European Union Risk Assessment Report

Chlorodifluoromethane

CAS-No. 75-45-6

EINECS No: 200-871-9

Risk Assessment

FINAL APPROVED VERSION

LEGAL NOTICE

Cataloguing data can be found at the end of this publication

Luxembourg: Office for Official Publications of the European Communities, [ECB: year]
ISBN [ECB: insert number here]

Printed in Italy

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Risk Assessment

November 2007

Italy

Rapporteur for the risk assessment of Chlorodifluoromethane is Italy.

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Date of Last Literature Search :	**2003**
Review of report by MS Technical Experts finalised:	**[insert month and year]**
Final report:	**[year]**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT[4]

CAS Number: 75-45-6
EINECS Number: 200-871-9
IUPAC Name: Chlorodifluoromethane

Environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

Human health

Human health (toxicity)

Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

Consumers

Conclusion (i) There is a need for further information and/or testing.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

Humans exposed via the environment

Conclusion (i) There is a need for further information and/or testing.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

[4] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

Combined exposure

Conclusion (i) There is a need for further information and/or testing.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

Human health (physico-chemical properties)

Conclusion (i) There is a need for further information and/or testing.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

Contents

EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

1 GENERAL SUBSTANCE INFORMATION

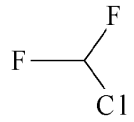
1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 75-45-6

EINECS Number: 200-871-9

IUPAC Name: Chlorodifluoromethane

Molecular formula: $CHClF_2$

Structural formula: 

Molecular weight: 86.47

Synonyms: R-22, HCFC-22

1.2 PURITY/IMPURITIES, ADDITIVES

Degree of purity (range): 99.9 %.

1.3 PHYSICO-CHEMICAL PROPERTIES

The validated data are reported in table 1.1.

The TGD (Part II, page 43) prescribes an environmental temperature of 12°C. We have therefore adopted this temperature in determining the values of those physico-chemical properties most sensitive to temperature, namely vapour pressure, solubility and Henry's Law constant. This is in line with the recommendations of the revised TGD (Part II, pages 24-25). Concerning water solubility, for the purpose of modelling we require the solubility at the saturated vapour pressure (7.135 atm at 12 °C). This value is:
4.22*7.135 = 30.1 g/l
and it will be used for Mackay and EUSES modelling.

Table 1.1 Summary of physico-chemical properties

Property	Value	REFERENCE
Physical state	gaseous	
Melting point	-160 °C	Kühn-Birett 1994
Boiling point	- 40,8 °C	Hoechst AG 1989
Relative density at 20°C	Gas at 1 atm: 0.0036 Liquid at sat. vap. Press.: 1.210	Calculated Defibaugh and Morrison (1992)

Property	Value	REFERENCE
Vapour pressure at 12° C Vapour pressure at 25°C	723 kPa (7.135 atm) 1045 kPa (10.31 atm)	Defibaugh and Morrison (1992) Defibaugh and Morrison (1992)
Water solubility at 25°C and 1 atm at 25° and saturated vapour pressure at 12°C and 1 atm at 12° and saturated vapour pressure	2.93 g/l 2.40 g/l 24.75 g/l 4.22 g/l 30.1 g/l	Hine and Mookerjee (1975) Calculated on the basis of the mean Henry's Law constant Calculated on the basis of the Henry's Law constant Calculated on the basis of Henry's constant Calculated
Partition coefficient n-octanol/water (log value)	log Pow = 1.13	CSCL Japan 1992
Flash point	not applicable	the product is not flammable
Autoflammability	630 °C	Sorbe 1993
Flammability	not flammable	Hoechst AG 1987
Explosive properties	not applicable	the product does not explode
Oxidizing properties	non oxidizer	Solvay S.A. 1995
Viscosity		
Henry's Law constant	3650 Pa.m^3/mol at 25°C 0.0205 atm.m^3/mole at 12°C	Mean value of the following references: Boggs and Buck (1958) : H = 3058 Pa.m^3/mol Chang and Criddle (1995) : H = 4779 Pa.m^3/mol Zheng *et al.* (1997) : H = 3116 Pa.m^3/mol Mean value of the following references: Boggs and Buck (1958) : H = 0.0179 atm.m^3/mol Chang and Criddle (1995) : H = 0.0241 atm.m^3/mol Zheng *et al.* (1997) : H = 0.0194 atm.m^3/mol

1.4 CLASSIFICATION

1.4.1 Current classification

Not in Annex I to directive 67/548/EEC

Rapporteur proposal

Hazard Symbol: N – Dangerous for the environment

Risk phrase: R 59 - Dangerous for the Ozone layer

Safety phrases: S 59 - Refer to the manufacturer/supplier for information on recovery/recycling.

Xn; Repro.Cat.3; R63 - Possible risk of harm to the unborn child.

S: (2-)36/37-46

This classification was agreed at TC C&L September 2007.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

The 10 HCFC-22 EU production sites are located as follows:

Atofina	Pierre-Bénite, France
	Zaramillo, Spain
Du Pont	Dordrecht, The Netherlands
Fluor Chemie	Hoechst, Germany
Ineos Fluor	Runcorn, UK
Phosphoric Fertilizer Industry	Thessaloniki, Greece
Rhodia Organique Fine	Avonmouth, UK
Solvay	Bad Wimpfen, Germany
	Spinetta, Italy
	Tarragona, Spain

Chlorodifluoromethane (HCFC-22, $CHClF_2$) does not have significant natural sources. Although concentrations of other fluorocarbons (CFCs 11 and 12) higher than in ambient air have been detected in volcanic vents, chlorodifluoromethane was not found, even when the vent contained a substantial concentration of its chemical precursor, chloroform (Isidorov, 1990).

Industrial production data have been provided by some thirteen companies from throughout the world and, together with their subsidiaries and associates, these constitute a maximum of 37 potential producers of whom seven are in Europe (AFEAS, 2003). The unit processes of these manufacturers are described in Table 3.1, together with the nature and quantity of their emissions to the environment.

Chlorodifluoromethane is generally manufactured by reacting anhydrous hydrogen fluoride with chloroform, mainly in liquid phase reactions employing antimony halide catalysts. The reagent mixtures are toxic and corrosive and the product has a high vapour pressure (911 kPa at 20oC) and so it is manufactured in enclosed equipment and stored as liquefied gas under pressure in closed cylinders prior to use (Hamilton, 1963). Due to the requirement to withstand high pressures safely, the equipment used for the transport and storage of chlorodifluoromethane is subject to European Community directives and local regulations governing design and testing. Consequently, fugitive emissions from the process tend to occur as continuous releases due to venting or short-term, intermittent releases during the cleaning and refilling of cylinders, rather than being infrequent releases that are large relative to the local dispersing power of the atmosphere. The fugitive emissions during the stages of processing, transport, storage and product formulation account for 2.5% of the global production.

2.1.2 Production capacity

Plant distribution by size is as follows:

More than 20,000 ton/year	3
Between 10,000 and 20,000 ton/year	3
Less than 10,000 ton/year	4
	10

Total European production for years from 1996 was (no data available for 1997)

1996: 162000 tonnes

1998: 177000 tonnes

1999: 169000 tonnes

2000: 149000 tonnes

2001: 153000 tonnes

2.2 USES

2.2.1 Introduction

Chlorodifluoromethane is used in potentially dispersive applications as an end product, either by itself or in blends with other substances; the other significant use is as feedstock for fluoropolymer manufacture. In the early 1990s, 65% of global production was used as an end product and the remainder was feedstock (Midgley & Fisher, 1993). By the year 2001 in the EU the proportion used as an end product was 40%, reflecting the greater importance of fluoropolymer feedstock in Europe (Cefic, 2003).
Chlorodifluoromethane that is used as a raw material feedstock from which other chemicals, such as fluoropolymers, are made is converted almost completely into the new product and relatively small amounts (less than 1% of usage) are emitted into the environment. On the other hand, chlorodifluoromethane that is used as an end product may be wholly released into the environment. The principal European manufacturing facilities that convert chlorodifluoromethane into other materials are described in Table 2.1, together with the nature and quantity of releases from them.

Of the potentially dispersive applications, the predominant one is the vapour compression refrigeration cycle where chlorodifluoromethane is the working fluid in equipment ranging from small domestic hermetically sealed units consuming less than a kilowatt to heavy duty industrial and commercial enclosed units of several hundred kilowatts (Fischer et al., 1991). It has been manufactured and sold for this purpose for some 50 years and may be used either alone or in blends with other fluorocarbons. The term “use as a refrigerant” will cover in this RAR all the applications of the vapour compression refrigeration cycle, including the use in commercial refrigeration, in air conditioning equipments, in chillers and in heat pump water heater.

During the service life of the equipment, the driving fluid containing chlorodifluoromethane may leak out, either slowly through valves, shaft seals and pipework joints, or rapidly when the equipment is dismantled for servicing or decommissioning.
Large scale equipment will have the potential for background emissions from continuous leakage, together with substantial short term emissions during servicing. On the other hand, hermetically sealed units, if they leak, lose all of their contents: the most likely causes being catastrophic failure or deliberate venting when the unit is scrapped. On average, the material originally deployed in refrigeration equipment is totally lost to atmosphere over a period of 10 years (Midgley & Fisher, 1993).
A loss time of only one year is assigned to the other major dispersive category which covers material used as an aerosol propellant, or to blow open-cell and extruded foam. For the minor category that includes closed-cell thermoplastic foams, however, the loss rate is very much slower and material is retained over 50 years.
Production of chlorodifluoromethane in developed countries for the potentially dispersive end uses (all uses other than chemical feedstock) averaged 249000 tonnes per year during the 1990s, with a standard deviation of 11000 tonnes per year. However, production fell significantly after year 2000 and was 217000 tonnes in 2001 (AFEAS, 2003). Estimated emissions over the same period rose to reach an average of 233000 tonnes per year (standard deviation 6000) from 1995 onwards. Of these, 93% were from refrigeration, 8% from short term release categories and 1% from the long term category (AFEAS, 2003). The short term release category includes fugitive emissions from the total production.
The pattern is mirrored in sales of chlorodifluoromethane within the European Union, where the proportion of potentially dispersive sales going into refrigeration was 84% in 2001 (Cefic, 2003).
Despite the fact that it is global emissions that govern regional environmental concentrations, some models purport to calculate regional concentrations from regional production and use. As input to such calculations, in 2001, production was approximately 153 kilo tonnes, with 39 kilo tonnes being sold into dispersive end uses and 56 kilotonnes being used as chemical feedstock. The reminder was exported from the European Union. For the exact tonnages used for EUSES calculations, see 3.1.1.

Foam blowing with HCFC-22 will be banned starting from 1 January 2004 (see 2.4) and the quantities allocated to this use are very low. For these reasons, the emissions deriving from this use will not be considered in the exposure calculations.

Table 2.1 Usage distribution in EU in 2001 (CEFIC, 2003)

Industry category	Use category	Quantity used kton	Percentage of total use
3 Chemical industry: chemicals used in synthesis	33 Intermediate	56	60%
6 Public domain	29 Heat transferring agent	33	34%
6 Public domain	25 Foaming agent	6	6%
Total		95	100%

2.2.2 Scenarios

HCFC-22 is now a controlled substance under the Montreal Protocol in countries that account for 90% of its dispersive use and will become controlled in the remainder. The scenario for future emissions is therefore relatively robust and was calculated for the 2002 Scientific Assessment of Ozone Depletion (Montzka et al., 2003). It is expected that, globally, production for dispersive uses will gradually reduce to about half of current values by 2015 and subsequently fall to zero by 2040. Under Regulation EU 2037/2000, HCFC production in the EU for dispersive use shall be reduced to 35% of 1997 levels by 2008. However, total production of HCFC-22 will not fall to the same extent because of continuing demand for feedstock material, which is exempted under the Montreal Protocol and EU Regulations and has remained almost constant in the past 6 years in the EU (Cefic, 2003).

2.2.3 Disposal

Material that has been released into the atmosphere is rapidly dispersed and cannot be recovered readily. It decomposes by natural oxidation with an atmospheric lifetime of 12.0 years (Montzka et al., 2003).

Due to its high volatility and low solubility in water, the atmosphere is the preferred environmental compartment for chlorodifluoromethane (Ballschmiter, 1992) and emissions are accumulating there so that concentrations in the troposphere have grown from 40 pmol/mol (parts per trillion by volume, pptv, 1 in 1012) in 1980 to 143 pmol/mol in 2000, a growth rate averaging about 5% per year (Montzka et al., 2003). In view of the plateau in global production during recent years, evident from the figures given above, and the dominance of refrigeration (with emissions over a ten year time-scale), it would be unwise to extrapolate growth in atmospheric concentration more than a few years in the future.

Although some leakage and release to the atmosphere is inevitable, it is theoretically possible to contain much of the chlorodifluoromethane used in refrigeration equipment and to recover and recycle it at the end of the service life (in a manner similar to CFC recovery), thus reducing the need to manufacture fresh material (Fischer et al., 1991; UKDTI, 2000).
Recovered material that is too heavily contaminated for economic recycle can be decomposed by thermal oxidation.
However, due to the low flammability of chlorodifluoromethane, only a small portion of waste can be fed to the incinerator and all the equipment must be capable of safely handling the acid exhaust gases that contain chlorides and fluorides.”.

2.3 TRENDS

Total production of HCFC-22 in the EU has fallen in recent years, mainly due to reductions in the quantity required for dispersive use. Thus, in the four years to 2001 (the last year for which there is audited data), sales to dispersive uses within the EU fell by 30% and net exports fell by 21% but use as feedstock stayed relatively constant (Cefic, 2003). The trend is driven by regulations - particularly EC 2037/2000 and the Montreal Protocol - and it is anticipated that the reduction in the quantities emitted from dispersive uses will continue.

2.4 LEGISLATIVE CONTROLS

HCFC-22 is an ozone depleting substance and, as discussed above, the principal regulation affecting HCFC-22 use is EC 2037/2000[5] which seeks to impose more rigorous constraints than the Montreal Protocol. Under the EU Regulation, use of HCFCs is already prohibited in aerosol propellants, most solvent applications, most new refrigeration and air-conditioning equipment and most foams. From 1 January 2004, this ban was extended to all new refrigeration equipment and foam blowing. On 31 December 2008, the remaining solvent applications (precision cleaning in aerospace and aeronautics) will be banned and virgin HCFC-22 will no longer be permitted for maintenance of refrigeration and air-conditioning equipment from 1 January 2010, with a complete ban from 1 January 2015.

Under the current provisions of EC 2037/2000, production of HCFCs for other than feedstock use will be reduced to 35% of the base level (in 1997) by 2008, to 20% by 2014, 15% by 2020 and completely phased out in 2025.

In addition to the controls on production and use, EC 2037/2000 also imposes a duty of containment when HCFC-22 is used as a feedstock and during the operating life of equipment, especially at disposal, when recovery of the HCFC for destruction or recycle is mandatory. Recent data show that containment is improving and that the rate of emissions, relative to the quantities produced and in service, is falling (McCulloch et al., 2006).

Chlorodifluoromethane is permitted for use as plastics additive in food contact materials legislation. Commission Directive 2002/72/EC refers and permits use with a specific migration limit of 6 mg/kg food and a content in the substance of no more than 1 mg/kg.

[5] REGULATION (EC) No 2037/2000 OF THE UEROPEAN PARLIAMENT AND OF THE COUNCIL of 29 June 2000 on substances that deplete the ozone layer; OJ L244/1; 29. 9. 2000

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

An evaluation of environmental exposure coming from significant uses of chloro difluoromethane has been performed in compliance with the Technical Guidance Document for Risk Assessment (TGD), European Chemicals Bureau, 2003.
For that purpose, the electronic prediction model EUSES 2.0 as proposed in the TGD, , was used. Production and use data of fiscal year 2001 have been used.
For emissions, monitoring data are used when available. EUSES default values are used when no data are available.
Three major causes of HCFC-22 emissions exist:
- its production process including (possible) formulation and storage,
- its use as an intermediate in chemical synthesis,
- its use as a cooling agent (replacement of lost refrigerant in air conditioning systems).

HCFC-22 uses as a foam blowing agent and as a solvent have not been considered, since in 2001 the amount used for those latter purposes were minor to minimal and will be discontinued from 1 January 2004 (CEFIC, 2003).
The following approach has been followed:

- Local PECs have been calculated using EUSES 2 for HCFC-22 production and use as a chemical intermediate for the European plants. The model has been run for each site assuming that the site is the only one producing HCFC-22 in Europe and only local results are considered.
- Regional PECs have been calculated in a worst case scenario, using the data of the region with the highest emissions of HCFC-22 (due to production and use) and considering also the background contribution of refrigeration emissions.
- Continental PECs for production and use have been calculated using EUSES 2. As input data, the total EU production and the total EU emissions are used.

The following Annexes are provided:

- Appendix 1: EUSES output files and detailed explanation of the approach for the local PECs estimation (containing confidential data)
- Appendix 2: EUSES output files and detailed explanation of the approach for the regional PECs estimation (containing confidential data)
- Appendix 3: EUSES output file and detailed explanation of the approach for the continental PECs estimation

Background information on production and use of HCFC-22 for year 2001 (CEFIC 2005 data collection)

EU production:	152,984 tons (153000 tons was used for EUSES modelling)
EU import:	0 tons
EU export:	47,316 tons
EU sales for feedstock:	60,440 tons
EU sales for refrigeration (replacement):	35,000 tons

The EU sales for feedstock include the on-site feedstock use. The difference between production and total sales + export is due to stocks.
Ten sites in EU were identified as producers of HCFC-22.
Four sites in EU were identified as users of HCFC-22 as intermediate for chemical synthesis.

3.1.2 Environmental releases

3.1.2.1 Release from production

Chlorodifluoromethane (HCFC-22) is produced by a wet process in closed system on a continuous basis. Emissions to air and waste water may occur during vessel cleaning or coupling and decoupling of pipelines for maintenance purposes or when filling of tanks.
Table 3.1 presents the input data for EUSES model for the 10 European production plants. When no measured or estimated data were available, EUSES default data (D) have been used. When the non-default values are zero (sites 1, 4, 7, 8, 9 and 10), there are no direct emissions to surface water from the site. The values "Emissions to waste water" are used to estimate the local concentration because they are more reliable than the emission to surface water. Concentrations of HCFC-22 in surface water are very low and difficult to measure.

Table 3.1 Collection of emission data during production of HCFC-22 (2001)

Site	Emissions to air (tons/year)	Emissions to waste water (tons/year)	Direct emission to surface water (tons/year)	Notes
1	22	8.8	0	
2	0.354	0.365	0 (D)	
3	74.7	69 (D)	4	
4	0.05	0	0	
5	75 (D)	9 (D)	0 (D)	
6	0	22.16 (D)	0 (D)	
7	7.5	2.9	0	The emission to air data include also the use of part of HCFC-22 as chemical intermediate, since the off-gases coming from the two processes are conveyed to a common emission point.
8	4.5	9	0	
9	91	0.15	0	
10	16	0.44	0	The emission to water data are based on a total AOX measure: worst case assumption that all AOX is HCFC-22

D = default.

3.1.2.2 Release from formulation

The formulation of blends of refrigerant gases takes place either on the producers or in the user site. During formulation, emissions are possible to air. These emissions are taken into account in the scenario on the use of HCFC-22 as a refrigerant (the 100% emission of the fluid is considered in this scenario: see 3.1.8.1).

