed for clinical abnormalities daily throughout the study. Body weights were recorded weekly for the first 12 weeks and thereafter every fourth week. Histopathological examinations of lungs, liver, spleen, kidneys and brain together with any tissue observed to be grossly abnormal were conducted on all animals. Bodyweight was significantly reduced in treated males but might have been associated with a dental problem starting at week 22. Mortality was greater in HCFC-31 treated rats compared to the control groups. All treated males had died by 100 weeks and females by 108 weeks. The incidence of malignant stomach neoplasms was 1/104 and 33/36 in male controls and treated males, respectively ($p<0.0001$) and 0/104 and 34/36 in female controls and treated females, respectively ($p<0.0001$). The (in total) 5 treated animals that did not develop stomach neoplasms died between week 8 and 79; all showing some degree of hyperplasia of the epithelium of the nonglandular stomach but no inflammation. (Longstaff et al. 1984 cited from IARC 1986b)

4.7.2.6 HCFC-133a

SPF Alpk/Ap (Wistar-derived) rats (36 animals/sex/group, 6 weeks old) were given HCFC-133a at 300 mg/kg bw in corn oil by gavage on 5 days/week for 52 weeks. An undosed (32 animals/sex) and a dosed control group (40 animals/sex) was included and the study was terminated at week 125. Animals were observed for clinical abnormalities daily throughout the study. Body weights were recorded weekly for the first 12 weeks and thereafter every fourth week. Histopathological examinations of lungs, liver, spleen, kidneys and brain together with any tissue observed to be grossly abnormal were conducted on all animals. Bodyweight was significantly reduced in treated males. The incidence of uterine carcinomas was 1/104 and 15/35 in female controls and treated females, respectively ($p<0.001$). The incidence of benign (often bilateral) interstitial-cell neoplasms of the testes was 16/104 and 29/36 in male controls and treated males, respectively ($p<0.001$). (Longstaff et al. 1984 cited from IARC 1986b and ECETOC 1990b)

4.7.3 Dermal contact

No data have been located regarding carcinogenicity of CFC-11, CFC-113, HCFC-21, HCFC-31 and HCFC-133a following dermal contact.

5. Regulations

5.1 Ambient air

Denmark (C-value): CFC-11: 1 mg/m^3 (based on the ozone depleting potential, i.e. not health-based).
HCFC-141b: 1 mg/m^3 (based on the ozone depleting potential, i.e. not health-based).

5.2 Drinking water

Denmark: -

5.3 Soil

Denmark: -

5.4 Occupational Exposure Limits

Denmark:

Chlorofluorocarbon	TWA ppm	TWA mg/m^3
CFC-11	500	2 810
CFC-12	500	2 475
CFC-113	500	3 800
HCFC-21	10	40
HCFC-31	-	-
HCFC-133a	-	-

TABLE 7
REFERENCE: AT (2007)

Germany: Maximum workplace concentration (MAK)

Chlorofluorocarbon	MAK ppm	MAK mg/m^3
CFC-11	1 000	5 700
CFC-12	1 000	5 000
CFC-113	500	3 900
HCFC-21	10	43
HCFC-31	-	-
HCFC-133a	-	-

TABLE 8
REFERENCE: MAK (2013)

5.5 Classification

No harmonised classifications exist for CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and HCFC-133a.

5.6 IARC

The IARC evaluated HCFC-31 and HCFC-133a to be not classifiable as to its carcinogenicity to humans (group 3) (IARC 1999).

5.7 US-EPA

CFC-11
Oral reference dose (RfD): 0.3 mg/kg bw/day (last revised 1992 although a screening-level review was conducted in 2002 which did not identify any critical new studies). The RfD is based on a LOAEL of 488 mg/kg bw/day (5 days/week) converted to 349 mg/kg bw/day on a 7-day exposure basis (NCI 1978). An uncertainty factor of 10 is used for LOAEL, 10 for interspecies extrapolation and 10 to protect sensitive populations (IRIS 2012a)

CFC-12
Oral RfD: 0.2 mg/kg bw/day (last revised 1995 although a comprehensive review of toxicological studies published through 2004 was conducted. No changes was made in the RfD as no new health effects data were considered useful in the revision of the existing RfD for CFC-12). The RfD is based on a NOAEL of 300 ppm in the diet, corresponding to 15 mg/kg bw/day in a long-term rat study (Sherman et al 1974). An uncertainty factor of 10 is used for interspecies extrapolation and 10 to protect sensitive populations (IRIS 2012b).

CFC-113
Oral RfD: 30 mg/kg bw/day (last revised 1996). The RfD is based on a NOAEL of 5 358 mg/m^3 converted to 273 mg/kg bw/day in humans (5 358 mg/m^3 * 10 m^3/day * (5 days/7 days) * (0.5/70 kg bw) based on an 8 hour human breathing volume of 10 m^3/day and an absorption factor of 0.5) (Imbus & Adkins 1972). An uncertainty factor of 10 is used for the interhuman variability (IRIS 2012c).