3.1.2.3 Release from industrial/professional use

3.1.2.3.1 Storage and transport

During storage (on or off site) emissions are possible to air and water and to soil during filling of containers and drums. Release to air (mostly during transport) is possible but is unlikely to occur due to shipment in closed (pressurised) vessels. No data are available on the emissions during storage and transport, but possible releases are considered to be minor and negligible compared to other activities involving chlorodifluoromethane.

3.1.2.3.2 Use as a refrigerant

The major use of chlorodifluoromethane is as a cooling fluid in commercial and industrial refrigeration installations. The emission during HCFC-22 use as a refrigerant can take place through small leaks in the pipe connections and valves, which is considered as a slow release that escapes practically totally to the atmospheric compartment. Possible soil contamination will occur from aerial deposition only.

As mentioned in the introduction of this document, environmental releases from refrigeration equipment are potentially important in large scale refrigeration units and more or less negligible in household refrigerators. Over the whole time that HCFC-22 has been produced up to the year 2001, global cumulative sales for refrigeration were 5151500 tonnes and the emission from that source up to that year was 4516100 tonnes (AFEAS, 2003; McCulloch et al., 2003). Material that has not been emitted remains in the "bank" in equipment and annual global emissions now represent 36% of the current bank (McCulloch et al., 2003).

3.1.2.3.3 Use as an intermediate for further synthesis

Chlorodifluoromethane can be used as an intermediate in synthesis of other chemicals. Emissions of the compounds in this specific activity are estimated to be less than 1% (see section 2.2).
In view of the assumption that synthesis is performed in modern sealed installations, practically all of the compound will be transformed to other products with very few releases. Table 3.2 presents the emission of chlorodifluoromethane during its use as an intermediate for the sites for which data is available (2001). All the production sites which use HCFC-22 as an intermediate provided data. For one site, the emissions for the use as an intermediate are

included in the production scenario. Data is also available for one site which is not a producer of HCFC-22.

Table 3.2 Collection of emission data during use of HCFC-22 as an intermediate (2001)

Site	Emissions to air (tons/year)	Emissions to waste water (tons/year)	Emissions to surface water (tons/year)	Notes
1	0.05	0	0	
2	2.725	1.78 (D)	0 (D)	
3	0.162	0	0	

D: default

3.1.2.3.4 Use as a closed cell foam blowing agent

The annual release originating from foam blowing activities is about 2% of the quantity used (AFEAS, 2003). Since this use historically amounted to only 3% of the production within the EU, the contribution of the chlorodifluoromethane trapped in foams is deemed negligible. Furthermore, as from 1 January 2004 use of HCFCs to blow foam is effectively banned within Europe under EU 2037/2000, and so this contribution will remain insignificant. Use of HCFC-22 for foam blowing will not be considered in the calculation of emissions for the evaluation of exposure.

3.1.2.4 Release from disposal

The most important releases of chlorodifluoromethane at disposal occur at scrapping of refrigeration systems when the cooling fluid is vented. No data are available on emissions of the compounds in this specific activity and, in the calculations of emissions described here, the worst case - total loss of the fluid - is assumed. Because regulations, such as those under IPPC, the WEEE Directive and EU2037/2000, place an obligation on users to contain HCFCs during use and recover them at the end of life of equipment (for re-use or destruction), total loss of fluid now represents the very worst case.

3.1.3 Environmental fate

3.1.3.1 Degradation in the environment

3.1.3.1.1 Atmospheric degradation

Atmospheric lifetime

The atmospheric degradation of chlorodifluoromethane is initiated primarily by reaction with the naturally occurring hydroxyl radicals (OH) in the troposphere (H-atom abstraction) (Atkinson et al., 1985). Other tropospheric oxidants (O_3, NO_3 and chlorine atoms) do not

make any significant contribution to degradation. Physical removal of chlorodifluoromethane, by wet or dry deposition, is negligible.
The small fraction of chlorodifluoromethane not destroyed in the troposphere slowly enters and mixes with a higher layer of the atmosphere, the stratosphere, where attack by OH radicals is also the dominant process contributing to the degradation of that fraction of chlorodifluoromethane. In this process, free radicals are released which catalyse the destruction of the ozone layer.
Reaction with excited oxygen atom (O^1D) and photolysis by ultraviolet radiation are minor processes (WMO, 1995; Seigneur et al., 1977). Photodecomposition by solar UV-radiation is a major loss process for the fully halogenated chlorofluorocarbons. It does not play a significant role in the distribution of chlorodifluoromethane and leads to the release of a relatively small amount of chlorine. Chlorodifluoromethane contributes approximately 1 % of the chlorine in the stratosphere which can react to deplete ozone. (Montzka et al., 2003).
The atmospheric lifetimes of reactive material are under continual review and change as understanding of atmospheric processes improves. The current best estimate of the overall atmospheric lifetime of chlorodifluoromethane is 12.0 years (Montzka et al., 2003) corresponding to a half-life of 8.3 years[6].
It should be noted that the lifetimes of fully halogenated chlorofluorocarbons are much longer (45 years for CFC-11 and 100 years for CFC-12) (Montzka et al., 2003).

Ozone depleting potential (ODP)

Since the above considerations indicate that most of the chlorodifluoromethane emitted is destroyed before it can reach the stratosphere, and because the material in this layer forms ozone destroying radicals less effectively than the CFCs, chlorodifluoromethane has only a small ozone depletion potential (ODP).
The ODP is defined as the calculated ozone depletion due to the emission of a unit mass of HCFC divided by the ozone depletion calculated to be due to the emission of the same mass of CFC 11; calculations are based on steady-state conditions (UNEP/WMO, 1989).
Based on the recommended atmospheric lifetime, the ODP of chlorodifluoromethane is calculated to be 0.04-0.05 on a unit-mass basis, relative to a reference value of 1.0 for CFC 11 (Montzka et al., 2003).
The official ODP value adopted for the purposes of the Montreal Protocol is 0.055 for chlorodifluoromethane (UNEP, 1993).
This means that continuous emissions of chlorodifluoromethane would have to be about 18 times as large as continuous emissions of trichlorofluoromethane (CFC 11) to have the same effect on ozone.
The primary effect of ozone depletion is an increase of surface UV radiation, which can lead to adverse effect on environment and human health.
To put the contribution of HCFC-22 to potential adverse effects into context, we might consider that the active agent in ozone depletion is halogen formed from decomposition of the ODS in the stratosphere. Based on the data presented in the 2002 Scientific Assessment of Ozone Depletion carried out for the WMO and UNEP (WMO, 2002), the contribution of HCFC-22 to such halogen will be about 4% of the total released from all ODS in 2010.
The current increase over the "baseline" of erythemal UV at 45 degrees N entering the lower atmosphere is calculated to be 4%, again from the 2002 Assessment. UV at ground level is mainly influenced by the sun angle and moving south by just over 2 degrees of latitude would

[6] Halflife is related to atmospheric lifetime mathematically: $T_{1/2}$ = ln2 x atmospheric lifetime. The atmospheric lifetime of 12 years is reviewed at each WMO of Stratospheric Ozone Depletion and has remained unchanged since 1998.

increase incident UV to the same extent as the whole 4% change. The one hundredth part of this that could be assigned to HCFC-22.
The indirect adverse effect on environment and human health in relation to this contribution to ozone layer depletion will not be further dealt with in this Risk Assessment

Global warming potential (GWP) (greenhouse effect)

Global Warming Potential is the conversion factor relating an emission of a gas such as chlorodifluoromethane to its equivalent mass of carbon dioxide (CO_2). Because CO_2 is a relatively permanent gas its effect on climate increases with time so that, for time horizons of 20, 100 and 500 years, the absolute global warming potentials (GWP) of CO_2 are 0.24, 0.77 and 2.46 W m^{-2} $ppmv^{-1}$, respectively. The relative Global Warming Potentials of chlorodifluoromethane, expressed on a unit-mass basis and relative to a reference value set at 1.0 for CO_2 at each of these time horizons are 4800, 1700 and 540, respectively (Ramaswamy et al., 2001).

Atmospheric degradation mechanism and products

The mechanism of decomposition of chlorodifluoromethane following the initial reaction with hydroxyl radicals has been studied and elucidated.
On the basis of laboratory studies, it may be concluded that chlorodifluoromethane will break down in the atmosphere to give carbonyl fluoride (COF_2) and HCl (Atkinson, 1985; Edney et al., 1992; WMO, 1995).
COF_2 will be taken up by cloud water (atmospheric water aerosols) and to a lesser extent by the oceans, and hydrolysed to CO_2 and HF, the latter being removed by precipitation. The estimated lifetime with respect to this process is a few days to a few weeks (WMO, 1995).
Although the peroxynitrate $CClF_2O_2NO_2$ and the hydroxide $CClF_2OOH$ will be formed to some extent during the atmospheric degradation of chlorodifluoromethane (WMO, 1995; Kanakidou et *al.*, 1995), they are short-lived intermediates which will not accumulate to significant concentrations. Indeed, the calculated atmospheric level of the peroxynitrate is negligible compared to that of COF_2, and the latter is itself present at a concentration which is orders of magnitude lower than that of the parent chlorodifluoromethane (Kanakidou et al., 1995).

3.1.3.1.2 Aquatic degradation

The only information available on biodegradability of chlorodifluoromethane is a closed bottle assay where chlorodifluoromethane is not ready biodegradable (0 % BOD after 28 days) (Chemical Inspection and Testing Institute Japan, 1992).
The rate of hydrolysis of chlorodifluoromethane is very low, below 0.01 g chlorodifluoromethane/l.yr at 30 °C (Downing, 1988; Du Pont, 1980). This source is however not very reliable since there is some confusion in the units employed.
Chlorodifluoromethane does not absorb UV radiation above 290 nm and therefore will not photolyse in water, air or on soil surfaces (Hubrich and Stuhl., 1980).

3.1.3.1.3 Degradation in soil

Chlorodifluoromethane is not present in the soil compartment (see 3.1.3.2).

3.1.3.1.4 Summary of environmental degradation

Chlorodifluoromethane will break down in the atmosphere to give carbonyl fluoride (COF_2) and HCl the latter being removed by precipitation. The estimated lifetime with respect to this process is a few days to a few weeks.

From the available information chlorodifluoromethane appears to be not ready biodegradable and will not photolyse in water, air or on soil surfaces.

3.1.3.2 Distribution

The distribution of chlorodifluoromethane to the different environmental compartment has been calculated with the Mackay Four Compartment Fugacity Level III model. Details on the input data are provided in Appendix 4.
Two Mackay Level III simulations were performed:

a) With no HCFC-22 present in the inflowing air advected through the evaluative environment. This leads to 99.8 % of the HCFC-22 present in the air compartment, at a concentration of 165 ng/m^3.

b) With a global background concentration of 502 ng HCFC-22/m^3 in the inflowing air. This leads to 99.9 % of the HCFC-22 present in the air compartment, at a concentration of 666 ng/m^3.

3.1.3.2.1 Adsorption

Chlorodifluoromethane is an inert gas and, based on its water solubility, about 3.3 g/l at 25 °C and 1 atmosphere pressure (Chemical Inspection and Testing Institute Japan 1992), a K_{OC} of 57.5 l/kg was estimated using a recommended regression equation (Lyman et al., 1982). Therefore, chlorodifluoromethane would not adsorb appreciably to sediment and suspended solids in the water column.
Results obtained from Roy and Griffin (1985) are in the same order with a calculated K_{OC} of 62 based on a water solubility of 3.3 g/l.
Since chlorodifluoromethane is an inert gas with a low adsorption to soil, most of the chemical released on land will be lost by volatilisation. Its low K_{OC} and density higher than water also indicate that it is highly mobile in soil and therefore will have a high potential for leaching into ground water (Roy and Griffin, 1985). However, the high volatility of chlorodifluoromethane should effectively reduce this potential.
The value of Koc used in EUSES simulations (Koc = 40.5) was calculated using the QSAR method for non-hydrophobic substances proposed in the TGD, part III, page 24. The value is in good agreement with the bibliographical references and it is calculated with an equation independent from water solubility.

3.1.3.2.2 Precipitation

The removal of chlorodifluoromethane from the atmosphere by wet deposition is a highly inefficient process and the volatility and Henry's Constant (see paragraph 1.3) of the material are such that any scavenged from the atmosphere in this way will revolatilise rapidly.

3.1.3.2.3 Volatilisation

In the atmosphere

As a result of its atmospheric lifetime, the chlorodifluoromethane released into the atmosphere will disperse globally and accumulate; its background concentration is relatively uniform. A minor fraction of the chlorodifluoromethane present in the lower atmosphere will be mixed into the stratosphere.
The small fraction of chlorodifluoromethane not destroyed in the troposphere slowly enters and mixes with the upper layer of the atmosphere, the stratosphere (IPCS, 1991).
Once emitted, chlorodifluoromethane is rapidly mixed within the lower region of the atmosphere, the troposphere, by the normal tropospheric mixing processes. Mixing is complete in the northern or southern hemisphere within months of the emission, and the entire troposphere within about two years of the emission."(ECETOC, 1989).
The tropospheric concentration of chlorodifluoromethane was still increasing in 2001 but the rate of increase is diminishing (Montzka et al., 2003).

In water

Chlorodifluoromethane will be removed from water predominantly by volatilisation because it has a very high Henry's Law Constant, is extremely stable in water and does not adsorb appreciably to sediment.
Chlorodifluoromethane is a gas with a moderate water solubility, 2.93 g/l at 25°C, 1 atm (Hine and Mookerjee, 1975) and a high volatility, vapour pressure of 723 kPa at 12°C (Defibaugh and Morrison, 1992); therefore it would be expected to volatilise rapidly from water. The experimental Henry's Law Constant for chlorodifluoromethane is 0.0205 $atm.m^3$/mole at 12°C (see table 1.1). Hence its volatilisation from water will be very rapid; the volatilisation rate will be limited by chlorodifluoromethane's diffusion through water (Lyman et al., 1982).
The half-life of chlorodifluoromethane in a model river 1 m deep, flowing at 1 m/sec, with a wind of 3 m/sec is estimated to be 2.7 hours (Lyman et al., 1982).

3.1.3.2.4 Distribution in wastewater treatment plants

HCFC-22 production plants do not discharge into municipal treatment plants. Furthermore, according to distribution calculations (3.1.3.2) the concentration of HCFC-22 in water or in sludge can be considered negligible.

3.1.3.3 Accumulation and metabolism

The bioconcentration factor (BCF) of chlorodifluoromethane, for which no experimental value is available, can be estimated from the correlation equation Log10BCF(fish) = 0.85 * $Log10P_{ow}$ - 0.70, taken from Veith et al. (1979) and recommended in the TGD. For $Log10P_{ow}$ = 1.13 (Table 1.1), this equation leads to Log10BCF = 0.26, or BCF = 1.8. This very low value indicates that chlorodifluoromethane should not bioconcentrate significantly in aquatic organisms.

3.1.4 Aquatic compartment (incl. sediment)

3.1.4.1 Calculation of predicted environmental concentrations (PEC_{local})

Local PECs are calculated via EUSES 2 as described in paragraph 3.1.1 for the following scenarios:

- production
- use as a chemical intermediate

Input data and detailed results are presented in Appendix 1.

3.1.4.1.1 Calculation of PEC_{local} for production

The $PECs_{local}$ calculated for the 10 production sites are reported in table 3.3

Table 3.3 Local PECs for water compartment for the 10 production sites

Site	PEC_{water} during emission episode (mg/l)	PEC_{water} average (mg/l)	$PEC_{sediment}$ (mg/kg)	Regional PEC in surface water (mg/l)
1	9.42E-2	7.74E-2	0.157	1.05E-5
2	3.17E-3	3.17E-3	5.28E-3	4.72E-6
3	0.145	0.105	0.241	1.68E-4
4	9.8E-12	9.8E-12	1.6E-11	9.28E-6
5	0.0966	0.0794	0.161	9.3E-6
6	0.158	0.151	0.263	1.68E-4
7	27.4E-3	25.9E-3	45.5E-3	3.29E-6
8	0.125	0.103	0.208	9.28E-6
9	1.28E-3	1.21E-3	2.12E-3	6.60E-6
10	4.6E-3	4.3E-3	7.6E-3	4.72E-6

3.1.4.1.2 Calculation of PEC_{local} for industrial/professional use

During the use as a refrigerant
Since the use as a refrigerant is wide and dispersive, no PEC_{local} has been calculated.

During the use as an intermediate in further synthesis
The $PECs_{local}$ calculated for the sites in which HCFC-22 is used as an intermediate are reported in table 3.4.

Table 3.4 Local PECs for water compartment for the sites in which HCFC-22 is used as an intermediate

Site	PEC_{water} during emission episode (mg/l)	PEC_{water} average (mg/l)	$PEC_{sediment}$ (mg/kg)	Regional PEC in surface water (mg/l)
1	2.23E-6	2.23E-6	3.71E-6	6.60E-6
2	0.0164	0.0157	0.0272	1.68E-4

3	0.15	0.124	0.25	1.68E-4

3.1.4.1.3 Calculation of PEC_{local} for disposal

No HCFC-22 is expected to be present in liquid waste (see paragraph 3.1.3.2 on distribution).

3.1.4.2 Measured levels

No data are available on levels of chlorodifluoromethane in surface water; significant levels in water are not suspected as chlorodifluoromethane has a very high Henry's Law Constant and will rapidly volatilise from water (see 3.1.3.2.3).
For other usages of chlorodifluoromethane, no measured concentrations in sewage influent and effluents are available.

No data are available on levels of chlorodifluoromethane in sediments; significant levels in sediments are not suspected as the adsorption potential of chlorodifluoromethane and its partition coefficient between octanol and water are both very low.

3.1.4.3 Comparison between predicted and measured levels

No data on measured concentrations of chlorodifluoromethane in surface water and sediments are available. Hence no comparison with the calculated PECs is possible.
The calculated PECs will serve as default values for comparison with the PNEC.

3.1.5 Terrestrial compartment

3.1.5.1 Calculation of PEC_{local}

3.1.5.1.1 Calculation of PEC_{local} for production

The calculated PECs for agricultural land, grassland, and porewater for production, storage and transport of HCFC-22 are presented in table 3.5.

Table 3.5 Local PECs for terrestrial compartment for the 10 production sites

Site	PEC agricultural soil av. 30 d (mg/kg)	PEC agricultural soil av. 180 d (mg/kg)	PEC grassland	PEC groundwater (mg/l)
1	4.53E-3	7.96E-4	1.98E-4	8.37E-4
2	1.52E-4	2.19E-3	5.13E-4	2.3E-3
3	0.0401	6.87E-3	1.55E-3	7.22E-3

4	8.04E-8	8.04E-8	8.04E-8	8.41E-8
5	4.73E-3	9.01E-4	2.88E-4	9.47E-4
6	7.54E-3	1.28E-3	2.76E-4	1.34E-3
7	1.28E-3	2.3E-04	5.8E-5	2.37E-4
8	5.99E-3	1.02E-3	2.26E-4	1.07E-3
9	2. 1E-4	1.6E-04	1.51E-4	1.68E-4
10	2.45E-4	6.3E-5	3.45E-5	6.7E-5

3.1.5.1.2 Calculation of PEC_{local} for industrial/professional use

During use as a refrigerant
Since the use as a refrigerant is wide and dispersive, no PEC_{local} has been calculated.

During use as intermediate for further synthesis
The calculated PECs for agricultural land, grassland, and porewater for the use of HCFC-22 as a chemical intermediate are presented in table 3.6.

Table 3.6 Local PECs for terrestrial compartment for the sites in which HCFC-22 is used as an intermediate

Site	PEC agricoltural soil 30 d (mg/kg)	PEC agricoltural soil 180 d (mg/kg)	PEC grassland	PEC groundwater (mg/l)
1	8.2E-8	8.2E-8	8.2E-8	8.63E-8
2	7.86E-4	1.37E-4	3.31E-5	1.44E-4
3	7.17E-3	1.06E-3	2.82E-4	1.12E-3

3.1.5.1.3 Calculation of PEC_{local} for disposal

No HCFC-22 is expected to be present in solid waste (see paragraph 3.1.3.2 on distribution).

3.1.5.2 Measured levels

No data are available on levels of chlorodifluoromethane in soil; significant levels in soil are not suspected as chlorodifluoromethane has a very high Henry's Law Constant and will rapidly volatilise from the upper soil layers; moreover, its adsorption potential is very low and indicates that chlorodifluoromethane is not persistent in soil.

3.1.5.3 Comparison between predicted and measured levels

No data on measured concentrations of chlorodifluoromethane in soil are available. Hence no comparison with the calculated PEC's is possible.
The calculated PECs will serve as default values for comparison with the PNEC.

3.1.6 Atmosphere

3.1.6.1 Calculation of PEC_{local}

3.1.6.1.1 Calculation of PEC_{local} for production

The calculated PECs for the atmospheric compartment for production, storage and transport of HCFC-22 are presented in table 3.7.

Table 3.7 Local PECs for the atmospheric compartment for the 10 production sites

Site	PEC atmosphere (mg/m^3)
1	0.0167
2	0.0228
3	0.0561
4	3.95E-5
5	0.0571
6	0.0122
7	5.7E-3
8	8.29E-3
9	0.0702
10	0.0125

3.1.6.1.2 Calculation of PEC_{local} for industrial/professional use

During the use as a refrigerant
Since the use as a refrigerant is wide and dispersive, non PEC_{local} has been calculated.

During the use as an intermediate in further synthesis
The calculated PECs for the atmospheric compartment for the use of HCFC-22 as a chemical intermediate are presented in table 3.8.

Table 3.8 Local PECs for the atmospheric compartment for the sites in which HCFC-22 is used as an intermediate

Site	PEC atmosphere (mg/m^3)
1	3.85E-5
2	2.1E-3
3	0.0305

3.1.6.1.3 Calculation of PEC_{local} for disposal

Since no HCFC-22 is expected to be present in liquid or solid waste (see paragraph 3.1.3.2 on distribution), no atmospheric releases of HCFC-22 will take place from landfills or incineration plants.

3.1.6.2 Measured levels

No measured levels of HCFC-22 in the atmosphere close to the emission sources are available.

3.1.7 Secondary poisoning

The low octanol-water partition coefficient indicated that chlorodifluoromethane is not likely to bioaccumulate. Therefore non-compartment specific effects relevant to the food chain have not to be considered.

3.1.8 Calculation of $PEC_{regional}$ and $PEC_{continental}$

For the use of HCFC-22 as a refrigerant, **$PECs_{regional}$** are calculated using EUSES model for a worst case scenario (region with the highest emissions due to production/use of HCFC-22). The refrigeration emissions contribute as a background level to regional concentration.

The main input data used are the following ones:

- Total amount of HCFC-22 used as refrigerant in 2001: 35,000 tons (CEFIC, 2005)
- Emission to air: 100% of the total amount (all the HCFC-22 sold as a refrigerant is used for replacement of emitted or leaked HCFC-22)
- Emissions to water: 0 (in this use, all emitted refrigerant goes to air)
- Emission data from the worst case region and emission data for the whole EU.

More details on the input and the EUSES reports are presented in Appendix 2.

$PEC_{continental}$ is calculated with EUSES 2 using as main input data:

- The total European production for HCFC-22
- The sum of emissions from local sites (for production and use as a chemical intermediate) and from the use as a refrigerant.

More details on the input data and the EUSES report are presented in Appendix 3.

3.1.8.1 Aquatic compartment

PEC regional

$PEC_{regional}$ in surface water (total):	8.88E -6 mg/l
$PEC_{regional}$ in sediment (total):	1.41E-5 mg/kg ww

PEC continental

PEC in surface water (total): 5.16E-6 mg/liter
PEC in sediment (total): 8.18E-6 mg/kg ww

3.1.8.2 Terrestrial compartment

PEC regional

$PEC_{regional}$ in agricultural soil (total): 6.39 E-6 mg/kg ww

PEC continental

PEC in agricultural soil (total): 5.41E-6 mg/kg ww

3.1.8.3 Atmospheric compartment

PEC regional
$PEC_{regional}$ in air (total): 2.12E-3 mg/m^3

PEC continental
PEC in air : 1.72E-3 mg/m3

Measured levels

Table 3.9 Measured background atmospheric concentrations of HCFC-22

Location	Year of measurement	Mean concentration ng/m³ (pmol/mol)	Reference
Global troposphere, 7 sites (between 82°N and 90°S)	2000	507(143)	CMDL (2001)
Global troposphere, 5 sites	2000	502(142)	AGAGE (2001)
Global troposphere, 7 sites (between 82°N and 90°S)	mid 1995	414 (117)	Montzka et al. (1996)
Global troposphere, 5 sites	mid 1995	407 (115)	Prinn et al. (1995)
Global troposphere, 7 sites (between 82°N and 90°S)	1992	361 (101.8)	Montzka et al. (1993)
Global atmosphere	1987	372 (105)	WMO (1991)
Global : - Northern hemisphere – Southern hemisphere	mid 1979	159 (45) * 177 (50) * 149 (42) *	Rasmussen et al. (1980)
Kitt Peak (32°N)	mid 1992	389-414 (110-117)	Zander et al. (1994)
Jungfraujoch (46.5°N)	mid 1992	395-449 (111.5-126.8)	Zander et al. (1994)
Arctic (68 to 80°N)	1988-1989	304 (85.9)	Pollock et al. (1992)
Kitt Peak (32°N)	1988 1980	241 (68) 35.4 (10)	Rinsland et al. (1989)
Point Barrow, Alaska (72°N)	1986	326 (92) *	NASA (1988)

Location	Year of measurement	Mean concentration ng/m³ (pmol/mol)	Reference
Point Barrow, Alaska (72°N) -winter –summer	1980-1981	 217 (61.2) * 198 (56) *	Khalil et al. (1983)
Arctic lower atmosphere (70°N) 0 to 4 km	May 1982	259 (73.2) *	Rasmussen et al. (1983)
North west Pacific (45°N) (100 air samples)	Apr 1978 - Jan 1981 Jan 1981	11.7 % per year increase * 230 (65) *	Khalil et al. (1981)
North west Pacific	Jan 1980	223 (63) *	Rasmussen et al. (1981)
Washington (State), USA	1980	110-190 (31-54)	Leifer et al. (1981)
Cape Grim (41°S)	mid 1992	333 (94.2)	Fraser et al. (1995b)
Cape Grim (41°S)	1987	322 (91)	WMO (1991)
South Pole	Jan 1980	159 (45) *	Rasmussen et al. (1981)

Natural occurrence

Chlorodifluoromethane is not known to occur as a natural product.
Stoibe et al. (1971) reported the presence of chlorodifluoromethane in volcanic emissions, but Rasmussen et al. (1980) did not observe any excess of this compound, compared with normal atmospheric levels, in their studies of volcanic emissions. In their analyses of air samples collected over the State of Washington, USA, Leifer et al. (1981) found that the concentrations of chlorodifluoromethane (100-195 ng/m^3) after the eruption of the Mount St. Helens volcano were not higher than normal.
Furthermore, Isidorov and co-workers (1990) could not detect chlorodifluoromethane in volcanic vents even when the precursor, chloroform, was present at substantial concentrations.

Environmental levels

As a result of its atmospheric lifetime, chlorodifluoromethane released to the atmosphere will disperse over the globe; its background concentration is relatively uniform geographically and is increasing in time due to accumulation in the troposphere.
Available concentration data are presented in table 3.9 and discussed below.
The global atmospheric mean concentration of chlorodifluoromethane was estimated from measurements during 2000 to be 141.9 pmol/mol, with a growth rate of 5.1 pmol/mol/year or 3.7%/year (CMDL, 2001).The results were based on air samples collected in flasks from seven sites located between 82° N and 90° S of latitude; analyses were carried out using GC-MS techniques. Similar measurements carried out within the Advanced Global Atmospheric Gases Experiment (AGAGE), showed a global mean concentration of 143.2 pmol/mol in the year 2000 and a growth rate of 5.4 pmol/mol/year (AGAGE, 2001).

The atmospheric lifetime of chlorodifluoromethane calculated using these data is 12 years (Montzka et al., 2003) and has not changed significantly from the value deduced from comparing the data in Montzka et al. (1993) with the emissions in Midgley and Fisher (1993) or the previous modelled lifetime (Prather and Spivakovsky, 1990) after correcting for recent changes in the OH field calibration.
Samples covering the period of 1978 to 1994 from the Cape Grim Air Archive were analysed using gas chromatography (GC) with oxygen doped ECD (Electron Capture Detection) (Fraser et al., 1995b). The concentration of 94.2 pmol/mol for Cape Grim (41° S of latitude) during mid 1992 is in agreement with results obtained for the Southern hemisphere by Montzka et al. (1993 and 1996).

Other results are also consistent with these. Pollock et al. (1992) reported a concentration of 85.9 pmol/mol from samples taken during the 1988/1989 AASE (Airborne Arctic Stratospheric Experiment) and analysed by gas chromatography/mass spectroscopy (GC/MS) technique.

Results have also been obtained by spectroscopic techniques i.e. Fourier Transform Infrared (FTIR) Spectroscopy by Rinsland et al. (1989) for the period 1980 to 1988 at Kitt Peak (32° N). These showed a rise in concentration from 38 ± 10 pmol/mol at the end of 1980 to 68 ± 17 pmol/mol in May 1988, a rate of increase of 7.8 ± 1 % per year. Other measurements carried out at the Jungfraujoch (46.5° N) and Kitt Peak by Zander et al. (1994) yielded estimates of the rate of increase of , respectively 7 ± 0.35 % and 7 ± 0.23 % per year. Atmospheric concentrations during 1992, inferred from the measured column of chlorodifluoromethane, at Kitt peak were 110 to 117 pmol/mol, at the Jungfraujoch station 115 to 127 pmol/mol.

Before these studies, discrepancies were observed both between measurements obtained from spectroscopic techniques and between the measurements and atmospheric concentrations inferred from emissions (Rasmussen et al., 1980). These early measurements (designated * in Table 1), were based on standards provided by the Oregon Graduate Institute of Science & Technology (OGIST). However, agreement between the results reported by Montzka et al. (1993 and 1996), Prinn et al. (1995) and Fraser et al. (1995 b) and other data from Pollock et al. (1992), Rinsland et al. (1989) and Zander et al. (1994) suggests that the OGIST standards were responsible for the discrepancies and that results based on them are probably in error.

Due to the inadequacy of the model for calculation of regional atmospheric concentrations, the measured European concentrations of chlorodifluoromethane in air do not bear comparison with the atmospheric PECs calculated using EUSES. However, the global background concentrations from long term measurements as shown in Table 3.1.6.2 have been consistent, over the past 20 years, with concentrations calculated from the atmospheric lifetime of HCFC-22 and global production and emissions during that time (Montzka et al., 2003).

Total atmospheric PEC

Since the emission sources (production sites, processing sites as an intermediate, and locations where the substance is used as a refrigerant) are considered to be geographically separated from each other (and more or less evenly spread over the EU area), the total HCFC-22 concentration on a continental scale only is relevant for risk assessment of exposure of environment and man.

Soil, sediment and surface water concentrations are so low for each emission source (nano-to picogram/kg range) that addition of emissions to those compartments will not significantly influence the risk characterisation on total HCFC-22 concentrations in those compartments.
Therefore only atmospheric total concentrations will be evaluated.
It should be noted that EUSES does not take existing background atmospheric levels of HCFC-22 into account (model assumption: HCFC-22-free air flowing into EU).

The resulting continental concentrations calculated by the EUSES model are considered to be at steady state (fraction of steady state =1)

Sum of total emitted HCFC-22 to atmosphere in EU is 82066 kg/d, yielding a continental atmospheric concentration of +/- 166 ng/m^3 (without existing background).

The background concentrations of HCFC-22 in 2001 are not available, but the observed background level was 502 ng/m^3 in 2000.
Assuming that the 2001 background level was comparable to that of 2000, the total atmospheric concentration in the EU would be 668 ng/m^3.

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)

3.2.1 Aquatic compartment (incl. sediment)

Very few experimental aquatic toxicity tests have been carried out using chlorodifluoromethane. This is probably because of the physical nature of the substance. Due to its high vapour pressure, it is very difficult to test chlorodifluoromethane meaningfully.
Its Henry's law constant (H = 0.0205 atm.m^3/mol or 2077 pa m^3/mol at 12°C) indicates that the preferred environmental compartment of chlorodifluoromethane is the atmosphere.
Any chlorodifluoromethane released will partition rapidly into the air even if the primary vehicle for the release was an aqueous solution (Ballschmiter, 1992; Mackay, 1985). Chlorodifluoromethane has been shown to accumulate in the atmosphere where it is dispersed rapidly and oxidised slowly (WMO, 1994).

3.2.1.1 Toxicity test results

3.2.1.1.1 Fish

Acute toxicity

Only two acute toxicity tests are available. Among them only the following is reliable:

Zebrafish, *Brachydanio rerio*	96h LC_{50}	777 mg/l

Static renewal test, closed system, measured concentration, conducted in accordance with OECD Good Laboratory Practice standard (Hoke, 1997)

The study was conducted under unaerated, static-renewal conditions with six nominal concentrations of HCFC-22, a dilution water control and an HCFC-22 control (1200 mg/L, no test organisms) at a mean temperature of 23°C. Nominal calculated water concentrations of HCFC-22 tested were 100, 200, 400, 800, 1200, 1600 mg/l. Mean, calculated water concentrations of HCFC-22 were 156, 314, 586, 1029, 1553, 1972 mg/l, respectively.

Exposure of zebrafish to mean calculated HCFC-22 water concentrations of 156, 314, 586, 1029, 1553, 1972 mg/l resulted in 0, 0, 0, 100, 100 and 100 % mortality, respectively, at the end of 96 hours. Sublethal effects observed at the end of the study were dark coloration, gasping for air, swimming at the surface, lethargy and partial loss of equilibrium at the calculated water concentration of 586 mg/l. Swimming at the surface and hyperactivity were the observed sublethal effects at the calculated water concentration of 314 mg/l at test end. Mortality and sublethal effects were not observed in the dilution water control fish. Mean, calculated water concentrations of HCFC-22 derived from measured headspace concentrations were used for the calculation of LC_{50} values.
The result was the following:
96-hour LC50 (95% confidence interval): 777 mg/l (614-982 mg/l)

Chlorodifluoromethane is known to act by a non specific mode of action (non polar narcosis) in aquatic species (Veith et al., 1979; Verhar et al., 1995). Therefore, it is possible to estimate effect concentrations using the method described in the Technical Guidance Document. In addition, the US EPA program ECOSAR (v0.99g) was used to obtain further predicted values for fish toxicity.
Using the method described in the Technical Guidance Document based on Verhaar et al. (1995) a 96h LC50 value for Pimephales promelas of 386 mg/l is predicted, while ECOSAR v0.99g gives a value of 708.37.

Long-term toxicity

No long-term toxicity tests on fish are available.

3.2.1.1.2 Aquatic invertebrates

Acute toxicity

An acute screening study is available for daphnia:

Daphnia magna	48h-EC50	433 mg/l

static test, closed system, nominal concentrations (Du Pont, 1994)

The screening was performed using nominal concentrations, a control and HCFC-22. Analytical controls indicated that nominal and measured concentrations were in agreement both in the control and the test chambers. Test chambers were 25 ml scintillation vials containing appropriate dilution water. Four test chambers per concentration with five daphnids (total 20 daphnids per concentration) in each were used.
The nominal concentrations tested were 0, 90, 180, 370, 750, 1500 mg/l. The percent immobility after 48 hours of exposure were 0, 10, 10, 45, 75 and 100%, respectively.The 48-hours EC50 was 433 mg/l, based on immobility and nominal concentrations (Du Pont, 1994).

As for fish toxicity, the daphnia toxicity of chlorodifluoromethane can be estimated using the methods described in the Technical Guidance Document (based on Verhaar et al., 1995) and the US ECOSAR v0.99g. A 48h EC50 of 349.5 mg/l is calculated with the TGD method while a value of 703 mg/l is predicted with US ECOSAR v0.99g.
The experimental value of 433 mg/l is in reasonable agreement with the predicted values.

Long-term toxicity

No long-term toxicity tests on aquatic invertebrates are available.

3.2.1.1.3 Algae

Acute toxicity

There are no acute toxicity tests available for algae.

As already described in § 3.2.1.1 and § 3.2.1.2, QSAR methods can be used to accurately calculate aquatic toxicity of chlorodifluoromethane.
Using the methods of the Technical Guidance document (based on Van Leuwen et al., 1992), a 72-96h EC50 of 377.6 mg/l is estimated while a 96h EC50 of 250 mg/l is predicted with the ECOSAR v0.99g program.

Long-term toxicity

No long-term toxicity tests on algae are available.

3.2.1.1.4 Microorganisms

There is only one result from a test on domestic sewage sludge. No inhibition effect was observed at both concentrations tested (180 and 400 mg/l) for a 24 hour exposure (Method: ETAD proposal of 1976, anaerobic fermentation tube test, no analytical monitoring, Hoechst, 1973). Due to the lack of information on the experimental conditions of this study, it is not considered as reliable. However, according to distribution calculations, (3.1.3.2) the concentration of HCFC-22 in water or in sludge can be considered negligible and no effect on microorganisms is expected.

3.2.1.1.5 Amphibians

No toxicity tests on amphibians are available.

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Determination of the PNEC for water compartment
There are only two reliable experimental results from tests on fish and daphnia for chlorodifluoromethane, giving a 96h LC50 and a 48h EC50 of 777 mg/l and 433 mg/l respectively. As described above, QSAR methods can be used to calculate accurately the aquatic toxicity of chlorodifluoromethane. Data from the QSAR methods suggest a similar sensitivity to fish, daphnia and algae for chlorodifluoromethane.

It is proposed to base the PNEC on the lowest EC50 obtained from the QSAR, which is 250 mg/l for a 96 hour exposure to algae.

An assessment factor of 1000 is applied.