5.8 WHO / JECFA

An ADI of 0-1.5 mg/kg bw was set for CFC-12 when used as food freezant based on a level of 3 000 mg/kg in the diet (equivalent to 150 mg/kg bw/day) causing no toxicological effects in a long-term rat study (Sherman et al. 1974 cited from JECFA 1975).

CFC-12 was classified to Cramer et al. (1978) Structural Class III by the JECFA (Joint FAO/WHO Expert Committee on Food Additives) i.e. substances of a chemical structure that permit no strong initial presumption of safety, or may even suggest significant toxicity (JECFA 1996).

6. Summary and evaluation

6.1 Description

Fully halogenated chlorofluorocarbons (CFCs) are compounds derived by the complete substitution of the hydrogen atoms in methane and ethane with both fluorine and chlorine atoms. CFC-11 (trichlorofluoromethane) and CFC-12 (dichlorodifluoromethane) are both methane derivatives and CFC-113 (1,1,2-trichloro-1,2,2-trifluoroethane) is an ethane derivative.

Partially halogenated chlorofluorocarbons (HCFCs) are compounds derived by the partial substitution of the hydrogen atoms in methane and ethane with both fluorine and chlorine atoms. HCFC-21 (dichlorofluoromethane) and HCFC-31 (chlorofluoromethane) are both methane derivatives and HCFC-133a (1-chloro-2,2,2-trifluoroethane) is an ethane derivative.

Fully halogenated chlorofluorocarbons (e.g., CFC-11, CFC-12, and CFC-113) are usually characterised by high vapour pressure and density and low viscosity, surface tension, refractive index, and solubility in water.

The partially halogenated chlorofluorocarbons (e.g., HCFC-21, HCFC-31 and HCFC-133a) are slightly or moderately soluble in water. Generally, hydrochlorofluorocarbons of low relative molecular mass are characterised by high vapour pressure, density, and refractive index, and low viscosity and surface tension.

The production and use of CFCs are banned according to the Montreal Protocol and the use of HCFCs is banned from 2020 in the industrial countries and from 2040 in the undeveloped countries.

6.2 Environment

Chlorofluorocarbons can be released into the environment during manufacture, handling, use, or disposal of wastes. Because of the high vapour pressure of chlorofluorocarbons at ambient temperatures, the release from different sources will primarily be to the atmosphere.

The chlorofluorocarbons are persistent in the environment because of their chemical stability. The average residence times in the atmosphere have been estimated to be 65, 110 and 90 years for CFC-11, CFC-12 and CFC-113, respectively. These long residence times will ensure diffusion into the stratosphere where, via photochemically-produced chlorine atoms, the chlorofluorocarbons will react with the ozone layer.
Reaction with naturally occurring hydroxyl radicals in the troposphere is thought to be the primary degradation route for the HCFCs. Based on the estimated trophospheric rate of the reaction of HCFCs with hydroxyl radicals the average residence has been estimated to be about 2, 1.6 and 4.8 years for HCFC-21, HCFC-31 and HCFC-133a, respectively.

Because of the high vapour pressure of the six chlorofluorocarbons evaluated in this document these chlorofluorocarbons will most likely volatilise to the atmosphere when released under ambient conditions into aquatic systems.
Chlorofluorocarbons generally exhibit a low rate of hydrolysis under ambient conditions and the rates of hydrolysis, which are greatly affected by temperature, pressure, and the presence of

catalytic materials (such as metals) are considered to be negligible compared with the rate of volatilisation of the chlorofluorocarbons and subsequent photo-dissociation.

The octanol/water partition coefficients of the six chlorofluorocarbons evaluated in this document indicate that adsorption onto organic particulates may be possible. In cases of significant sorption to soils, the volatilisation of these compounds will be slower than in aquatic systems, though volatilisation may still be the major transport process from soils.

Biodegradation of CFC-11, CFC-12, HCFC-21, HCFC-31 and CFC-113 has been reported to occur in various environmental media under special circumstances, predominantly under anaerobic conditions. No data on the biodegradation of HCFC-133a have been located.
The biodegradation of chlorofluorocarbons in general has only been reported to occur under co-metabolic conditions, either under anaerobic conditions with electron-donating compounds or under aerobic co-oxidation conditions with primary substrates that induce monooxygenase activity. Oxidation of chlorinated solvents by the methane monooxygenase expressed by methylotrophic organisms to oxidize methane is a classic example of co-metabolism. Under anaerobic conditions, a common form of co-metabolism is the reaction of reduced enzyme cofactors with chlorinated solvents, resulting in their reductive dehalogenation.

Reported biodegradation intermediates/products of CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31 and CFC-113 are presented in Table 3. A more detailed description of the biodegradation of CFC-11 (including HCFC-21 and HCFC-31) and CFC-113 are presented in Figure 1 and 2, respectively.