Therefore: **PNEC aqua = 250 mg/l / 1000 = 250 µg/l**

Determination of the PNEC for the sediments

In the absence of any toxicological data for the sediment dwelling organisms, the PNEC is calculated using the equilibrium partitioning method (TGD, part ii, paragraph 3.6.2.1, page. 117).

$$PNEC_{sediment} = (K_{susp\text{-}water} / RHO_{susp}) \times PNEC_{water} \times 1000 \quad (1)$$

where:

- $K_{susp\text{-}water}$ is the partition coefficient suspended matter-water;
- RHO_{susp} is the bulk density of suspended matter;

$K_{susp\text{-}water}$ can be calculated from the equation:

$$K_{susp\text{-}water} = Fair_{susp} \times K_{air\text{-}water} + Fwater_{susp} + Fsolid_{susp} \times (Kp / 1000) \times RHO_{solid} \quad (2)$$

Where:
Fx_{susp} is the fraction of phase x in the sediment compartment;
$K_{air\text{-}water}$ is the air water partitioning coefficient ($K_{air\text{-}water}$ = HLC /RT); R = 8.31 J/mol/K; T = 298 °K; HLC + 2496 Pa m3/mol (calculated at 25 °C, by EUSES 2).
K_p is the solids-water partition coefficient in the compartment. $K_p = K_{oc} \times$ fraction of organic carbon.
.

Parameters used:

- K_{oc}: a value of 40.5 l/kg was considered for K_{oc}. The estimation is derived from EUSES 2, considering HCFC-22 as a non-hydrophobic substance. The low K_{ow} of HCFC-22 justifies this assumption.
- Fraction of organic carbon: 0.1 (*)
- $K_p = K_{oc}$ x fraction of organic carbon = 4.05 l/kg
- RHO_{solid}: 2500 kg/m^3
- $Fair_{susp}$: 0 (*)
- $Fwater_{susp}$: 0.9(*)
- $Fsolid_{susp}$: 0.1 (*)
- RHO_{susp}: 1150 kg/m^3 (*)

*default values, taken from TGD, part II, paragraph 2.3.4, table 5, page. 43.

The PNEC value for sediment dwelling organisms is calculated to be **416 µg/kg** wet weight (1910 µg/kg dry weight).

3.2.2 Terrestrial compartment

No experimental results on terrestrial plants and soil dwelling organisms are available.

3.2.2.1 Calculation of Predicted No Effect Concentration (PNEC)

In the absence of any toxicological data for the terrestrial organisms, the PNEC is calculated using the equilibrium partitioning method (TGD, part ii, paragraph 3.6.2.1, page. 117).
The equations used are the same of the PNEC calculation for sediments (3.2.1.2).

$PNEC_{soil} = (K_{soil\text{-}water} / RHO_{soil}) \times PNEC_{water} \times 1000$

where:

- $K_{soil\text{-}water}$ is the partition coefficient soil-water;
- RHO_{soil} is the bulk density of wet soil;

$K_{soil\text{-}water}$ can be calculated from the equation:

$K_{soil\text{-}water} = Fair_{soil} \times K_{air\text{-}water} + Fwater_{soil} + Fsolid_{soil} \times (Kp / 1000) \times RHO_{solid}$

The input parameters specific for the terrestrial compartment are the following:

- Fraction of organic carbon: 0.02 (*)
- $K_p = K_{oc}$ x fraction of organic carbon = 0.81 l/kg
- $Fair_{soil}$: 0.2 (*)
- $Fwater_{soil}$: 0.2(*)
- $Fsolid_{soil}$: 0.6 (*)
- RHO_{soil}: 1700 kg/m^3 (*)

*default values, taken from TGD, part II, paragraph 2.3.4, table 5, page. 43.

The PNEC value for terrestrial dwelling organisms is calculated to be **239 µg/kg** wet sediment (271 µg/kg dry weight).

3.2.3 Atmosphere

No test results are available. For possible abiotic effects of HCFC-22 due to ozone depletion and global warming potential, see paragraph 3.1.3.1.1.

3.2.4 Secondary poisoning

As chlorodifluoromethane does not present indications of a bioaccumulation potential, a risk assessment for secondary poisoning is not necessary.

3.3 RISK CHARACTERISATION [7]

3.3.1 Aquatic compartment (incl. sediment)

Surface water

Table 3.10 Estimated PEC/PNEC ratios for the surface water at local scale

Scenario		PEC emission period (mg/l)	PNEC (mg/l)	PEC/PNEC	Conclusion
Production	1	0.0942	0.250	0.377	ii
	2	3.17E-3	0.250	0.0127	ii
	3	0.145	0.250	0.578	ii
	4	9.81E-12	0.250	3.92E-11	ii
	5	0.0966	0.250	0.386	ii
	6	0.158	0.250	0.632	ii
	7	0.0274	0.250	0.109	ii
	8	0.125	0.250	0.5	ii
	9	1.28E-3	0.250	5.12E-3	ii
	10	4.58E-3	0.250	0.0183	ii
Use as an intermediate	1	2.23E-6	0.250	8.93E-6	ii
	2	0.0164	0.250	0.0655	ii
	3	0.15	0.250	0.601	ii
Combined production + use as an intermediate	Site 9 + 1	1.28E-3	0.250	5.12E-3	ii
	Site 6 + 2	0.174	0.250	0.70	ii

Table 3.11 Estimated PEC/PNEC ratios for the surface water at regional and continental level

Scenario	PEC (mg/l)	PNEC (mg/l)	PEC/PNEC	Conclusion
Regional scenario	8.88E-6	0.250	3.56E-5	ii
Continental scenario	5.16E-6	0.250	2.06E-5	ii

Sediment

[7] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Table 3.12 Estimated PEC/PNEC ratios for the sediment water at local scale

Scenario		PEC (mg/kg)	PNEC (mg/kg)	PEC/PNEC	Conclusion
Production	1	0.157	0.416	0.377	ii
	2	5.28E-3	0.416	0.0127	ii
	3	0.241	0.416	0.578	ii
	4	1.63E-11	0.416	3.74E-11	ii
	5	0.161	0.416	0.386	ii
	6	0.263	0.416	0.632	ii
	7	0.0455	0.416	0.109	ii
	8	0.208	0.416	0.5	ii
	9	2.12E-3	0.416	5.09E-3	ii
	10	7.62E-3	0.416	0.0183	ii
Use as an intermediate	1	3.71E-6	0.416	8.93E-6	ii
	2	0.0272	0.416	0.0655	ii
	3	0.25	0.416	0.601	ii
Combined production + use as an intermediate	Site 9 + 1	2.12E-3	0.416	5.09E-3	ii
	Site 6 + 2	0.290	0.416	0.697	ii

Table 3.13 Estimated PEC/PNEC ratios for the sediment water at regional and continental scale

Scenario	PEC (mg/kg)	PNEC (mg/kg)	PEC/PNEC	Conclusion
Regional scenario	1.41E-5	0.416	3.4E-5	ii
Continental scenario	8.18E-6	0.416	1.9E-5	ii

Conclusions to the risk assessment for the aquatic compartment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to the scenarios production, use as a chemical intermediate and use as a refrigerant.

3.3.2 Terrestrial compartment

Table 3.14 Estimated PEC/PNEC ratios for the terrestrial compartment at local scale

Scenario	**PEC agr soil 30 d (**mg/kg**)**	**PNEC (**mg/kg**)**	**PEC/PNEC**	**Conclusion**

Production	1	4.53E-3	0.239	0.0190	ii
	2	1.52E-4	0.239	6.39E-4	ii
	3	0.0401	0.239	0.169	ii
	4	8.04E-8	0.239	3.36E-7	ii
	5	4.73E-3	0.239	0.0199	ii
	6	7.54E-3	0.239	0.0315	ii
	7	1.28E-3	0.239	5.36E-3	ii
	8	5.99E-3	0.239	0.0251	ii
	9	2.10E-4	0.239	8.8E-4	ii
	10	2.45E-4	0.239	1.03E-3	ii
Use as an intermediate	1	8.2E-8	0.239	3.45E-7	ii
	2	7.86E-4	0.239	3.31E-3	ii
	3	7.17E-3	0.239	0.0301	ii
Combined production + use as an intermediate	Site 9 + 1	2.10E-4	0.239	8.8E-4	ii
	Site 6 + 2	8.33E-3	0.239	0.0348	ii

Table 3.15 Estimated PEC/PNEC ratios for the terrestrial compartment at regional and continental scale

Scenario	PEC (mg/kg)	PNEC (mg/kg)	PEC/PNEC	Conclusion
Regional scenario	6.39E-6	0.239	2.7E-5	ii
Continental scenario	5.41E-6	0.239	2.26E-5	ii

Conclusions to the risk assessment for the terrestrial compartment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

3.3.3 Atmosphere

Based on its physical-chemical properties, the air compartment is the preferred target for chlorodifluoromethane. As no experimental data on environment organisms exposed through the gas phase are available, no biotic assessment is possible for the atmosphere. In view of the very low atmospheric concentration calculated with EUSES and the very high NOECs found

in experimental testing (inhalation toxicity studies in mammals), we can conclude that there is no risk for the atmospheric environment.
For the evaluation of an atmospheric risk, abiotic effects can be considered. The atmospheric lifetime of chlorodifluoromethane is 12.1 years. It has a very low ozone depletion potential (ODP); the value adopted for the purpose of the Montreal Protocol is 0.055. Its Global Warming potential (GWP) is 1700 on a unit-mass basis relative to a reference value of 1 for CO_2 at an Integration Time Horizon of 100 years (Ramaswamy *et al.*, 2001). WMO (2001) predicts for 2010 a maximum tropospheric concentration of 183 pptv (only 29 % above the 2000 level). However, as a Montreal Protocol substance, chlorodifluoromethane is not included in the Kyoto Protocol on greenhouse gas emissions. The EU Regulation 2037/2000 bans all dispersive uses of HCFC-22 (see paragraph 2.4).

Conclusions to the risk assessment for the atmosphere:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

3.3.4 Secondary poisoning

The low octanol-water partition coefficient indicated that chlorodifluoromethane is not likely to bioaccumulate. Therefore non-compartment specific effects relevant to the food chain have not to be considered.

Conclusions to the risk assessment for secondary poisoning:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

At all ambient temperatures at which exposure can be predicted chlorodifluoromethane is a gas. Thus exposures will predominately be by inhalation. Dermal contact with the liquefied gas escaping from cylinders can occur, but such exposures will only occur rarely in the occupational setting. The limited water solubility presents a theoretical possibility of ingestion in drinks.

The main uses of chlorodifluoromethane, as reported in section 2.2, are:
1. Refrigerant fluid
2. Chemical intermediate

The main categories of persons likely to be exposed the chlorodifluoromethane are workers involved in its production and use. Exposure of consumers and general public to HCFC-22 is not expected, except in accidental case. Some cases of acute intoxication from intentional inhalation abuse have been reported (Garriot and Petty, 1980; Kamm, 1975; Kurbat et al., 1998).
The human health section covers the health related effect from direct and indirect exposure to chlorodifluoromethane. As regulation concerning the ozone depleting potential of the substance is in place, it is not the intention of this risk assessment report to cover the indirect human health effects from increased UV-radiation caused by the stratospheric ozone layer depleting potential of the substance

4.1.1.2 Occupational exposure

As discussed in Section 2, chlorodifluoromethane is produced in closed systems, in order to contain the toxic and corrosive feedstocks. As the product is a gas, it is stored liquefied under pressure. With such a system, leaks and thus exposures are well controlled. Some exposure is possible during specific operations, such as coupling and decoupling of pipelines for maintenance purposes, sampling, loading of tanks for transport.
Not all production plants conduct monitoring for chlorodifluoromethane as it is a low toxicity material. The precursor materials (e.g. hydrogen fluoride and chloroform) are more hazardous, and thus monitoring may be directed at these precursor materials. The available monitoring data as well as exposure data calculated with modelling are reported in section 4.1.1.2.1 for some scenarios.
Workers' exposure to HCFC-22 is usually evaluated thanks to personal monitoring. HCFC-22 in the atmosphere is pumped onto a Perkin-Elmer ATD tube packed with a suitable adsorbent (Spherocarb 60-80 mesh). HCFC-22 is then desorbed on an Automatic Thermal Desorber (ATD-400). The desorbed gas is passed into a gas chromatograph, analyzed and the results processed using a Varian Star Data System.

Monitoring data submitted by HCFC-22 producers (EU and US) are of good quality, in a number sufficient to enable a statistical analysis and covering the different operations. For HCFC-22 use as an intermediate, few data are available from an EU plant. For the use as a refrigerant, some studies are available in the literature. The study by Gjølstad et al. (2003) presents a large number of data, details on the monitoring techniques and a statistical analysis.

4.1.1.2.1 Occupational exposure from production

Potential exposure during HCFC-22 production can only be via inhalation.

Inhalation exposure

In a HCFC-22 production plant, the main **tasks** of workers are the following ones:

- *Normal activity*: operation of manual valves; control of process parameters, preparation of maintenance activities; doing rounds including visual checks of piping, pumps, valves, etc. Since the production process is closed, during this activity the only potential exposure is from accidental leaks.
- *Maintenance:* control, revision, repair of all mechanic or electronic components. Coupling and decoupling of pipelines can take place for maintenance purposes. During maintenance, joints are leak tested using soapy water or electronic leak detectors. Maintenance activities are covered by specific plant operating instructions. During maintenance activities, there is a potential for exposure during coupling and decoupling of pipelines.
- *Filling and packaging activities:* the final product generally leaves the plant via road tanks or one tonne cylinders (for uses such as servicing of small refrigeration systems). During filling activities, there could be a potential exposure during the disconnection/connection of hoses for the filling of tanks. This activity usually takes place in the open air or in well ventilated rooms.
- *Sampling and analysis:* there could be a potential exposure for the analysts who control the quality of the product for sale, during sampling operations.

Concerning **PPE use**, *g*loves and goggles are worn to protect against cold burns during activities like maintenance or filling. Masks with gas filter and breathing apparatus are available and their use is compulsory for emergency situations (i.e. in case of leaks). There is no need to wear a respiratory protection during normal work.
Concerning Occupational Exposure Limit (**OEL**), a MAK value of 1000 ppm (3500 mg/m^3) is applied to HCFC-22.

Measured data

Measured data on workers' exposure to HCFC-22 during production are available for two sites in the EU (1996, 1999, 2000, 2001) (see table 4.1) and for two sites in the US (1999, 2002, 2003) (see table 4.2). Data are available for different tasks: plant operator (normal work, no potential exposure except in accidental case), packaging and filling (potential exposure during connection/disconnection of hoses) and sampling and laboratory analysis (potential exposure during the sampling or in some phases of the analysis).

For the plant operator, the original data represent personal monitoring values and are reported as 8-hour or 12-hours Time Weighted Averages (TWAs). Therefore, they can be considered to represent an estimation of typical exposure in the different tasks.

For packaging/filling and laboratory operations, some data have been measured as instantaneous sampling and gas chromatographic analysis (detection limit: 0.5 ppm, 1.75 mg/m^3), some as personal monitoring TWA (detection limit: 0.4 ppm, 1 mg/m^3). The personal monitoring values represent an estimation of the typical exposure during this task. In these scenarios, the highest measured values are due to major leaks and can be considered peak values, not representative of normal full shift exposure.

Table 4.1 Exposure data measured in EU plants

Activity	Number of measures	Ranges (mg/m^3)	Median (mg/m^3)	90th percentile (mg/m^3)	95th percentile (mg/m^3)
Plant operator	185	< 2 - 50	2	3.8	7.3
Packaging/filling	15	< 2 - 16	< 2	4.6	7.7

Table 4.2 Exposure data measured in US plants

Activity	Number of measures	Ranges (mg/m^3)	Median (mg/m^3)	90th percentile (mg/m^3)	95th percentile (mg/m^3)
Plant operator	16	1.4 – 13.3	1.7	2.5	5.2
Sampling/laboratory	34	1.4 - 266	3	49.7	219.1
Packaging/filling	36	2.1 - 315	30.5	126.7	150

Production processes in EU and US are similar and workers' exposure level can be considered equivalent. Therefore, US exposure data will be used when EU data are not available or scarce.

Modelled data

The EASE model for HCFC-22 production predicts that inhalation exposure is **0 to 0.35 mg/m^3** when there is no system breaching (normal work).

Temperature of the process: 60 °C
Physical state: gas or vapour
Exposure type: gas/vapour/liquid aerosol
Use pattern: closed system
Significant breaching is false
The pattern of control is full containment
The predicted gas/vapour/liquid aerosol exposure to HCFC-22 is 0-0.1 ppm (0 – 0.35 mg/m^3)

The EASE model has been applied also in case of system breaching (coupling and decoupling during maintenance, sampling, filling operations) for two different patterns of control: LEV and segregation (normal patterns of control for HCFC-22 production plants). The input parameters and the results are reported below.

Temperature of the process: 60 °C
Physical state: gas or vapour
Exposure type: gas/vapour/liquid aerosol
Use pattern: closed system
Significant breaching is true
The use pattern is non dispersive use
The pattern of control is LEV
The predicted exposure is **100-200** ppm (350 – 700 mg/m^3)

Temperature of the process: 60 °C
Physical state: gas or vapour
Exposure type: gas/vapour/liquid aerosol
Use pattern: closed system
Significant breaching is true
The use pattern is non dispersive use
The pattern of control is segregation
The predicted exposure is **200-500** ppm (700 - 1750 mg/m^3)

Since EASE model predicts values as 8 hour time weighted average, the short term exposure values need to be corrected according to the duration of exposure.

For the scenario *packaging/filling* the short-term exposure duration is estimated to be 1.5 hours/day. Therefore, the predicted exposure is:

- 100 * 1.5/8 = 18.75 ppm (66.38 mg/m^3)
- 200 * 1.5/8 = 37.5 ppm (132.56 mg/m^3)
- 500 * 1.5/8 = 93.75 ppm (281.25 mg/m^3)

These values are close to the ones measured in US plants (maximum and 90-percentile). This confirms that the highest measured values are peaks, representing a short term exposure to leakages.

For the scenario *sampling/laboratory* the short-term exposure duration is estimated to be 0.1 hours/day. Therefore, the predicted exposure is:

- 100 * 0.1/8 = 1.25 ppm (4.4 mg/m^3)
- 200 * 0.1/8 = 2.5 ppm (8.75 mg/m^3)
- 500 * 0.1/8 = 6.25 ppm (21.87 mg/m^3)

The minimum value obtained is close to the 90-percentile of the measured values. This confirms the highest measured values are peaks, representing a short term exposure to leakages.

Summary/statement of the exposure level

For *normal work*, the measured exposure levels are equivalent in the EU and in US. The measured levels are higher than those calculated with the model. The 90-percentile value for the EU plants (**3.8 mg/m^3**) can be retained for risk characterisation as reasonable worst case. No highest measured values are retained for short term exposure because they are probably due to accidental leaks.

For *packaging and filling operations*, the highest exposure values are measured in US plants. The values obtained with EASE model in case of system breaching are close to the highest measured values.

The highest measured values are considered to represent peak exposure due to leaks possibly during connection and disconnection of hoses for the filling of the tanks and are not representative of a normal exposure level (full shift). Therefore, the median value from US plants (**30.5 mg/m^3**) can be retained as a reasonable worst case for the long term exposure (full shift) and the 90-percentile value (**126.7 mg/m^3**) can be retained as a reasonable worst case for short term exposure (connection and disconnection of pipelines).

For *sampling and laboratory activities*, measured exposure values are available only for US plants. The highest measured values are considered to represent peak exposure due to leaks and are not representative of a normal exposure level (full shift). Therefore, the median value from US plants (**3 mg/m^3**) can be retained as a reasonable worst case for the long term exposure (full shift) and the 90-percentile value (**49.7 mg/m^3**) can be retained as a reasonable worst case for short term exposure (opening of the system for sampling).

For *maintenance*, no specific information is available. During normal control activities, the exposure will be probably similar to that of production, normal work scenario. Therefore, the value **3.8 mg/m^3** can be retained for long term exposure. High exposure levels for short periods of time are possible in the case of coupling and decoupling of pipelines. We can reasonably consider the 90th-percentile measured during filling operations (**126.7 mg/m^3**) as a reasonable worst case for short term exposure during maintenance.

Dermal exposure

Since HCFC-22 is a gas at ambient temperature and pressure, no dermal exposure is expected. In accidental case, direct contact with liquefied HCFC-22 may result in frostbite.

4.1.1.2.2 Occupational exposure from formulation

Formulation takes place on production sites. Evaluation of exposure from formulation is then included in the production section.

4.1.1.2.3 Occupational exposure from end uses

Inhalation exposure

Potential exposure during HCFC-22 use can only be via inhalation.

Use as a refrigerant
HCFC-22 is used as a refrigerant in a wide range of installations such as supermarket freezers, refrigerators, refrigerated transport (road, rail and marine) and air conditioning units. All installations are subject to losses of gas either through continual low-level leakage or during servicing.
Exposure of workers in the refrigeration sector to HCFC-22 is possible during the assembly and servicing of the installations, when the cylinders are connected to the installation to be filled or re-filled. Respiratory protection should be worn when performing all operations during which there could be a potential for significant exposure. An adequate ventilation system should be installed in all filling and storage areas.
No data are available on the recycling of HCFC-22 in refrigeration, but it is assumed that the amount of recycled HCFC-22 is very low. The operational practices are considered to be equivalent to those described in the refrigeration scenario.

Use as a chemical intermediate
Chlorodifluoromethane is used as a precursor in the manufacture of fluoropolymers such as polytetrafluoroethylene. It may also be used in the manufacture of other fluorochemicals. In these industries there are similar constraints on operations due to the gaseous nature of chlorodifluoromethane so most systems are closed. One plant in Europe reports a batch system. Exposure of workers during the use of HCFC-22 as a chemical intermediate is possible during coupling and decoupling of pipelines for maintenance purposes.

Use as a refrigerant

Measured data

Some monitoring data on the levels of HCFC-22 occurring during refrigeration repair has been published. Antti-Poika et al. (1990) reported levels of chlorodifluoromethane, measured during the servicing of refrigeration equipment, ranging from 170 ppm (595 mg/m3) to 815 ppm (2852 mg/m^3), equating to 8 hour averages of 25 ppm (87.5 mg/m^3) to 254 ppm (889 mg/m^3). These data refer to levels occurring during large scale repair work on industrial refrigerators, which the authors report to be an unusual event.

Gjølstad et al. (2003) have reported the levels of various refrigerants, including HCFC-22 measured during the normal repair of a range of smaller installations like refrigerators, freezers and air conditioners. Personal monitoring was performed and the concentration of HCFC-22 was measured during 30 maintenance/repair occasions (when the exposure was considered to be the highest). The total measuring time was equal to the working periods of the repairmen. The average air concentration was 235 mg/m$^{3.}$ (range 10.6-2171). The study also reported an average peak level of 1627 mg/m^3, the average duration being 5 to 8 minutes. The authors of the study calculated a 90-percentile for the whole database of 2027 mg/m^3 (personal communication, 2004).

In the paper of Gjølstad et al. (2003) the following sentence is reported: *" Althought the cumulative air concentrations were generally low, the direct reading photoacustic IR analyser showed that short periods of higher concentration were quite prevalent. The concentrations were arbitrarily defined to be "high" if the concentration measured during a specific period was at least 3 times higher than the concentration level previously measured. This implies that such periods of peak exposure may represent quite low concentrations if the exposure in general is low. The average duration of these peaks was 5 to 8 min (range 1-21 min). On average, there were 2.7 "high" concentration period when HCFC-22 was the refrigerant . Periods with high exposure were associated with specific tasks such as avacuating the coolers and draining and refilling of the compressor oil. The air concentrations during the periods between such work operations were considerably lower and sometimes even hardly detectable."*
On the basis of this information, we think that the 90-percentile value is influenced by the peak values, which represent a short term exposure (average peak duration: 5 to 8 minutes) during specific tasks which do not represent the typical refrigeration work. For this reason, we think that the median value better represents the long term exposure.

Modelled data

The exposure for refrigeration workers can also be calculated with EASE model. If we assume a closed system, the EASE model predicts an exposure of **0-0.35 mg/m^3**.

Temperature of the process: 60 °C
Physical state: gas or vapour
Exposure type: gas/vapour/liquid aerosol
Use pattern: closed system
Significant breaching is false
The use pattern is non dispersive use
The pattern of control is full control
The predicted exposure is **0-0.1** ppm (0 – 0.35 mg/m^3)

The predicted values appear too small, if compared to the average air concentration, probably because of the frequent system breaching during repair activities.

The EASE model was run also in the case of system breaching (i.e., during maintenance of refrigeration systems), with the following input data:

Temperature of the process: 25 °C
Physical state: gas or vapour
Exposure type: gas/vapour/liquid aerosol
Use pattern: closed system
Significant breaching is true
The use pattern is non dispersive use
The pattern of control is segregation
The predicted exposure is **200-500** ppm (700 - 1750 mg/m^3)

Temperature of the process: 25 °C
Physical state: gas or vapour
Exposure type: gas/vapour/liquid aerosol
Use pattern: closed system
Significant breaching is true
The use pattern is non dispersive use
The pattern of control is direct handling
The predicted exposure is **500 - 1000** ppm (1750 - 3500 mg/m^3)

The data obtained with segregation as pattern of control are in agreement with those reported by Gjølstad et al. (2003) for the average peak level concentration. This is consistent with the frequent system breaching required by the normal activity of a refrigeration repair worker..

Use as a chemical intermediate

Measured data

Data on monitored exposures coming from one EU plant for the production of TFE (CEFIC, 1996) (table 4.3) give an indication that substance loss is well controlled and exposures are below 3 mg/m^3. The data have been measured as instantaneous sampling and gas chromatographic analysis during a normal working period (detection limit: 0.5 ppm, 1.75 mg/m^3).

The basic process is the same in all EU plants: the high temperature cracking of HCFC-22 followed by low temperature distillation to yield TFE. There will be proprietary differences in the method used to crack HCFC-22. The reaction takes place in a closed vessel and emissions are possible only in case of coupling and decoupling. Therefore, there will be no significant differences in exposure among the EU plants and the data in table 4.3 can be considered representative for Europe.

Table 4.3 Exposure data for the use of HCFC 22 as chemical intermediate

Activity	Number of measures	Ranges (mg/m^3)	Median (mg/m^3)	90th percentile (mg/m^3)	95th percentile (mg/m^3)
Plant operator	15	< 2 - 3	< 2	< 2	< 2

Modelled data

The resulting concentration in the work floor atmosphere is calculated to be **0 to 0.35 mg/m^3** for HCFC-22 use as a chemical intermediate. This calculation is made under the assumptions of a closed system, no breaching.

Temperature of the process: 20 °C
Physical state: gas or vapour
Exposure type: gas/vapour/liquid aerosol
Use pattern: closed system
Significant breaching is false
The use pattern is non dispersive use
The pattern of control is full control
The predicted exposure is **0-0.1** ppm (0 – 0.35 mg/m^3)

During this use, there will be no system breaching for sampling before the reaction takes place. Therefore, the only possible exposure to HCFC-22 during its use as chemical intermediate could happen during coupling and decoupling of the pipelines containing HCFC-22 (before the reaction takes place) for maintenance purposes. The results of EASE model for production of HCFC-22 in case of system breaching can be used for the short term exposure during the use as a chemical intermediate.

Summary/statement of the exposure level

Use as a refrigerant
For HCFC-22 use as a refrigerant, the 90-percentile value reported by Gjølstad et al. (2003) (**2027 mg/m^3**) will be retained for risk characterisation for acute toxicity (short term exposure). This is justified by the fact that the average duration of the peaks is very short (5 to 8 minutes). The average value measured by Gjølstad et al. (**235 mg/m^3**) is the most appropriate value for long term exposure during the normal activities of refrigeration repair workers and can be considered a reasonable worst case, since the study only takes into consideration tasks with a potentially high exposure (maintenance and repair).

Use as a chemical intermediate
For HCFC-22 use as a chemical intermediate, the 90-percentile value of values measured during production, normal activity (**3.8 mg/m^3**) will be retained for the risk characterisation for long term exposure. This is based on the similarities of the tasks.

Dermal exposure

Since HCFC-22 is a gas in normal conditions of use, no dermal exposure is expected.

4.1.1.2.4 Summary of occupational exposure

Available data on occupational exposure are summarized in table 4.4. Frequency and duration have been estimated by making an average of the information provided by some plants. It has to be stressed that, for some activities such as maintenance, operational practices can be very different from one site to the other. In each scenario, short term exposure data refer to specific cases in which an exposure is possible because of system breaching (filling, sampling, decoupling, etc.). For normal operation work during production, no short term exposure value is reported, because the exposure can only take place in case of accidental leaks. As HCFC-22 is a gas under normal conditions of production and use, only inhalation exposure is possible.

Table 4.4 Conclusions of the occupational exposure assessment

Scenario	Activity [1]	Frequence Days/year	Duration Hours/day	Inhalation				Dermal			
				Reasonable worst case		Typical concentration		Reasonable worst case		Typical concentration	
				mg/m³	Method [2]	mg/m³	od [2]	Unit	Method [2]	Unit	Method [2]
Production											
Subscenario 1	Full shift	160	10	3.8	Measured			NR		NR	
Normal activity											
Subscenario 2	Full shift	46	7	3.8	Measured			NR		NR	
Maintenance	Short term			126.7	Measured						
Subscenario 3	Full shift	160	10	30.5	Measured			NR		NR	
Packaging/filling	Short term	160	1.5	126.7	Measured						
Subscenario 4	Full shift	3	10	3	Measured			NR		NR	
Sampling/lab	Short term	50	0.1	49.7	Measured						
Uses											
Subscenario 1	Full shift		7	235	Measured			NR		NR	
Use as a refrigerant	Short term		0.2	2027	Measured						
Subscenario 2	Full shift			3.8	Measured			NR		NR	
Use as an intermediate											

1: Full shift, short term, etc.
2: Measured, EASE, Expert judgment, Calculated, etc.
NR: not relevant

4.1.1.3 Consumer exposure

HCFC-22 was used in the past in domestic refrigeration and air conditioning equipments. In these applications, refrigeration units are hermetically sealed and maintenance is carried out only by professionals. Therefore, there is no direct consumer exposure to HCFC-22.

4.1.1.4 Humans exposed via the environment

HCFC-22 does not bioaccumulate, therefore no significant human exposure via the environment is expected. According to EUSES modelling, indirect exposure of humans to HCFC-22 via food, air and drinking water is negligible. Table 4.5 shows the regional and local total daily intake for the local scenarios (see Appendix 1).

Table 4.5 Regional and local total daily intake for local scenarios

	Site	Regional total daily intake (mg/kg/day)	Local total daily intake (mg/kg/day)
Production site	1	1.08E-6	6.12E-3
	2	6.35E-7	1.33E-4
	3	6.22E-6	1.79E-2
	4	7.20E-7	1.12E-5
	5	2.54E-6	1.77E-2
	6	6.22E-6	6.11E-3
	7	3.57E-7	2.06E-3
	8	7.20E-7	4.16E-3
	9	2.73E-6	2.01E-2
	10	6.35E-7	3.63E-3
Use as an intermediate site	1	7.39E-8	1.10E-5
	2	1.67E-7	8.73E-4
	3	2.62E-6	4.98E-3
Combined production + use	9+1	2.73E-6	2.01E-2
	6+2	9.83E-7	6.98E-3

4.1.2 Effects assessment: Hazard identification and dose (concentration)-response (effect) assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

Absorption

The relationship between inhaled concentrations of chlorodifluoromethane and blood levels was studied in the anaesthetised rats by Carney (1977). Chlorodifluoromethane concentrations in air were metered through a mixing chamber and pumped to a canula inserted into the exposed trachea. After 15 minutes a sample of blood was withdrawn from the carotid artery, the supply of chlorodifluoromethane was stopped and further blood samples were taken at timed intervals to estimate the rate of clearance from the blood. Four male and four female rats were used for experiments using nominal air concentrations of either 10,000 or 50,000 ppm (35,000 or 175,000 mg/m^3). The results showed a direct correlation between the inhaled air and blood concentrations of chlorodifluoromethane. With an inhaled concentration of 10,000 ppm, the mean blood concentration was 31 mg/litre. At 50,000 ppm (175,000 mg/m^3) the mean blood concentration was 155 mg/litre. After exposure the clearance of chlorodifluoromethane from blood was rapid, with a half-life of approximately 3 minutes.

Comparable results have been reported by Sakata et al. (1981) with experiments in rabbits. Animals which had been anaesthetised with phenobarbitone (25 mg/kg ip) received chlorodifluoromethane/air mixture via a plastic mask and blood samples were taken from a catheter in a femoral artery. The concentration of chlorodifluoromethane inhaled ranged from 50,000 ppm (175,000 mg/m^3) to as high as 400,000 ppm (1400,000 mg/m^3).

Blood concentrations of chlorodifluoromethane increased rapidly from the beginning of inhalation at every concentration. Saturation was reached in about 5 minutes. The blood concentration was directly proportional to the inhaled concentration of chlorodifluoromethane. When exposure ceased, the blood concentration decreased rapidly, with a maximum half-life of 1 minute. After 15-30 minutes, blood chlorodifluoromethane concentrations were at a similarly low level, irrespective of the inhaled concentration. It took a further hour for the blood concentration to fall below the limit of detection.

Ding et al. (1980) reported the alveolar absorption rate to be 3.15% of the total dose in rabbits exposed to 1000 ppm (3500 mg/m^3) chlorodifluoromethane. The study cannot be evaluated because of the lack of details.

Pregnant rats were exposed to atmospheric concentrations between 250 and 175,000 ppm of chlorodifluoromethane (875 and 612500 mg/m^3). Blood samples taken at various intervals again showed that chlorodifluoromethane rapidly reached equilibrium with blood and were eliminated quickly following removal from exposure. At the highest dose the blood level reached 118.5 mg/l after 30 minutes with no significant increase (121 mg/l) after another 5.5

hours of exposure. Thirty minutes following cessation of exposure the blood level had decreased to 3.55 mg/l (Woollen, 1988).

Distribution

Sakata et al. (1981) determined the amount of chlorodifluoromethane in the tissues of rabbits receiving up to 400,000 ppm (1400,000 mg/m^3) by inhalation (details described above). No major differences were found in the tissue concentrations except for fat tissue in which there was a difference after prolonged (higher) and short (lower) inhalation times. The authors postulated the effect was related to the poor vascular blood supply of adipose tissue which would comparatively delay absorption, but that the final concentration would be higher due to greater solubility in fat.

Metabolic Transformation

In vivo experiments were carried out by Salmon et al. (1979) using ^{14}C and $^{36}C1$ radiolabelled chlorodifluoromethane. Rats were exposed individually to atmospheres of chlorodifluoromethane in specially constructed chambers in which all surfaces in contact with gas were either glass or metal. With the ^{14}C material exposures were either 500 or 10,000 ppm (1750 or 35,000 mg/m^3) in air each in three experiments, the exposure times being 15-24h. Exhaled CO_2 was collected by absorption in barium hydroxide and the radioactivity was subsequently measured. Separate collection of urine and faeces into containers cooled to 0°C was followed by radiochemical counting, directly in the case of urine and after appropriate oxidation for the faeces. Similar exposure and collection conditions were used for the $^{36}C1$ experiments, in which the concentration of chlorodifluoromethane was 10,000 ppm (35,000 mg/m^3) for a 17.5 h exposure.

These experiments showed that metabolism of chlorodifluoromethane in the rat were minimal. The amount of $^{14}CO_2$ released was equivalent to approximately 0.1% of the inhaled chlorodifluoromethane at an air concentration of 500 ppm (1750 mg/m^3) and 0.06% at 10,000 ppm (35,000 mg/m^3) chlorodifluoromethane. The amounts of 14-C label in the urine were also small, equivalent to approximately 0.03 and 0.01% of the inhaled doses (1750 and 35,000 mg/m^3 chlorodifluoromethane respectively). Insignificant quantities were found in the faeces.

In the experiments with the $^{36}C1$ label only 0.01% of the inhaled dose was detected in the urine, supporting results obtained in the ^{14}C label studies. It is questionable whether the minimal metabolism observed was related to chlorodifluoromethane or of an impurity present in the test compound. Salmon et al. (1979) also conducted in vitro studies incubatin hepates microsomes from Arochlor 1254 induced rat, NADPH and $^{36}C1$ labelled chlorodifluoromethane (concentration range 0.2 -1.3 mM) in a repeat-dosing syringe. Samples were taken for analysis at 2 minutes intervals.

Released $^{36}C1$ ion was isolated as AgC1 and estimated by scintillation counting. Under these experimental conditions, there was no release of chloride ion from chlorodifluoromethane further indicating the compounds resistance to breakdown in biological systems.

Peter et al. (1986) found that chlorodifluoromethane was not metabolised by Wistar rats after ip injection. Rats received a single ip injection of chlorodifluoromethane after which they were placed in a closed system with a gas sample loop connected to a chromatograph. The

chamber concentration of chlorodifluoromethane increased over one hour, as it was exhaled by the rats. The subsequent reduction in concentration in the system was quite slow In addition, pre-treatment of the animals with phenobarbital or DDT did not alter the obtained results. The authors concluded that there was no detectable metabolic elimination of chlorodifluoromethane. It is stated that these experiments were confirmed in B6C3F1 mice, although no data are provided.

Elimination

Experiments to detect metabolites of chlorodifluoromethane (Salmon et al., 1979) showed that rats exposed to 35,000 mg/m³ chlorodifluoromethane only yielded 0.01% of the dose in the urine (see above).

Elimination of chlorodifluoromethane was studied in rabbits after exposures ranging from 50,000 to 400,000 ppm (175,000 to 1400,000 mg/m^3) (Sakata et al., 1981). After exposure ceased, the blood concentration decreased rapidly with a maximal half-life of 1 minute. After 15-20 minutes, blood chlorodifluoromethane concentration was 27 - 31 mg/l irrespective of the inhaled concentration. It took a further hour for values to fall below the sensitivity of analysis. When the partial pressure of chlorodifluoromethane in alveolar air became zero, chlorodifluoromethane was rapidly cleared from the blood, followed by moderate elimination from poorly perfused tissues.

4.1.2.1.2 Human data

Absorption and Elimination

The uptake and elimination of chlorodifluoromethane in man has been studied by Woollen et al. (1992). Two groups of 3 male subjects were exposed to average atmospheric concentrations of 327 or 1833 mg/m^3 (92 or 517 ppm) chlorodifluoromethane for 4 hours. Blood and expired air samples were taken during the exposure period and for up to 26 hours after exposure and analysed for chlorodifluoromethane. Urine samples were collected for up to 22 hours after exposure and analysed for chlorodifluoromethane and fluoride ion. During the exposure period blood chlorodifluoromethane concentrations approached a plateau; the maximum blood concentrations (0.25 and 1.36 µg/ml) were proportional to levels of exposure.