The low octanol/water partition coefficients of the six chlorofluorocarbons evaluated in this document indicate a low potential for bioaccumulation.

6.3 Human exposure

In general, human exposure levels are considered negligible in comparison with the high concentrations of chlorofluorocarbons that cause signs of adverse effects in humans and in experimental animals.

6.4 Toxicokinetics

The available data on absorption of CFCs indicate that these compounds can be absorbed across the alveolar membrane following inhalation, the gastro-intestinal tract following ingestion, and the skin following dermal contact. Following inhalation, CFCs are absorbed rapidly and are distributed by blood into practically all tissues. Relatively high concentrations are found in fat, but also in organs with good blood supply. The available studies suggest that CFCs are metabolised to a very small extent in mammals following inhalation and they appear to be eliminated almost exclusively through the respiratory tract.

No data are available on the absorption and distribution of the HCFCs evaluated in this document. However, it may be inferred from the toxicity studies that absorption occurs. Limited data are available on the elimination of the HCFCs evaluated in this document. However, based on the information on the CFCs, it is likely that the main route of excretion for the HCFCs is through the respiratory tract.

6.5 Human toxicity

6.5.1 Single dose toxicity

The CFCs evaluated in this document is of low acute inhalation toxicity in humans. No data have been located regarding acute inhalation toxicity of the HCFCs evaluated in this document.

No relevant human data have been located regarding acute oral and dermal toxicity of the chlorofluorocarbons evaluated in this document.

6.5.2 Irritation

No relevant human data have been located regarding irritation (skin, eye, respiratory tract) of the chlorofluorocarbons evaluated in this document.

6.5.3 Sensitisation

Allergic contact eczema was reported in patch tests performed on three patients that had a prior history of skin reactions to deodorant sprays. All three patients showed mild to strong reactions to CFC-11 and one patient showed a mild reaction to CFC-12.
No human data have been located regarding skin sensitisation of the other chlorofluorocarbons evaluated in this document.

No human data have been located regarding respiratory sensitisation of the chlorofluorocarbons evaluated in this document.

Several special studies have shown cardiac sensitisation and arrhythmia (predominantly asphyxia or adrenaline-induced) after high doses (> 40 000 mg/m^3) of chlorofluorocarbons in a number of animal species.

6.5.4 Repeated dose toxicity

Decrease in cognitive test performance has been reported in subjects exposed to CFC-11 at 5 600 mg/m^3, 8 hours/day, 5 days/week, for 2-4 weeks, whereas no effects in cognitive test performance were seen in subjects exposed to CFC-12 at 5 000 mg/m^3 (similar dose regimen).
No neurotoxic effects were reported in human subjects exposed to CFC-113 at concentrations of up to 8 000 mg/m^3 for 180-min periods in the morning and afternoon on 5 days. No effects have been reported for workers occupationally exposed to CFC-113 at 500 mg/m^3 for 11 years or 5 400 mg/m^3 for 2.77 years.

No data have been located regarding repeated inhalation toxicity of the HCFCs evaluated in this document.

No data have been located regarding repeated oral or dermal toxicity of the chlorofluorocarbons evaluated in this document.

6.5.5 Toxicity to reproduction

No data have been located regarding reproductive toxicity of the chlorofluorocarbons evaluated in this document.

6.5.6 Mutagenic and genotoxic effects

No data have been located regarding mutagenic and genotoxic effects of the chlorofluorocarbons evaluated in this document.

6.5.7 Carcinogenic effects

No data have been located regarding carcinogenic effects of the chlorofluorocarbons evaluated in this document.

6.6 Animal toxicity

6.6.1 Single dose toxicity

The symptomatology of acute intoxication in experimental animals is characterised by central nervous system effects and secondary effects on the cardiovascular and respiratory systems. These

effects have been observed only at very high exposure concentrations, i.e. the acute toxicity of the chlorofluorocarbons evaluated in this document is very low.

6.6.2 Irritation

The CFCs evaluated in this document have been reported to cause slight skin irritation following repeated dermal contact.
HCFC-21 was reported to produce mild skin irritation when applied at concentrations higher than 25 %. No data have been located for HCFC-31 and HCFC-133a.

CFC-11 and CFC-12 have been reported to cause slight eye irritation following repeated eye contact.
HCFC-21 was reported to produce mild eye irritation when applied as a 15 % solution; at a higher concentration (50 %), various degrees of injury were observed.
No data have been located for CFC-113, HCFC-31 and HCFC-133a.

No data have been located regarding respiratory tract irritation of the chlorofluorocarbons evaluated in this document.

6.6.3 Sensitisation

No evidence of skin sensitisation with HCFC-21 was found in guinea-pigs.
No data have been located for CFC-11, CFC-12, CFC-113, HCFC-31 and HCFC-133a.

No data have been located regarding respiratory sensitisation of the chlorofluorocarbons evaluated in this document.