The concentrations of chlorodifluoromethane in expired air were similar to the exposure concentrations during the exposure period. The ratio between blood and expired air concentrations towards the end of the exposure period was, on average, 0.77. This is consistent with in vitro measurements of the solubility of chlorodifluoromethane in human blood (blood/air partition coefficient = 0.79).

In the post-exposure period 3 phases of elimination of chlorodifluoromethane were apparent with half lives of 0.005, 0.20 and 2.6 hours. The first phase, which could be identified only from expired air measurements, is thought to correspond to elimination from blood and rapidly perfused tissues. The second and third phases are believed to correspond to the elimination from slowly perfused tissues and fat respectively.

Chlorodifluoromethane was detected at low concentrations (0.02 and 0.15 mg for the two exposure group) in urine samples taken in the post-exposure period at both dose levels. The concentration rapidly declined post-exposure, and the rate of decline was consistent with the terminal rate of elimination determined from blood and breath measurements. The elimination half-life for excretion of HCFC-22 in urine was 2,8 hours.

The average amounts on HCFC-22 recovered in breath in the post exposure period were 18.7 and 95.1 mg for the two dose levels of 327 and 1833 mg/m^3, respectively. In both cases this is only a small proportion (<2.7%) of the total amount inhaled during the exposure period.

Distribution

Three days after a fatal accident on board of a fishing vessel, samples of major tissues were taken from two of the deceased for estimation of chlorodifluoromethane content by gas chromatography. The findings are given in Table 4.6a. The concentrations were similar to those found in a rabbit examined 3 days after death by asphyxiation with chlorodifluoromethane (Morita et al., 1977).

In a survey of organic compounds found in human milk, chlorodifluoromethane was detected in one of the twelve samples. Chlorodifluoromethane was one of 184 compounds detected in the survey. No information on exposure or quantification of the amount found is given (Pellizzari et al., 1982).

Two seamen were overcome by chlorodifluoromethane and, as a result, died. This accident happened due to the entrance of the first individual into a ship's compartment filled with chlorodifluoromethane (the concentration was not given) following the unrepaired rupture of a filter during routine dockside maintenance of the ship's refrigerant system. The second individual entered the same room in order to assist his shipmate. Sixteen hours after the accident, a post-mortem examination was carried out on both victims and samples of blood, urine, bile and vitreous humour were taken for the estimation of chlorodifluoromethane content using GC/MS. The findings are presented in Table 4.6b. (Kintz et al., 1996).

Table 4.6 Chlorodifluoromethane levels in post-mortem samples from deceased victims following over-exposure.

a) from Morita et al., 1977 (levels in µl/g)

	Brain	Lung	Liver	Kidney	Blood
Subject A	68	18	71	18	69
Subject B	100	20	92	8	130

b) from Kintz et al., 1996 (levels in µl/ml)

	Urine	Bile	Vitreous Humour	Blood
Subject A	**1.7**	**1.3**	**1.0**	**37.1**
Subject B	**0.9**	**1.3**	**0.7**	**26.0**

Transformation

There are no data on the transformation of chlorodifluoromethane in man except the report of no increase in fluoride ion in urine of volunteers exposed to 92 or 517 ppm (322 or 1809.5

mg/m^3) chlorodifluoromethane for 4 hours, suggesting a limited metabolism (Woollen et al. 1992).

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

The studies in animals show that chlorodifluoromethane is rapidly absorbed into the blood stream by the inhalation route, since 75-80% of the inhaled concentration equilibrated with the blood. It is not metabolised to any significant extent and is very rapidly (half-life $\leq$ 1 minute) and extensively eliminated unchanged in the exhaled air, indicating very limited period of retention within the body.
The inhalation absorption figure will therefore depend on the exposure duration within each day with high absorption during the beginning of exposure and lower absorption when the equilibrium is reached. It is recognised that route specific NOAELs are available from studies of sufficiently long daily exposure. Thus this phenomenon of reaching equilibrium is included in these NOAELs and does not have to be taken into account in the risk characterisation.
Only a very small amount of radiolabelled material (<<0.1 % of administered dose) has been detected in urine. A similar profile is seen in humans, where, after rapid equilibration with the blood (blood/expired air partition ratio 0.77), chlorodifluoromethane is rapidly eliminated in the breath; the compound metabolism is minimal and excretion into the urine extremely limited. Thus it can be reasonably assumed that animal studies suitably model toxicokinetics of chlorodifluoromethane in man.
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4.1.2.2 Acute toxicity

Oral and dermal toxicity

The acute oral and acute dermal toxicity of chlorodifluoromethane has not been investigated, for two reasons:

1) Chlorodifluoromethane is a gas at normal temperature and pressure with a boiling point of -40°C. The substance could not be dosed orally as it is maintained as a liquid only under pressure. It would be possible to dissolve chlorodifluoromethane in an organic solvent for oral dosing as was reported by Longstaff et al. (1984). They gave repeated doses of a 3% solution of chlorodifluoromethane orally to rats, giving a daily dose of 300 mg/kg. However, increasing the dose above this level is likely to result in the volatilisation of the material in the stomach of the animal, resulting in adverse physical effects.
Regarding dermal exposure, it would be possible to retain vapour against the skin, but this would provide only a minimal dose of the substance.
2) The oral and dermal routes of exposure are not relevant to acute human exposure to chlorodifluoromethane. As the product is a gas, most human exposures in the workplace will result from fugitive emissions of vapour. The possibility of oral exposure in the workplace is very remote. Similarly, dermal exposure is uncommon and will only occur when there is a sudden leak or uncontrolled release. On contact with the skin, the liquid chlorodifluoromethane will volatilise rapidly, resulting in freeze burns as a consequence of the local cooling of the skin. Contact with the liquid will be for such a short time that dermal absorption will not occur.

Despite these comments, there is one report of an oral toxicity study on chlorodifluoromethane in the literature. Antonova et al. 1983 reported that no signs of toxicity

were noted in rats administered 4 ml of an aqueous chlorodifluoromethane solution at a concentration of 2700 mg/l by oral route. The significance of the data is questionable, however, since chlorodifluoromethane has a high Henry's law constant (> 2500 Pa m^3/mol) and it is likely that the actual concentration of the substance was far below the nominal concentration.

4.1.2.2.1 Studies in animals

Inhalation toxicity

Several inhalation toxicity studies on chlorodifluoromethane have been reported in the literature. Deaths have been reported in rats, mice, and guinea pigs exposed to chlorodifluoromethane at concentrations of 220,000 to 365,000 ppm (770,000 to 1277500 mg/m^3) for periods of 15-240 minutes. A summary of the lethal range of chlorodifluoromethane seen in these studies is given in table 4.7.
Chlorodifluoromethane has a low order of toxicity in a range of mammalian species and the effects seen are characteristic of a depressant effect on the CNS. The threshold concentration for clinical signs of CNS depression in the rat exposed to chlorodifluoromethane is 5.0%, no effects being seen after exposure for 120 minutes to 2.5% (Weigand, 1971). The signs of toxicity in rats were tremor of the limbs and head, convulsions, narcosis, shallow respiration and death from respiratory depression. Death always occurred during exposure. Recovery from non-lethal exposure was rapid. Rats appeared normal within 10 min and showed no delayed after-effects. The EC 50 in rats for CNS effects after 10 minutes exposure was 140,000 ppm (490,000 mg/m^3) (Clark and Tinston 1982).
Rabbits were exposed either to increasing concentrations of chlorodifluoromethane (up to 40% for up to 70 minutes) or to stable concentrations ranging from 50,000 or 400,000 ppm (175,000 to 1400,000 mg/m^3) for 30 minutes. Signs of toxicity in rabbits were similar to those observed in the rats, namely in coordination and other signs of CNS depression. The sequence of symptoms was described as a) reeling, b) weakness of the forelegs, c) falling down, d) flow of mucous fluid from mouth and nose, mydriasis and lacrimation, e) violent movement of body and extremities i.e. running, f) cyanosis and, at high concentrations (>300,000 ppm, 1050,000 mg/m^3), g) death. Post mortem examination of rabbits confirmed that the cause of death was asphyxiation (Sakata et al. 1981).

Table 4.7 Acute inhalation studies - lethality

Species	Concentration ppm	Exposure period min.	Effects	Reference
Monkey	200,000	5	Non lethal	Aviado & Smith 1974
Dog	700,000	90	Lethal	Poznak & Artusio 1960
Rabbit	300,000	30	Minimum Lethal Concentration	Sakata et al. 1981
Guinea Pig	400,000	120	Lethal	Weigand 1971
Guinea pig	300,000	120	Non lethal	Weigand 1971
Guinea pig	>200,000	120	Approximate lethal Concentration	Nickolls 1940 cited in Waritz 1971

Rat	600,000	2	Non lethal	Pantaleoni & Luzi 1975a,b
Rat	400,000	120	Lethal	Weigand 1971
Rat	350,000	15	LC50	Clark & Tinston 1982
Rat	300,000	120	Minimum lethal concentration	Weigand 1971
Rat	250,000	240	Minimum lethal concentration	NIOSH 1976
Rat	220,000	240	LC50	Litchfield & Longstaff 1984
Rat	200,000	120	Non lethal	Weigand 1971
Mouse	370,000	120	Minimum Lethal Concentration	Karpov 1963b
Mouse	320,000	120	Non lethal	Karpov 1963b
Mouse	280,000	30	LC50	Sakata et al. 1981

4.1.2.2.2 Human data

Cases of accidental exposure

A principal hazard associated with fluorocarbons in general is the potential for these compounds to accumulate in low spaces resulting in oxygen displacement. In these circumstances, some deaths have been due to asphyxiation. Some papers describe accidental exposure to HCFC 22 in the refrigeration industry or in the use of large refrigeration units.
Morita et al. (1977) reported six deaths from refrigerant gas exposure in a deep-sea fishing boat. Two of the victims were subjected to a post-mortem examination which revealed no outstanding macroscopic features. Histopathology of all the major organs showed that the lungs were oedematous and that fine lipid droplets were present in the cytoplasm of hepatocytes, mainly in the peripheral zone. No other findings that could be regarded as being associated with death were discovered. The authors considered that the cause of death could be ascribed to suffocation from oxygen deficiency. A similar case of asphyxiation following over-exposure to chlorodifluoromethane has also reported by Haba and Yamamoto (1985).

Several cases of death due to asphyxiation were also reported for workers in refrigeration repair. Unconsciousness and death following over-exposure to chlorodifluoromethanehas been have been reported by an anonymous source (1992). A further case report involved the death of a plumber who was believed to have been made unconscious following over-exposure to chlorodifluoromethane, leading to death by drowning in the water issuing from the pipes that were being worked on (Dal Grande et al.,1992). In another case study (Kintz et al., 1996), two individuals were overcome by chlorodifluoromethane resulting in their deaths (see 4.1.2.1.2 for a description of the scenario). Both victims were subjected to a post-mortem

examination, the findings being described as “unremarkable” with the exception of the presence of pulmonary oedema.

4.1.2.2.3 Cardiac sensitisation and other cardiac effects

Studies in animals

Chlorofluorcarbons have been known to sensitise the heart to adrenaline -induced arrhythmia (Reinhardt et al. 1971; Zakhari & Aviado 1982).

A summary of data on the cardiovascular effects of chlorodifluoromethane is reported on table 4.8.

Reinhardt et al. (1971) and Mullin (1975) assessed the ability of chlorodifluoromethane to induce cardiac sensitisation to adrenaline in groups of 12 beagle dogs exposed to either 25,000 or 50,000 ppm (87,500 or 175,000 mg/m^3) via a gas mask. After 5 minutes of exposure, a challenge injection of adrenaline (0.008 mg/kg) was given. No cardiac sensitisation was observed in dog exposed to 25,000 ppm (87,500 mg/m^3) chlorodifluoromethane. Two out of 12 animals exposed to 50,000 ppm (175,000 mg/m^3) did exhibit cardiac sensitisation.

The EC_{50} for the induction of cardiac sensitisation to adrenaline in 50 % of the dogs exposed for 5 minutes to chlorodifluoromethan, was determined to be 140,000 ppm (490,000 mg/m^3) (Clark & Tinston, 1982).

Aviado and Belej (1974) exposed anaesthetised Swiss mice to 200,000 ppm (700,000 mg/m^3) and 400,000 ppm (1400,000 mg/m^3) for 6 minutes via a face mask. The experiments were conducted either with adrenaline injection (0.006 mg/kg after 1 min of exposure) or without adrenaline injection. Arrhythmia was recorded only at the higher exposure level with adrenaline. Arrhythmia was also noted in cats exposed to 40% (400,000 ppm, 1400,000 mg/m^3) chlorodifluoromethane in air for 10 minutes and subsequent injection of 0.1 or 1 µg/kg adrenaline (Branch et al. 1990).

Other cardiac effects were observed. Belej et al. (1974) evaluated the effects of chlorodifluoromethane on the cardiovascular system of monkeys anaesthetised with pentobarbitone.
The compound was administered via a tracheal cannula at concentration of ca. 100,000 ppm (350,000 mg/m^3) and 200,000 ppm (700,000 mg/m^3) for 5 minutes. After that time, cardiac function was assessed. The only changes found were a slight but significant depression of myocardial contractility and a drop in aortic blood pressure in monkeys exposed to either concentrations.

Pantaleoni and Luzi (1975a,b) exposed rats at very high concentration (15, 30 and 60% in air) and measured various cardiac functions. Exposure to 300,000 to 593000 ppm (1050,000 to 2075500 mg/m^3) in air of chlorodifluoromethane for 2 minutes produced a decrease in heart rate, decrease in cardiac contractile strength followed by a decrease in carotid pressure, arterial hypotension and changes in ECG.

In both experiments, the parameters returned to normal within 2 minutes of breathing normal air.

Table 4.8 Cardiovascular function studies

Species	Concentration ppm	Duration minutes	Effects	References
Cardiac sensitisation				
Dog	50,000	5	Lowest concentration causing cardiac sensitisation with exogenous adrenaline	Mullin, 1975
	50,000 25,000	5	Cardiac sensitisation with exogenous adrenaline No effects with exogenous adrenaline	Reinhardt et al., 1971
	140,000	5	EC50 for cardiac sensitisation with exogenous adrenaline	Clark & Tinston 1982
Other cardiac effects				
Mouse	200,000 400,000	6	No arrhythmia with or without exogenous adrenaline Arrhythmia seen only with exogenous adrenaline	Aviado & Belej 1974
Rat	300,000-593000	2	Decreased heart rate and changes in ECG	Pantaleoni & Luzi 1975 a
	300,000-593000	2	Decreased myocardial contractility, ECG changes and arterial hypotension	Pantaleoni & Luzi 1975 b
Monkey	100,000 200,000	5	Depression of myocardial contractility Decreased aortic blood pressure	Belej et al. 1974

Human data

Based on animal data, and like many other fluorocarbons, cardiac sensitization is a potential hazard for human exposed at extremely high concentration. However no clear case of cardiac sensitisation has been reported in human.

Other cardiac effects (palpitations or other cardiac rhythm changes) have been reported. However, no clear evidence of association has been shown between the effects and the exposure (Speizer et al., 1975; Antti-Poika et al., 1990; Edling et al., 1990).

Several cases of acute intoxication from intentional inhalation abuse have been reported. One case was reported in which a young boy was found dead in a small room with his mouth around the nozzle of a tank of chlorodifluoromethane (Garriot and Petty, 1980). In another case, a young person (16-years of age) intentionally inhaled propellant from an aerosol container that also contained aluminium phenylsulfonate as an anti-perspirant (Kamm, 1975). Autopsy findings revealed generalized tissue congestion and edema with death due to ventricular fibrillation.

4.1.2.2.4 Other effects

Chlorodifluoromethane was tested by Aviado & Smith (1974) in one anaesthetised monkey. The animal was anaesthetised by intravenous injection of 30 mg/kg sodium pentobarbital and the trachea was cannulated. Electrocardiogram measurements and femoral arterial blood pressure were recorded. Pulmonary airway resistance and compliance were estimated from measurements of tracheal air flow and transpulmonary pressure. On exposure to 200,000 ppm (700,000 mg/m^3) chlorodifluoromethane there was no significant change in pulmonary resistance, pulmonary compliance, heart rate or aortic blood pressure. At 200,000 ppm (700,000 mg/m^3) the only change noted was a slight, yet significant elevation in pulmonary resistance.

4.1.2.2.5 Summary of acute toxicity

Chlorodifluoromethane has an extremely low order of acute toxicity by the inhalation route. Despite the variety of conditions used and the different laboratories involved, there is a consistency between the effects seen in the different animal species. The primary toxic effect following acute inhalation of chlorodifluoromethane was central nervous system depression, which occurred only at extremely high concentrations.

The oral and dermal routes of exposure are not significant for chlorodifluoromethane. No informative studies of its acute toxicity by these routes have been reported.

As with many other fluorocarbons chlorodifluoromethane causes cardiac sensitisation in animal testings, but only at extremely high acute exposure concentration. The threshold concentration for inducing cardiac sensitisation to adrenaline in dogs is 50,000 ppm (175,000 mg/m^3) and the NOAEC is 25,000 ppm (87,500 mg/m^3). At very high concentrations, respiratory effects have also been noted in animal testing.

The available data on acute toxicity can be summarized as follows:

Mortality: LC50/4h/rat = 219,000 ppm (766,500 mg/m^3); LOAEC/2h/rat = 297,000 ppm (1050,000 mg/m^3).
Cardiac sensitisation in dog: LOAEC in dog = 50,000 ppm (175,000 mg/m^3) and NOAEC = 25,000 ppm (87,500 mg/m^3).
The overall **NOAEC** for acute toxicity is 25,000 ppm (**87,500 mg/m^3**) and the overall LOAEC is 50,000 ppm (**175,000 mg/m^3**).

4.1.2.3 Irritation

4.1.2.3.1 Skin irritation

As chlorodifluoromethane is a gas at room temperature, it has not been tested as such in a skin irritation assay. However, the results from the acute and repeated dose inhalation toxicity studies did not show any indication of skin irritation during clinical observations of the animals exposed to very high concentrations.
As liquefied form, chlorodifluoromethane has been tested in a rabbit skin irritation test (Gonnet and Guillot, 1986) according to the protocol published in the J.O.R.F on 21.2.1982.
The test compound was applied (0.5 ml) under a polypropylene capsule for 24 hours to the intact and abraded skin of 6 rabbits. Assessment of erythema and edema were performed at

removal of the capsule and 48 h later corresponding to 24h and 72h after the application. The mean scores (24h+72h) for erythema and edema were 1.8 and 1.5 respectively, that do not meet the actual criteria for a classification as a skin irritant. The slight irritant effect was most probably caused by freezing of tissues due to the physical status of the gas rather than to the intrinsic irritation properties of chlorodifluoromethane.

Human data

Due to its liquefied form (under pressure), chlorodifluoromethane may induce skin frostbite in case of accidental skin contact.

Wegner et al. (1991) reported a case of severe frostbite following contact with chlorodifluoromethane liquid released from a pressurized container.

A 17-year old male attempted to get "high" breathing chlorodifluoromethane from a container. As a refigerant, chlorodifluoromethane has a cooling effect on evaporation. Instead of getting "high" the anesthetic properties of this substance caused him to fall asleep. He was found by his brother and taken to the hospital with severe facial frostbite and frostbite on his left hand. The frostbite on the face was so severe that he could not open his eyes and had to be intubated to maintain an airway. The patient recovered, but required skin grafting on his face (Kurbat et al., 1998).