Several special studies have shown cardiac sensitisation and arrhythmia (predominantly asphyxia or adrenaline-induced) after high doses (> 40 000 mg/m^3) of chlorofluorocarbons in a number of animal species.

6.6.4 Repeated dose toxicity

CFC-11
In general, no adverse effects were observed in the available inhalation studies in experimental animals exposed to high concentrations of CFC-11. In one study in rats the lowest reported effect level was 68 500 mg/m^3 (4 hours/day for 10 days), at which pathological changes in the brain, liver, lung and spleen were observed.
Following oral administration (gavage) of CFC-11 for 78 weeks, mortality was observed in both rats and mice at the lowest dose level tested (rats: 488 mg/kg bw/day; mice: 1 960 mg/kg bw/day).

CFC-12
In general, no adverse effects were observed in the available inhalation studies in experimental animals exposed to high concentrations of CFC-12. In one study in guinea-pigs the lowest reported effect level was 4 100 mg/m^3 (continuously for 90 days), at which pathological changes in the liver were observed.
Following oral administration (gavage) of CFC-12 for 2 years, decreased body weight gain was observed in rats at 150 mg/kg bw/day, but not at 15 mg/kg bw/day. No effects were observed in dogs following dietary administration of CFC-12 up to 80 mg/kg bw/day for 2 years.

CFC-113
In general, no adverse effects were observed in the available inhalation studies in experimental animals exposed to high concentrations of CFC-113. In a 2-year study in rats (5 days/week), decreased body weight was observed at 76 600 mg/m^3, but not at 15 300 mg/m^3.
No oral toxicity studies have been located for CFC-113.

HCFC-21
Histopathological changes were observed in the liver in the available inhalation studies in experimental animals exposed to HCFC-21. In a 90-day study in rats (6 hours/day, 5 days/week), the changes were observed at the lowest concentration tested (213 mg/m^3).
No oral toxicity studies have been located for CFC-21.

HCFC-31
Histopathological changes in a number of organs were observed in a 2-week inhalation study in rats exposed to HCFC-31 at 28 000 mg/m^3 (5 days/week). Similarly, histopathological changes were observed in the liver in monkeys exposed to HCFC-31 at 14 000 mg/m^3 (for 19-20 days), but not at 11 000 mg/m^3 (for 19-20 days).
Following oral administration (gavage) of HCFC-31 for 1 year (5 days/week), adverse effects were observed in rats at 300 mg/kg bw/day.

HCFC-133a
A number of effects were observed in rats exposed by inhalation to HCFC-133a at 48 000 mg/m^3 (6 hours/day, for 90 days), whereas no effects were observed in dogs exposed by inhalation to HCFC-133a at 24 000 mg/m^3 (6 hours/day, for 90 days).
Following oral administration (gavage) of HCFC-133a for 1 year (5 days/week), adverse effects were observed in rats at 300 mg/kg bw/day.

6.6.5 Toxicity to reproduction

None of the three fully halogenated chlorofluorocarbons evaluated in this document (CFC-11, CFC-12, and CFC-113) showed any evidence of reproductive or developmental toxicity following inhalation at concentrations up to 1 558 000 mg/m^3 (CFC-11 and CFC-12) or up to 195 000 mg/m^3 (CFC-113) or following oral administration at dose levels up to 150 mg/kg bw/day (CFC-12).

In rats exposed by inhalation to HCFC-21 (42 700 mg/m^3 6 hours/day on days 6-15 of gestation) 15/25 mated rats had no implants or viable foetuses; no other effects on pregnancy or foetal development were observed. Maternal toxicity in terms of a substantial weight loss was noted in treated animals.

Cervical ribs were found in 8/208 foetuses exposed *in utero* to HCFC-31 (2 800 mg/m^3 6 hours/day on days 6-15 of gestation); the number of cervical ribs in the control group was not reported.
Minimal to slight hypospermatogenesis was observed in male rats exposed to HCFC-31 at 14 000 mg/m^3 6 hours/day for 20 days, and at 2 800 mg/m^3 6 hours/day for 13 weeks (65 exposures), but not at 2 800 mg/m^3 (6 hours/day for 20 days).
Pregnancy rate was reduced in unexposed females throughout a 16 week period when mated weekly with male rats exposed to HCFC-31 at 2 800 mg/m^3 for 10 weeks.

In a series of dominant lethal and combined dominant lethal fertility studies mice were exposed to HCFC-133a by inhalation to concentrations between 0 and 98 000 mg/m^3 (6 hours/day for 5 consecutive days). Reduced male fertility (evaluated as exposure-related decreases in the proportion of pregnant females) was observed at concentrations of 2 500 mg/m^3 and above; no effect on fertility was observed at 500 mg/m^3. Degeneration of spermatogenic cells were observed at concentrations of 5 000 mg/m^3 and above.
HCFC-133a was reported to be embryotoxic in a developmental inhalation toxicity study in rats at exposure concentrations that did not produce clear evidence of maternal toxicity (2 500 mg/m^3 6 hours/day on gestation days 6 to 15).
Following oral administration of HCFC-133a to male rats (300 mg/kg bw in corn oil by gavage on 5 days/week for 52 weeks) arrest of spermatogenesis and seminiferous tubular atrophy were observed.