However frostbite has to be considered as a physical hazard and not a toxicological response.

4.1.2.3.2 Eye irritation

Studies in animals

As chlorodifluoromethane is a gas at room temperature, it has not been tested as such in an eye irritation assay. The observations from the acute inhalation toxicity studies did show lacrymation only at very high concentrations, but no evidence of eye damage .

As liquefied form, chlorodifluoromethane has been tested in a rabbit eye irritation was performed by Gonnet and Guillot. (1986) according to the protocols published in the J.O.R.F. on 24.10.1984 and 9.2.1985.

Chlorodifluoromethane was sprayed in the form of a liquefied gas to the right eyes of 6 rabbits for 5 seconds in one assay and for 30 seconds in the second assay, with no rinsing.

Observations were scored after 1h, 24, and every day until day 7. In both assays, a slight chemosis and a slight redness was observed at 1h. These effects were partially reversible at 24h and no more present at 48h. The effects were a little bit more pronounced in the 30s spray assay. The mean scores (24h+48h+72h) were 0.27 for chemosis and 0.05 for edema respectively for the 30s spray assay.

Chlorodifluoromethane is considered to be only slightly irritant under these experimental conditions. The criteria for a classification as irritant to eyes are not met.

Human data

No reports of eye irritation observed in human exposed to chlorodifluoromethane are available. Due to its liquefied form (under pressure), chlorodifluoromethane may induce eye frostbite in case of accidental eye contact.

4.1.2.3.3 Respiratory tract irritation

Studies in animals

There is no indication of any irritant effect to the respiratory tractus in animal toxicity studies.

Human data

There is no case report of respiratory tractus irritation in human.

4.1.2.3.4 Summary of irritation

As chlorodifluoromethane is a gas at room temperature, it has not been tested as such in rabbit skin and eye irritation tests. However, the clinical observations during acute and/or repeated inhalation toxicity studies did not show any indication of skin irritation nor any evidence of eye damage. Only lacrymation was reported but at very high concentrations.

Chlorodifluoromethane, when applied as a liquefied gas, is very slightly irritant to eyes and slightly irritant to skin in rabbit assays. These irritant effects are mainly due to its liquefied form under pressure, causing tissue freezing. Such effects have been observed in accidental conditions in human.

However, as reported above, frostbite has to be considered as a physical hazard and not as toxicological response.

4.1.2.4 Corrosivity

As stated under chapters 4.1.2.3.1 to 4.1.2.3.4, chlorodifluoromethane has no corrosive properties.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

The skin sensitisation potential of chlorodifluoromethane was carried out in guinea pigs using a technique derived from the Magnusson and Kligman maximisation test (Gonnet and Guillot, 1986).

During the induction period the test compound was applied in liquefied conditions under a polypropylene capsule for 48 at the dose of 0.5 ml. At challenge the test compound was applied in the same condition at the dose of 0.25 ml. No vehicle was used.

Macroscopic and histological evaluation of skin reaction was scored up to 48 hours after removal of the occlusive capsule.

Under these experimental conditions, chlorodifluoromethane did not produce any cutaneous sensitising reaction.

Respiratory tract

No sensitisation effects on the respiratory track have been reported for HCFC-22.

4.1.2.5.2 Human data

Skin

There is no case report in humans exposed to chlorodifluoromethane.

Respiratory tract

There is no case report in humans exposed to chlorodifluoromethane.

4.1.2.5.3 Summary of sensitisation

Chlorodifluoromethane has no skin sensitising potential in experimental testing. There is no skin or respiratory sensitisation case reported in human.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

In vivo studies

Inhalation

Leuschner et al. (1983) did not observe any effects on ECG and circulatory function in dogs exposed to chlorodifluoromethane for 6/hour a day, 7 days a week for 90 days at 4940 ppm (17290 mg/m^3).

Eighty male and eighty female Alderley Park Swiss mice per group were exposed to concentrations of 0, (two groups) 1000, 10,000 or 50,000 ppm (0, 3500, 35,000, 175,000 mg/m^3) chlorodifluoromethane, 5 hr/d, 5 d/wk for up to 83 weeks (females) and 94 weeks (males).
The study was terminated at this time because mortality was approaching 80% in one of the exposed groups, the protocol specifying that the exposure should continue until mortality in any one group approached 80%. The mortality of each group of mice at the termination of the study is shown in Table 4.9.

Table 4.9. Mortality of mice exposed to chlorodifluoromethane following long-term repeated exposure by inhalation (Tinston et al., 1981a)

Sex	Week of termination	% Mortality in rats following long-term exposure to chlorodifluoromethane (ppm).				
		Control I	Control II	1000	10,000	50,000
Male	83	72.2	54.2	72.0	70.6	68.8

Female	93	55.0	63.3	68.0	73.5	75.0

At week 38, 10 mice per group were killed in order to perform blood and biochemical assays including red and white blood cell measurements, platelet count, prothrombin and kaolin-cephalin clotting times and bone marrow examination. Plasma ALT (alanine transaminase) and AST (aspartate transaminase) activity as well as urine analyses were also undertaken. The only consistent finding was hyperactivity in male mice exposed to 50,000 ppm chlorodifluoromethane. No effects were noted on mortality, body weight gain, haematology and biochemistry nor in histopathology. The No Observed Adverse Effect Concentration (NOAEC) for chlorodifluoromethane in this study was 10,000 ppm (35,000 mg/m^3). This study was conducted according to GLP (Tinston et al., 1981a).

Eighty male and eighty female Alderley Park rats per group were exposed to concentrations of 0, (two groups) 1000, 10,000 or 50,000 ppm chlorodifluoromethane (0, 3500, 35,000 or 175,000 mg/m^3), 5 hr/d, 5 d/wk for up to 117/118 weeks (females) and 130/131 weeks (males),. The study was terminated at this time because 80% mortality had been achieved in two of the exposed groups, the protocol specifying that exposure should continue until mortality in any one group reached 80%. Groups of 10 rats from each group were sacrificed during weeks 52 to 44 for interim analysis. The mortality of each group of rats at the termination of the study is shown in Table 4.10.

Table 4.10. Mortality of rats exposed to chlorodifluoromethane following long-term repeated exposure by inhalation (Tinston et al., 1981b)

Sex	**Week of termination.**	**% Mortality in rats following long-term exposure to chlorodifluoromethane (ppm and mg/m^3).**				
		Control I	Control II	1000 3500	10,000 35,000	50,000 175,000
Male	130/131	72.6	77.0	69.9	85.6	85.6
Female	117/118	77.0	62.7	67.0	77.1	71.7

The same investigations were done as for the mouse study. No clinical abnormalities, increased mortality or haematological or biochemical changes were attributed to chlorodifluoromethane at any exposure level. At the highest exposure level (50,000 ppm, 175,000 mg/m^3) there was a decrease in body-weight gain in males (up to week 80) and increased liver, kidney, adrenal and pituitary weights in the females. A number of non-neoplastic lesions were observed histologically in all groups but there was no evidence of an increased incidence due to chlorodifluoromethane. The No Observed Adverse Effect Concentration (NOAEC) for chlorodifluoromethane in this study was 10,000 ppm (35,000 mg/m^3). This study was conducted according to GLP (Tinston et al., 1981b).

Groups of rats, guinea-pigs, dogs and cats were exposed to 50,000 ppm (175,000 mg/m^3) chlorodifluoromethane by inhalation, 3.5 hr/d, 5 d/wk for 4 weeks. No effects were seen on body weight, haematology, urine analysis, organ weights or macroscopic and microscopic appearance of tissues (Weigand, 1971).

Groups of 16 male Sprague-Dawley rats were exposed to 0 (control) or 50,000 ppm (0 or 175,000 mg/m^3) chlorodifluoromethane for 5 hr/day for 8 weeks (Lee and Suzuki, 1981), after which six rats in each group were killed and blood and tissue samples taken for haematological and biochemical assays and for histopathological examination. The remaining animals were retained for a fertility study (see section 4.1.2.9.1). No signs of toxicity were apparent in the chlorodifluoromethane exposed animals and body weight was not affected. The weights of a range of organs were not significantly affected, although prostate weight was decreased slightly. No exposure-related histopathological lesions were found in any of the organs examined. Haematological parameters were unaffected but both plasma glucose and triglyceride levels were depressed and plasma cholesterol was slightly raised in the treated group.

Groups of 20 male and 20 female Sprague-Dawley rats and 3 male and 3 female beagle dogs were exposed whole-body to 10,000 and 5000 ppm (35,000 or 17,500 mg/m^3) chlorodifluoromethane (rats and dogs respectively) for 6 hr/d for 13 weeks (Leuschner et al., 1983). Clinical behaviour, body weight, haematology, clinical biochemistry, organ weights and histopathology were examined in both species and dogs were also subjected to ECG measurements and to examination of circulatory function. The clinical biochemistry examinations included assay for serum alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase activities. Histopathological examinations were undertaken on many tissues. No exposure-related effects were seen. The No-Observed-Effect Concentration (NOEC) for chlorodifluoromethane was at least 10,000 ppm (35,000 m/m^3) in the rat and 5000 (17500 mg/m^3) ppm in the dog.

In a limited experiment in rabbits designed to determine whether exposure for 5 hr/d, 5 d/wk for 8-12 weeks to 60,000 ppm (210,000 mg/m^3) chlorodifluoromethane might induce cardiac arrhythmia, only one out of 14 rabbits, which was also receiving sodium phenobarbital in the drinking water, developed an arrhythmia (Van Stee and McConnell, 1977). Since no controls were used, the value of this one observation is questionable.

The effects of chlorodifluoromethane were studied in rats (n=36), mice (n=30) and rabbits (n=7) exposed to 14,000 ppm and in rats (n=30) and mice (n=30) exposed to 2000 ppm (7000 mg/m^3) for 6 hr/d on 6 d/wk over a 10-month period. Body weights, oxygen consumption, "nerve function" and biochemical and haematological parameters were recorded and histopathological examination of some tissues was undertaken at termination of the test. Changes noted in the animals at 14000 ppm (49,000 mg/m^3) included depressed body weight gain in mice after 4-6 months, depressed oxygen consumption in the rat, "nerve function" changes in the rat and mouse, decreased haemoglobin concentration in the rabbit and histopathological (dystrophic) changes in the liver, lungs and nervous tissue. No effects due to chlorodifluoromethane were seen in rats or mice exposed to 2000 ppm (7000 mg/m^3) chlorodifluoromethane. None of the effects seen in rats and mice exposed to 14000 ppm (49000 mg/m^3) have been confirmed in subsequent studies even at much higher exposure levels (Karpov, 1963a)

In a separate study Karpov (1963b) exposed rats to 10,000 ppm (35,000 mg/m^3) chlorodifluoromethane for 6 hours/day for 63 days. No histopathological effects were observed.

Dermal

No studies of the effect of dermal administration of chlorodifluoromethane were available.

Oral

Chlorodifluoromethane was administered in drinking water to male and female rats for up to six months at doses equivalent to 0, 0.5, 1.5, 4.5 or 13.5 mg/kg bw/day. A total of 265 animals were used in this study, but the size of each dose group was not described. At 1, 3 and 6 months, the rats were examined for clinical pathological and pathological changes. A neurobehavioural assessment of the rats was made at the end of the study using a range of techniques.

Reduced body weight gain (about 28%) was reported in rats receiving 13.5 mg/kg chlorodifluoromethane. Their conditioned reflexes were also inhibited. This effect was manifested by a prolonged latency of the reflex reaction to the sound of a bell, and a reduced speed of training and reinforcement of a positive conditioned reflex. Dose-related haematological and clinical chemical changes were reported to have occurred, although it is not clear from the report that these changes occurred at all sampling periods. Hyperemia of internal organs and microscopic changes to the neurones (swelling, lysis of cell bodies, sclerosis) were reported in exposed rats. No effects were reported in rats receiving the low dose, 0.5 mg/kg, which was considered to be a NOAEC (Antonova et al., 1983).

Groups of 36 male and 36 female Alderley Park rats received 300 mg/kg chlorodifluoromethane by gavage in corn oil, 5 days/week for 52 weeks. Vehicle control groups of 36 males and 36 females received corn oil alone, and further control groups of 36 males and 36 females received no treatment. The study was terminated after 125 weeks. Chlorodifluoromethane had no effects on body weights or mortality (Longstaff et al., 1984; Longstaff, 1988).

4.1.2.6.2 Human data

In vivo studies

Inhalation

In a hospital pathology laboratory, aerosols of chlorodifluoromethane were used in the preparation of frozen sections. Following the death of one worker from myocardial infarction, others reported experiencing episodes of palpitations. A questionnaire survey was undertaken (Speizer et al., 1975), which concluded that there was an association between chlorodifluoromethane exposure and excess palpitation. However, reporting of such episodes is subjective and no comparable control group was examined. Estimation of exposure was made only from the number of frozen sections produced. The study therefore has low reliability.

A case of peripheral neuropathy in a refrigeration repair man prompted a survey of the health of refrigeration repair workers (Gunter et al., 1982; Campbell et al., 1986). A group of 27 refrigeration workers was studied. They were likely to have been exposed to chlorodifluoromethane, dichlorodifluoromethane and chloropentafluoroethane, and to their thermal degradation products including hydrogen chloride, hydrogen fluoride, phosgene, carbon dioxide and chlorine. A control group of 14 workers from allied trades with no

exposure to refrigerants was used. No cases of peripheral neuropathy were identified. Chest radiographs, pulmonary function tests, electrocardiograms and blood and urine results were all within normal limits. A questionnaire completed by all subjects indicated that lightheadedness and palpitations were more common in the refrigeration workers than in the unexposed controls. Again the study design was inadequate and no conclusions can be drawn from it.

A study of 539 refrigeration workers exposed to a combination of chlorofluorocarbons revealed 5 deaths due to cardiovascular disorders, compared to 9.63 expected. There were 6 deaths due to cancer versus 5.7 expected and 2 deaths from lung cancer versus 1.0 expected (Szmidt et al., 1981). The authors concluded that there was no association between exposure to chlorofluorocarbons and adverse health effects.

Dermal

No human data of repeated dose toxicity via the dermal route are available.

Oral

No human data of repeated dose toxicity via the oral route are available.

4.1.2.6.3 Summary of repeated dose toxicity

Two oral exposure studies have been conducted with chlorodifluoromethane, however since the potential risk for exposure to chlorodifluoromethane is by inhalation, oral exposure studies are considered of limited value for a risk assessment. Furthermore, these studies were poorly reported.

Several repeat-dose inhalation toxicity studies on chlorodifluoromethane have been conducted in a range of species, with durations ranging from 4 to 131 weeks. Rabbits, rats, guinea-pigs, dogs, cats and mice all reflected the generally low level of target organ toxicity shown by chlorodifluoromethane.

The most robust studies were conducted according to GLP standard in mice and rats, which were exposed to chlorodifluoromethane at concentrations up to 50,000 ppm until 80% mortality occurred for male and female mice and rats respectively. No organ-specific toxicity was identified in these studies at any exposure concentration. The overall No Observed Adverse-Effect Concentration (NOAEC) for repeated inhalation exposure of chlorodifluoromethane in long-term inhalation studies with rats and mice was **10,000 ppm** (**35,000 mg/m^3**) based on clinical signs of hyperactivity in mice and body weight changes in rats exposed, respectively, to 50,000 ppm.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies in vitro

A number of bacterial and yeast reverse and forward mutation in vitro assays have been performed (table 4.11). In assays performed under carefully controlled gaseous exposures Chlorodifluoromethane is mutagenic to *Salmonella typhimurium* strains TA1535 and TA100

in the presence and in the absence of an exogenous metabolic system (Longstaff and McGregor 1978, Bartsch 1980, Russell et al. 1980). Results were negative in tests using *Schizosaccharomyces pombe*, and *Saccharomyces cerevisiae* (Loprieno and Abbondandolo 1980). In tests with non-bacterial cells such as mutation induction at the *HGPRT* locus of Chinese hamster cells (CHO) (McCooey, 1980) or V-79 cells (Loprieno and Abbondandolo 1980) mutagenicity has not been demonstrated. No induction of unscheduled DNA synthesis was observed in the human EUE cell line (Loprieno and Abbondandolo 1980) and negative data were obtained in the BHK21 cell transformation assay (Longstaff, 1984)

4.1.2.7.2 Studies in vivo

On exposure of rats to chlorodifluoromethane for 6 hr/d for 5 days there was an apparent increase in chromosomal damage at the lowest exposure level of 1000 ppm (3500 mg/m^3). However, this was not observed at exposures of 10,000 and 150,000 ppm (35,000 and 525,000 mg/m^3) (Anderson et al., 1977). The experiment was repeated at 1000 ppm (3500 mg/m^3) and at the lower exposure levels of 10, 100 and 500 ppm (35, 350 and 1750 mg/m^3). Although there was an increase in chromosomal damage, it was again not exposure concentration related. In addition there were widely differing findings at the 1000 ppm (3500 mg/m^3) dose level between the two experiments (Anderson and Richardson, 1979).

An experiment in which chlorodifluoromethane was administered by gavage at a dose of 816 mg/kg in corn oil to CD1 mice to test for chromosomal changes in the bone marrow also gave negative results (Loprieno and Abbondandolo, 1980).

Using the mouse bone marrow micronucleus protocol, Howard et al. (1989) administered chlorodifluoromethane at concentrations up to 150,000 ppm (525,000 mg/m^3) for 6 hours together with concurrent positive (vinyl chloride) and negative (nitrogen) inhalation controls. No evidence of clastogenicity was found.

A dominant lethal assay in rats using exposures of 50,000 ppm (175,000 mg/m^3) chlorodifluoromethane, 5 hr/d for 8 weeks, gave no evidence of an effect due to exposure (Lee and Suzuki, 1981). In mice, two dominant lethal assays spanning dose levels of 10-100,000 ppm (35-350,000 mg/m^3) gave some statistically significant differences from control values. The results were not reproducible at the same dose levels in the two studies, nor was there evidence of a dose-response relationship. Overall it was concluded that chlorodifluoromethane did not exert a dominant lethal effect in these studies (Anderson et al., 1977; Hodge et al., 1979). All results are summarized in table 4.11.