6.6.6 Mutagenic and genotoxic effects

No evidence of *in vitro* mutagenic activity was observed for CFC-11, CFC-12, CFC-113, HCFC-21 or HCFC-133a.
HCFC-31 was reported to be mutagenic in two *Salmonella typhimurium* strains at high vapour concentrations (2.5-10 %) and induced concentration- and time-dependent increases in 6-thioguanine-resistant mutants in Chinese hamster ovary cells also at high vapour concentrations.

No evidence of *in vivo* mutagenic activity was reported for CFC-12, CFC-113 or HCFC-31.
HCFC-133a gave positive results in two out of three dominant lethal assays in mice (small increases in the incidences of early deaths) but was negative in a rat bone marrow test.
No *in vivo* data have been located for CFC-11 and HCFC-21.

6.6.7 Carcinogenic effects

The fully halogenated chlorofluorocarbons evaluated in this document did not show evidence of a carcinogenic potential in rats (CFC-11, CFC-12, CFC-113) and mice (CFC-11 and CFC-12) following inhalation. No data have been located for HCFC-21, HCFC-31 and HCFC-133a.

When administered by oral gavage, no evidence of a carcinogenic potential was seen in rats (CFC-11 and CFC-12) or in mice (CFC-11). For HCFC-31 and HCFC 133a tumours were observed following oral gavage in corn oil (300 mg/kg bw/day, 5 days/week) for 1 year. No data have been located for CFC-113 and HCFC-21.

6.7 Evaluation

The chlorofluorocarbons evaluated in this document can be absorbed following inhalation, ingestion and dermal contact. Following inhalation, the chlorofluorocarbons are distributed to practically all tissues with relatively high concentrations found in fat. The chlorofluorocarbons are metabolised to a very small extent in mammals following inhalation and they appear to be eliminated almost exclusively through the respiratory tract.

The chlorofluorocarbons evaluated in this document are of low acute inhalation toxicity in humans and of very low acute toxicity in experimental animals.

The chlorofluorocarbons evaluated in this document have been reported to cause slight skin and eye irritation in experimental animals. The potential for respiratory tract irritation cannot be evaluated as no data have been located for the chlorofluorocarbons evaluated in this document.

The potential for skin and respiratory sensitisation cannot be evaluated based on the very limited data or no data, respectively, available for the chlorofluorocarbons evaluated in this document. Several special studies have shown cardiac sensitisation and arrhythmia (predominantly asphyxia or adrenaline-induced) after high doses (> 40 000 mg/m^3) of chlorofluorocarbons in a number of animal species. Such studies are not considered relevant for the health effect assessments following environmental exposure (air, water and soil) to the chlorofluorocarbons evaluated in this document.

The short-term inhalation toxicity of CFC-11 is low in experimental animals with no adverse effects observed in rats, guinea-pigs, dogs, or monkeys at concentrations up to 57 000 mg/m^3 (continuous exposure for 90 days) which is considered as a NOAEC for CFC-11.
Following oral administration of CFC-11 (gavage, 5 days/week, for 78 weeks), mortality was observed in both rats and mice at the lowest dose level tested (rats: 488 mg/kg bw/day; mice: 1 960 mg/kg bw/day). The LOAEL for CFC-11 is 488 mg/kg bw/day.

The short-term inhalation toxicity of CFC-12 is low in experimental animals with no adverse effects observed in rats, guinea-pigs, rabbits, dogs, or monkeys at concentrations above 4 100 mg/m^3 (for

90 days). However, one study in guinea-pigs showed pathological changes in the liver at 4 100 mg/m^3 (continuously for 90 days), which is therefore considered as a conservative LOAEC for CFC-12.
Following oral administration of CFC-12 (gavage, 2 years), decreased body weight gain was observed in rats at 150 mg/kg bw/day, but not at 15 mg/kg bw/day. No effects were observed in dogs following dietary administration of CFC-12 up to 80 mg/kg bw/day for 2 years, which is therefore considered as a NOAEL for CFC-12.

The short-term inhalation toxicity of CFC-113 is low in experimental animals with no adverse effects observed in mice, rats, guinea-pigs, rabbits, dogs, or monkeys at concentrations ranging from 16 000 mg/m^3 (mice, monkeys, for 2 weeks) to 156 000 mg/m^3 (rat, for 90 days). In a study in rats, decreased body weight was observed at 76 600 mg/m^3 (5 days/week, for 2 years), but not at 15 300 mg/m^3 (5 days/week, for 2 years); 15 300 mg/m^3 is therefore considered as a NOAEC for CFC-113.
No oral toxicity studies have been located for CFC-113.

Histopathological changes were observed in the liver in experimental animals (rats, guinea-pigs and dogs) exposed by inhalation to HCFC-21. In rats (6 hours/day, 5 days/week, for 90 days), the changes were observed at the lowest concentration tested (213 mg/m^3), which is therefore considered as a LOAEC for HCFC-21.
No oral toxicity studies have been located for HCFC-21.

Histopathological changes were observed in rats exposed by inhalation to HCFC-31 (28 000 mg/m^3, 5 days/week, for 14 days) and in monkeys (14 000 mg/m^3, for 19-20 days). No histopathological changes were observed in monkeys exposed at 11 000 mg/m^3 (for 19-20 days), which is therefore considered as a NOAEC for HCFC-31.
Following oral administration of HCFC-31 (gavage, 5 days/week, for 1 year), adverse effects were observed in rats at 300 mg/kg bw/day, which is therefore considered as a LOAEL for HCFC-31.

Adverse effects were observed in rats exposed by inhalation to HCFC-133a (49 000 mg/m^3, 6 hours/day, for 90 days). No effects were observed in dogs exposed by inhalation to HCFC-133a (24 000 mg/m^3, 6 hours/day, for 90 days), which is therefore considered as a NOAEC for HCFC-133a.
Following oral administration of HCFC-133a (gavage, 5 days/week, for 1 year), adverse effects were observed in rats at 300 mg/kg bw/day, which is therefore considered as a LOAEL for HCFC-133a.

None of the three fully halogenated chlorofluorocarbons evaluated in this document (CFC-11, CFC-12, and CFC-113) showed any evidence of reproductive or developmental toxicity in experimental animals following inhalation or oral administration of very high concentrations / doses.
Minimal to slight reproductive and/or developmental toxicity has been reported for HCFC-21 and HCFC-31 at relatively high concentrations.
HCFC-133a was reported to be embryotoxic in a developmental inhalation toxicity study in rats at exposure concentrations that did not produce clear evidence of maternal toxicity (2 500 mg/m^3, 6 hours/day on gestation days 6 to 15). Arrest of spermatogenesis and seminiferous tubular atrophy were observed in male rats following oral administration of HCFC-133a (gavage, 300 mg/kg bw/day, 5 days/week, for 1 year).

In general, the chlorofluorocarbons evaluated in this document did not show evidence of mutagenic or genotoxic effects in the available *in vitro* tests and *in vivo* studies.
HCFC-31 was reported to be mutagenic in the two available *in vitro* tests.
HCFC-133a gave positive results in two out of three dominant lethal assays in mice (small increases in the incidences of early deaths); both a negative and a positive result were reported in two different studies with identical exposure conditions (12 000 mg/m^3, 6 hours/day, 5 days/week).

As the positive results have only been reported at high vapour concentrations it is considered that the mutagenic and genotoxic potential of the chlorofluorocarbons evaluated in this document is very low, if any, following environmental relevant exposure levels (air, water and soil).

No evidence of a carcinogenic potential of the CFC's evaluated in this document was seen in experimental animals following inhalation (CFC-11, CFC-12 and CFC-113) and oral administration (CFC-11 and CFC-12) at high concentrations / dose levels.
For HCFC-31 and HCFC 133a tumours were observed following oral gavage in corn oil (300 mg/kg bw/day, 5 days/week) for 1 year. These studies have been evaluated by IARC and it was concluded that there is limited evidence in experimental animals for the carcinogenicity of HCFC-31 (IARC 1986a, 1999) and HCFC-133a (IARC 1986b, 1999) and both substances were placed in Group 3 (not classifiable as to its carcinogenicity to humans).
Based on the available data the chlorofluorocarbons evaluated in this document are not considered to have a carcinogenic potential at environmental relevant exposure levels (air, water and soil).

6.7.1 Critical effects and NOAELs

CFC-11
In repeated inhalation toxicity studies in experimental animals; no adverse effects were observed at concentrations up to 57 000 mg/m^3 (continuous exposure for 90 days) which is considered as a NOAEC for CFC-11.
In repeated oral toxicity studies in experimental animals, mortality was observed in rats and mice. A NOAEL cannot be set for CFC-11 based on the available data; the LOAEL is 488 mg/kg bw/day (rat, gavage, 5 days/week for 78 weeks), corresponding to 349 mg/kg bw/day for continuous exposure.

CFC-12
One repeated inhalation study in guinea-pigs showed pathological changes in the liver at 4 100 mg/m^3 (continuously for 90 days), which is considered as a conservative LOAEC for CFC-12.
In a repeated oral toxicity study in rats, decreased body weight gain was observed in rats at 150 mg/kg bw/day, but not at 15 mg/kg bw/day. No effects were observed in dogs following dietary administration up to 80 mg/kg bw/day for 2 years, which is considered as a NOAEL for CFC-12.

CFC-113
In a 2-year inhalation study in rats (5 days/week), decreased body weight was observed at 76 600 mg/m^3, but not at 15 300 mg/m^3; 15 300 mg/m^3 is considered as a NOAEC for CFC-113, corresponding to 10 900 mg/m^3 for continuous exposure.
No oral toxicity studies have been located for CFC-113.

HCFC-21
In repeated inhalation toxicity studies in experimental animals, histopathological changes were observed in the liver of rats, guinea-pigs and dogs; the changes were observed at the lowest concentration tested (213 mg/m^3) in a 90-day study (6 hours/day, 5 days/week) with rats, which is considered as a LOAEC for HCFC-21, corresponding to 38 mg/m^3 for continuous exposure.
No oral toxicity studies have been located for HCFC-21.

HCFC-31
In repeated inhalation toxicity studies in experimental animals, histopathological changes were observed in rats and in monkeys. No histopathological changes were observed in monkeys exposed at 11 000 mg/m^3 (for 19-20 days), which is considered as a NOAEC for HCFC-31.
Following oral administration (gavage) for 1 year (5 days/week), adverse effects were observed in rats at 300 mg/kg bw/day, which is considered as a LOAEL for HCFC-31, corresponding to 215 mg/kg bw/day for continuous exposure.

HCFC-133a

In a 90-day inhalation study in rats (6 hours/day), adverse effects were observed in rats at 48 000 mg/m^3. No effects were observed in dogs exposed at 24 000 mg/m^3 (6 hours/day, for 90 days). Embryotoxicity was reported in a developmental inhalation toxicity study in rats at exposure concentrations that did not produce clear evidence of maternal toxicity (2 500 mg/m^3 6 hours/day on gestation days 6 to 15), which is considered as a very conservative LOAEC for HCFC-133a, corresponding to 625 mg/m^3 for continuous exposure.

Following oral administration (gavage) for 1 year (5 days/week), adverse effects were observed in rats at 300 mg/kg bw/day, which is considered as a LOAEL for HCFC-133a, corresponding to 215 mg/kg bw/day for continuous exposure.

7. TDI and quality criteria

7.1 TDI

CFC-11
The TDI is calculated based on a LOAEL of 349 mg/kg bw/day:

$$TDI = \frac{LOAEL}{UF_I * UF_{II} * UF_{III}} = \frac{349 \text{ mg/kg b.w./day}}{10 * 10 * 3} = 1.2 \text{ mg/kg bw/day}$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because of using a LOAEL instead of a NOAEL.

CFC-12
The TDI is calculated based on a NOAEL of 80 mg/kg bw/day:

$$TDI = \frac{NOAEL}{UF_I * UF_{II} * UF_{III}} = \frac{80 \text{ mg/kg b.w./day}}{10 * 10 * 1} = 0.8 \text{ mg/kg bw/day}$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 1 because of using a NOAEL.

HCFC-31
The TDI is calculated based on a LOAEL of 215 mg/kg bw/day:

$$TDI = \frac{LOAEL}{UF_I * UF_{II} * UF_{III}} = \frac{215 \text{ mg/kg b.w./day}}{10 * 10 * 3} = 0.7 \text{ mg/kg bw/day}$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because of using a LOAEL instead of a NOAEL.

HCFC-133a
The TDI is calculated based on a LOAEL of 215 mg/kg bw/day:

$$TDI = \frac{LOAEL}{UF_I * UF_{II} * UF_{III}} = \frac{215 \text{ mg/kg b.w./day}}{10 * 10 * 3} = 0.7 \text{ mg/kg bw/day}$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because of using a LOAEL instead of a NOAEL.

CFC-133 and HCFC-21
A TDI cannot be calculated as no oral toxicity data are available and as route-to-route extrapolation from the available inhalation data is not considered scientifically valid.

7.2 Health-based quality criteria in drinking water

The text in the following paragraph is an MST contribution requested to be inserted at this place in the document:
"*Drinking water quality criteria are used as basis for determining the groundwater quality criteria related to the percolation of soil contamination. Groundwater quality criteria are used to secure groundwater of such a high quality that it can meet the drinking water requirements / quality criteria, cf. "Methods for establishing health-based quality criteria for chemical substances in soil, ambient air and drinking water", DEPA Guidance No. 5, 2006, p. 8.*"

CFC-11
The health-based quality criterion in drinking water QC_{dw} is calculated based on the TDI of 1200 µg/kg bw/day and assuming a daily ingestion of 0.08 litres/kg bw/day of drinking water for a child (1-10 years old):

$$QC_{dw} = \frac{TDI}{ingestion_{dw}} = \frac{1200\ \mu g/kg\ bw/day}{0.08\ litres/kg\ bw/day}$$

$$= 15\,000\ \mu g/l$$

A health-based quality criterion of 15 000 µg/l in drinking water has been calculated for CFC-11.

CFC-12
The health-based quality criterion in drinking water QC_{dw} is calculated based on the TDI of 800 µg/kg bw/day and assuming a daily ingestion of 0.08 litres/kg bw/day of drinking water for a child (1-10 years old):

$$QC_{dw} = \frac{TDI}{ingestion_{dw}} = \frac{800\ \mu g/kg\ bw/day}{0.08\ litres/kg\ bw/day}$$

$$= 10\,000\ \mu g/l$$

A health-based quality criterion of 10 000 µg/l in drinking water has been calculated for CFC-12.

HCFC-31
The health-based quality criterion in drinking water QC_{dw} is calculated based on the TDI of 700 µg/kg bw/day and assuming a daily ingestion of 0.08 litres/kg bw/day of drinking water for a child (1-10 years old):

$$QC_{dw} = \frac{TDI}{ingestion_{dw}} = \frac{700\ \mu g/kg\ bw/day}{0.08\ litres/kg\ bw/day}$$

$$= 8\,800\ \mu g/l$$

A health-based quality criterion of 8 800 µg/l in drinking water has been calculated for HCFC-31.

HCFC-133a

The health-based quality criterion in drinking water QC_{dw} is calculated based on the TDI of 700 µg/kg bw/day and assuming a daily ingestion of 0.08 litres/kg bw/day of drinking water for a child (1-10 years old):

$$QC_{dw} = \frac{TDI}{ingestion_{dw}} = \frac{700\ \mu g/kg\ bw/day}{0.08\ litres/kg\ bw/day}$$

$$= 8\,800\ \mu g/l$$

A health-based quality criterion of 8 800 µg/l in drinking water has been calculated for HCFC-133a.

CFC-133 and HCFC-21

Health-based quality criteria in drinking water cannot be calculated as no oral toxicity data are available and as route-to-route extrapolation from the available inhalation data is not considered scientifically valid.

7.3 Health-based quality criteria in ambient air

CFC-11

The health-based quality criterion in air QC_{air} is calculated based on a NOAEC of 57 000 mg/m^3:

$$QC_{air} = \frac{NOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{57\,000\ mg/m^3}{10 * 10 * 1}$$

$$= 570\ mg/m^3$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 1 because of using a NOAEC.

A health-based air quality criterion of 570 mg/m^3 has been calculated for CFC-11.

CFC-12

The health-based quality criterion in air QC_{air} is calculated based on a LOAEC of 4 100 mg/m^3:

$$QC_{air} = \frac{LOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{4\,100\ mg/m^3}{10 * 10 * 3}$$

$$= 14\ mg/m^3$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because of using a LOAEC instead of a NOAEC.

A health-based air quality criterion of 14 mg/m^3 has been calculated for CFC-12.

CFC-113

The health-based quality criterion in air QC_{air} is calculated based on a NOAEC of 10 900 mg/m^3:

$$QC_{air} = \frac{NOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{10\,900\ mg/m^3}{10 * 10 * 1}$$

$$= 109\ mg/m^3$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 1 because of using a NOAEC.

A health-based air quality criterion of 109 mg/m^3 has been calculated for CFC-113.

HCFC-21

The health-based quality criterion in air QC_{air} is calculated based on a LOAEC of 38 mg/m^3:

$$QC_{air} = \frac{LOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{38\ mg/m^3}{10 * 10 * 3}$$

$$= 0.13\ mg/m^3$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because of using a LOAEC instead of a NOAEC.

A health-based air quality criterion of 0.13 mg/m^3 has been calculated for HCFC-21.

HCFC-31

The health-based quality criterion in air QC_{air} is calculated based on a NOAEC of 11 000 mg/m^3:

$$QC_{air} = \frac{NOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{11\,000\ mg/m^3}{10 * 10 * 3}$$

$$= 37\ mg/m^3$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because no subchronic toxicity data were available.

A health-based air quality criterion of 37 mg/m^3 has been calculated for HCFC-31.

HCFC-133a

The health-based quality criterion in air QC_{air} is calculated based on a LOAEC of 625 mg/m^3:

$$QC_{air} = \frac{LOAEC}{UF_I * UF_{II} * UF_{III}} = \frac{625 \text{ mg/m}^3}{10 * 10 * 3}$$

$$= 2.1 \text{ mg/m}^3$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because of using a LOAEC instead of a NOAEC.

A health-based air quality criterion of 2.1 mg/m^3 has been calculated for HCFC-133a.

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Chlorofluorocarbons: CFC-11, CFC-12, CFC-113, HCFC-21, HCFC-31, HCFC-133a

The Danish EPA has requested documentation for health-based quality criteria in air and groundwater for the following six chlorofluorocarbons: CFC-11, CFC-12, HCFC-21, HCFC-31, CFC-113 (1,1,2-trichloro-1,2,2-trifluoroethane) and HCFC-133a (1-chloro-2,2,2-trifluoroethane). A concern for toxic effects of these chlorofluorocarbons related to soil contamination at old industrial sites, as well as of a carcinogenic potential has been expressed and therefore this issue will be addressed in the documentation.

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