Table 4.11 The genetic toxicology of chlorodifluoromethane in vitro and in vivo studies

ASSAY	STRAIN/TYPE	METABOLIC ACTIVATION	RESULT	COMMENT	REFERENCE
Schizosaccharomyces Pombe	Forward Mutation	+/- S-9	-ve	Tested as a gas	Loprieno & Abbondandolo (1980)
Saccharomyces Cerevisiae	Mitotic Gene Conversion	+/- S-9	-ve	Tested as a gas	Loprieno & Abbondandolo (1980)
Salmonella Typhimurium	TA1535, TA1538, TA98, TA100	+/- Arochlor induced rat liver S-9	S-9 independent +ve for strains TA1535, TA100	Incubated with 50% atmosphere of chlorodifluoromethane for 24 hrs	Longstaff & McGregor (1978)
Salmonella Typhimurium	TA100	+/- Phenobarbitone or Aroclor induced rat liver S-9	+ve	Tested as a gas 50% for 24 hrs	Bartsch et al. (1980)
Salmonella Typhimurium	TA100 TA1535	+/- Auxiliary metabolising systems	unrepeatable +ve in strain TA1535	6 hr exposure up to 40% chlorodifluoromethane. 32 hr to air. Result not considered biologically significant.	Butterworth (1976)
Salmonella typhimurium	TA100 TA1535	+/- Auxiliary metabolising systems	S-9 independent +ve for strains TA1535, TA100	48 hr exposure to up to 40% chlorodifluoromethane	Russel et al. (1980) Krahn (1977)
Salmonella Typhimurium	Not stated	Not stated	-ve	Liquid suspension protocol. Flasks gassed and maintained for 2 hrs.	Russel et al. (1980)
Host mediated assay – mouse	Sc. pombe or S. cerevisiae	-	-ve		Loprieno and Abbondandolo (1980)
Chinese Hamster Cell (CHO) – mutation	HGPRT locus	+/- metabolic activation	-ve	Tested as a gas at 0, 33, 67 and 100% atmospheres	MCooey (1980)
Chinese Hamster V-79 – mutation	HGPRT local	+/- S-9	-ve		Loprieno and Abbondandolo (1980)
Unscheduled DNA synthesis	Human Hetherploid EUE cell line	-	-ve		Loprieno and Abbondandolo (1980)
Rat	Dominant lethal	175,000 5 hrs/day for 8 weeks	-ve		Lee & Suzuki (1981)
Mouse	Cytogenetics bone marrow	816 mg/kg in corn oil, gavage	-ve		Loprieno & Abbondandolo (1980)

- ve = negative - + ve =positive

4.1.2.7.3 Summary of mutagenicity

Chlorodifluoromethane exerts some mutagenic activity in some bacterial strains.

HCFC 22 was not active in the three studies using yeast (Schizosaccharomyces Pombe and Saccharomyces Cerevisiae). It was not active in the three studies conducted using mammalian cell cultures (CHO cell HGPRT, V-79 HGPRT and unscheduled DNA synthesis). It was also not active in two in vivo studies (rat dominant lethal and mouse cytogenetics). It only showed limited activity in TA 1535 and TA 100 in 3 of 5 Ames assays. This activity was independent of the S-9. It did not show any activity with TA 1538 and TA 98. Taking all of this data into account, there is strong support for the conclusion of Litchfield and Longstaff (1984), that this activity appears to be the result of a bacterial specific metabolism.

The in vivo cytogenetic and dominant lethal studies in the rat and mouse provide no evidence of consistent or dose-related genotoxic activity. Taken with the negative result of the inhalation micronucleus test, the findings indicate that chlorodifluoromethane does not possess genotoxic activity in vivo.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

In vivo studies

Inhalation

Maltoni et al., (1982, 1988) exposed groups of 60 male and 60 female Sprague-Dawley rats and Swiss mice to chlorodifluoromethane by inhalation of atmospheric concentrations of 0, 1000 or 5000 ppm. Exposure was 4 hr/d, 5 d/wk for 104 weeks (rats) or 78 weeks (mice). No compound-related effects were observed.

In another study (Litchfield and Longstaff, 1984), groups of 80 male and 80 female Alderley Park, Wistar-derived rats were exposed to chlorodifluoromethane by inhalation of concentrations of 0 (two groups), 1000, 10,000 or 50,000 ppm for 5 hr/d, 5 d/wk for 118 weeks in females and 131 weeks for males by which time mortality had reached approximately 80% in at least one group (see Table 4.12 for details).

Table 4.12 Mortality at 104 weeks and at the end of the study

Males

	Exposure concentration of CFC (ppm)				
Week	0	0	1000	10,000	50,000
104	35.1	36.9	31.2	40.9	32.5
131	72.6	77.0	69.9	85.6	85.6

Females

	Exposure concentration of CFC (ppm)				
Week	0	0	1000	10,000	50,000
104	48.3	42.6	45.4	61.3	56.1
118	77.0	62.7	67.0	77.1	71.7

No clinical abnormalities, increased mortality or haematological or biochemical changes due to chlorodifluoromethane were observed at any dose level. The only abnormalities were a body weight reduction in males exposed to 50,000 ppm (175,000 mg/m^3) (up to week 80) and increased liver, kidney, adrenal and pituitary weights in females. In males there was no increase in the number of benign tumours but there was a slight increase in the number of animals bearing malignant tumours, and this increase was primarily due to an increased incidence of animals bearing fibrosarcomas (table 4.13). The only site that was consistently associated with this increase was the salivary gland, but the authors state that it was difficult to identify the origin of the tumours, which may have been generalized subcutaneous fibrosarcomas developing at submandibular site and involving the salivary gland only by chance. The increase in fibrosarcomas was observed only in the late stages of the study. One was observed in the group of male rats that died between weeks 53 and 104, the other 6 occurred in rats that died between weeks 105 and the study termination. The increase in the overall incidence of fibrosarcomas in the 50,000 ppm male rats was found to be "statistically significant", although the original study does not report a p value. Four male rats in the 50,000 ppm (175,000 mg/m^3) group were found to have Zymbal gland tumours; however, they could not be distinguished from squamous cell carcinomas of the ear canal. In addition, significant increases in squamous cell carcinomas of the skin were observed in male rats treated with high doses: 5 and 4 such tumours arose in the 10,000 and 50,000 ppm groups, respectively, while the control and lowest dose groups showed none. Most squamous cell carcinomas (4 of 5 and 3 of 4 in the 10,000 and 50,000 ppm groups, respectively) were observed late in the study, between week 105 and study termination. Females did not exhibit a significant increase in any tumour type in any of the exposure groups.

Table 4.13 Incidence of fibrosarcomas in male rats exposed to Chlorodifluoromethane

Dose (ppm)	**Incidence of Fibrosarcomas**		
	Examined	**Total**	**Involving Salivary gland**
0	80	5	1
0	80	7	0
1000	80	8	1
10,000	80	5	0
50,000	80	18	7

From Litchfield and Longstaff, 1984

In an analogous mouse study (Tinston et al., 1981a; Litchfield and Longstaff, 1984), groups of 80 male and 80 female Alderley Park Swiss derived mice were exposed to chlorodifluoromethane by inhalation at levels of 0, (two groups), 1000, 10,000 or 50,000 ppm (3500, 35,000 or 175,000 mg/m^3). Exposures were 5 hr/d, 5 d/wk for up to 83 weeks (males) or 94 weeks (females). At these times the mortality rate was approximately 80%. The only finding which could consistently be related to exposure was hyperactivity in mice in the 50,000 ppm (175,000 mg/m^3) group. There were no significant increases in the incidences of benign or

malignant tumours in treated male or female mice compared to controls. There was a small increase in the incidence of liver nodules in males receiving 50,000 ppm (175,000 mg/m^3) but this was within the range of historical control values for the Alderley Park Swiss derived mouse.

Dermal

No carcinogenicity studies via the dermal route are available.

Oral

No carcinogenicity studies via the oral route are available.

4.1.2.8.2 Human data

The limited epidemiological investigation available does not show evidence of an increase in the cancer incidence in people occupationally exposed to chlorodifluoromethane in the refrigeration industry.
A study was conducted on 539 refrigeration workers exposed to a combination of chlorofluorocarbons. There were 6 deaths due to cancer compared to 5.7 expected of which two deaths due to lung cancer compared to 1 expected. (Szmidt et. al. 1981). The authors concluded that the study failed to show an association between exposure to chlorofluorocarbons and adverse health effects (see: Szmidt et al. 1981)

4.1.2.8.3 Summary of carcinogenicity

The animal studies provide limited evidence for the carcinogenicity of chlorodifluoromethane in rats only. In one rat inhalation study, increases in the incidence of fibrosarcomas at different sites and squamous cell carcinomas of the skin were noted in male animals at the highest doses. A significant incidence of Zymbal gland squamous cell carcinomas was also observed in male rats at 50,000 ppm, even though they could not be distinguished with certainty from squamous cell carcinomas of the ear canal. In the latter case, however, they would further increase the number and significance of total squamous cell carcinomas. These observations are somewhat mitigated by the occurrence of significant tumor increases in male rats only. In addition, most tumors appeared beyond week 105 of the study.
A clear **NOAEC** of **1000 ppm** (**3500 mg/m^3**) was demonstrated in the male rats. No increased tumor incidence attributable to chlorodifluoromethane exposure was diagnosed in female rats or in mice of either sex.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Studies in animals

No dedicated reproduction study has been undertaken. However, repeated dose studies in a number of species, of durations from 8 weeks to 2 years, have examined the reproductive organs of both males and females. No changes in gonadal organ weights were reported and

histopathological examination showed no effects in either male or female reproductive organs from exposure to chlorodifluoromethane.

The effects of chlorodifluoromethane on male reproduction were assessed in rats and in mice.
Lee and Suzuki (1981) exposed 16 male Sprague-Dawley (CD strain) rats to chlorodifluoromethane by inhalation at a concentration of 50,000 ppm (175,000 mg/m^3), 5h/day for 8 weeks. A control group of the same size was exposed to filtered air under identical conditions. At the end of the 8-week period, 6 rats from each group were sacrificed for organ examinations (weight and histology) and blood haemato-biochemical examinations. The remaining 10 animals had a blood sample taken immediately after the last exposure day for follicle stimulating hormone (FSH) and luteinizing hormone (LH) analysis. These rats were then engaged in serial matings to assess reproductive outcome and, as a consequence, male fertility. Each male was housed singly with a virgin female for 7 days. After the seven day period, the female rats were replaced by other virgin females and this regime was followed for a 10 week period. 9 days after removal from the male, each female was sacrificed and examined for gestation parameters (number of corpora lutea and implants).
The weights and histological aspects of the major organs of the chlorodifluoromethane-exposed male rats, including testes, epididymes and seminal vesicles, did not differ from those of control rats except for the prostate and coagulating gland whose weights were slightly lower relative to brain weights but without any histological alteration. Moreover, prostatic fructose and acid phosphatase levels were unaltered. FSH and LH were not different in exposed and control male rats. There were no statistically significant differences between exposed and control animals regarding mating behaviour, number of corpora lutea, implantation numbers, dead implants.

Thus, the study demonstrated that male reproduction was not affected but for a slight effect on sex accessory gland at 50,000 ppm, and that no dominant lethal or teratological effects were present due to chlorodifluoromethane exposure throughout the entire spermatogenic cycle of male Sprague-Dawley-CD rats. These results were consistent with FSH and LH levels and with testicular examination. Since a single dose group was tested, a NOEC can not be derived. The dose level of 50,000 consequently may be therefore considered as a marginal LOEC.

Anderson et al. (1977) and Hodge et al. (1979) conducted two Dominant lethal assays in mice (see section 4.1.2.7). Groups of 20 CD-1 fertile male mice were exposed to chlorodifluoromethane at concentrations ranging from 10 to 100,000 ppm (35 to 350,000 mg/m^3), 6h/d for 5 days. After dosing these males were mated with two virgin females each week over an eight week period.
Overall, there was no evidence of a reproducible reduction of male fertility, which remained high throughout the two experiments as measured by the number of successfully mating males and number of pregnant females.

4.1.2.9.2 Developmental toxicity

Studies in animals

The developmental effects of chlorodifluoromethane were assessed in a rabbit teratogenicity assay and in a particularly large number of rat teratogenicity studies.

Palmer et al., (1978a) exposed groups of 14 to 16 New-Zealand albino female rabbits to chlorodifluoromethane concentrations of 0 (air control), 100, 1000 or 50,000 ppm (0, 350,

3500 or 175,000 mg/m^3) for 6h/d during days 6 to 18 of pregnancy inclusive. Animals were sacrificed on day 29 of pregnancy, litter values determined and foetuses examined for major malformations (teratogenic effects), minor anomalies and skeletal variants.
Among parent animals there were no clinical signs of toxicity or treatment related mortalities and pregnancy was normal. In rabbits exposed to 50,000 ppm (175,000 mg/m^3) chlorodifluoromethane, slight weight loss occurred during the first four days of exposure but, thereafter, weight gains were comparable with those of the controls. Litter size, post-implantation loss, litter weights and mean foetal weights were not significantly affected by exposure to chlorodifluoromethane exposure. There were two major malformations in the same litter from dams exposed to 1000 ppm (3500 mg/m^3) chlorodifluoromethane. One foetus showed cebocephaly, bilateral microphthalmia, unilateral lenticular cataract and folded retina; a second foetus showed unilateral lenticular cataract and folded retina. One major malformation was seen in the control group, a foetus showing cebocephaly. No major malformations were seen in the low and high level groups. The incidences of minor anomalies and skeletal variants were lower in all test groups than among controls. Due to lack of dose-effect relationships, all findings are likely to be coincidental and not treatment related.

A series of 3 conventional rat teratogenicity studies of conventional size have been conducted on chlorodifluoromethane (Culik et al., 1976; Culik and Crowe, 1978). Groups of 20 to 40 pregnant Sprague-Dawley CD rats were exposed to chlorodifluoromethane at various concentrations ranging from 100 ppm to 20,000 ppm (350 to 70,000 mg/m^3) for 6h/d either from day 4 to 13 or from day 6 to 15 of gestation. There was no evidence of maternal or foetal overt toxicity in any of the exposed dams or their offspring. No teratogenic abnormalities were found except for a few cases of anophthalmia or microphthalmia in some groups but with no dose-relationship trend (See study 1-3 results in table 4.9). None of the individual group incidences were statistically significant. The NOAEC for both maternal and developmental toxicity in two of these studies was 10,000 ppm (35,000 mg/m^3) and, in the third, was 20,000 ppm (70,000 mg/m^3).

The observation of a very low incidence of anophthalmia and microphthalmia in the conventional studies led to the decision to conduct a further teratogenicity study on the same strain of rats in another laboratory (ECETOC 1989; IPCS, 1991). This study was conducted in a very large number of rats (equivalent to 19 times the normal group size) and was designed to improve the sensitivity of the study to investigate the significance of the low incidence of anophthalmia and microphthalmia (Palmer et al., 1978b). The study was not designed to determine the NOAEC for any significant finding of developmental toxicity, hence the large spread between the exposure levels selected in the study.

In this study, female pregnant Sprague-Dawley CD rats were exposed to concentrations of 100, 1000 and 50,000 ppm (350, 3500 and 175,000 mg/m^3) chlorodifluoromethane for 6h/d from day 6 to 15 of gestation. On day 20 of pregnancy foetuses were delivered by hysterectomy and subsequently the heads of all foetuses were sectioned and the incidence of anophthalmia and microphthalmia determined. Nineteen batches of timed mated females were employed over a one year period. More than 6000 control foetuses and more than 4000 foetuses from each test group were available for examination. Among the dams no apparent adverse effects were reported except for a slightly but consistently lower body weight gain in those exposed to 50,000 ppm (175,000 mg/m^3) chlorodifluoromethane compared to their respective control groups in the 19 batches. This effect was not quantified in the study report, but the mean reduction in bodyweight gain for high dose dams with viable young versus control has been calculated to be 6.8% across the 19 batches (with a range of -0.2 to 16.5%).

Taking only the critical period for eye development from days 6 to 10, there was a much greater reduction in bodyweight gain in the high dose dams. For this time period there was a mean reduction in bodyweight gain of 42.4% (with a range of –13.5 to 86.2%). However, there was no clear correlation between incidence of eye defects and individual maternal bodyweight gain. No effects on body weight gain were observed in the dams exposed to 1000 or 100 ppm (3500 or 350 mg/m^3) chlorodifluoromethane.

For all groups in all batches, litter parameters for the control groups were within the laboratory standard range. In most batches of litters from exposed dams, litter size, post-implantation loss, litter weight and, except for those dams exposed at 50,000 ppm (175,000 mg/m^3) chlorodifluoromethane, mean foetal weight did not differ significantly from concurrent control values. In litters from dams exposed to 50,000 ppm (175,000 mg/m^3) mean foetal weight was slightly lower than concurrent controls in 12 batches. Incidences of obvious abnormalities, other than those in the eyes, were not statistically significant in any of the exposed groups. A statistically significant increase of anophthalmia and combined anophthalmia+microphthalmia was seen in the offspring of dams exposed to 50,000 ppm (175,000 mg/m^3) chlorodifluoromethane but not from those exposed to 1000 or 100 ppm (3500 or 350 mg/m^3) (see study 4 results in the table 4.14). The intergroup differences in the incidence of microphthalmia were not significant.

The results of the large replicate study (Palmer et al., 1978b) were compared with the data of rats of the same strain in the same laboratory in the 10 year period following the chlorodifluoromethane experiment (ECETOC, 1989). More than 15,000 litters were arranged into 9 sets of similar size to those in the chlorodifluoromethane study and in a chronological progression, allowing for the examination of eye anomalies from approximately 4000 foetuses per group in each set. A significantly increased incidence of anophthalmia (1.6% in litters of treated group vs 0.16% in controls) and combined anophthalmia+microphthalmia (2.6% in litters treated group vs 0.5% in controls) was present in the offsprings of dams exposed to 50,000 ppm. The historical controls showed from 0 to 0.8% of incidence of anophthalmia and from 0 to 2.6% of incidence of anophthalmia+microphthalmia per litters.
This very large study, which was conducted to resolve the significance of the very low and random incidences of anophthalmia and microphthalmia seen in earlier studies, has shown an increased incidence of these malformations in the offspring of dams exposed to 50,000 ppm (175,000 mg/m^3), but not 1000 ppm (35,000 mg/m^3) chlorodifluoromethane. In addition, at 50,000 ppm (175,000 mg/m^3), a high concentration corresponding to 25% of the 4h-LC50 in rats, chlorodifluoromethane was shown to cause both maternal and foetal toxicity.
Nevertheless, the incidence of anophthalmia in the large study is higher than in the historical controls and the incidence of anophthalmia+microphthalmia is comparable to the upper limit of historical controls. Maternal toxicity at 50,000 ppm is related only to slight reduction of body weight gain, in fact no other adverse effect was recorded. Due to the high specificity of this kind of malformations (anophthalmia and anophthalmia+microphthalmia) in laboratory animals, it is unlikely that they are related to maternal toxicity.

When taking all of the available information in the rat from the conventional studies and the very large study, it can be concluded that the NOAEC for developmental toxicity is 1000 ppm (3500 mg/m^3), irrespective of whether one concludes that the effect seen in the offspring of rats exposed to 50,000 (175,000 mg/m^3) is exposure-related or not.

Table 4.14 Eye malformations in rat teratogenicity studies conducted on chlorodifluoromethane

Conc.	Eye defect	Study 1 Culick et al. (1976)		Study 2 Culick et al. (1976)		Study 3 Culick and Crowe (1978)		Study 4 Palmer et al. (1978b)	
		/ litters	/ foetuses	/ litters	/ foetuses	/ litters	/ foetuses	/ litters	/ foetuses
Current control	**A**	**0**/*21*		**0**/*34*		**0**/*38*		**1**/607	**1**/*6348*
	M	**0**/*21*		**0**/*34*		**0**/*38*		**2**/607	**2**/*6348*
	A+M	**0**/*21*		**0**/*34*		**0**/*38*		**3**/607	**3**/*6348*
100 ppm	**A**					**0**/*40*		**1**/395	**1**/*4216*
	M					**1**/*40*		**4**/395	**4**/*4216*
	A+M					**1**/*40*		**5**/395	**5**/*4216*
300 ppm	**A**					**0**/*35*			
	M					**0**/*35*			
	A+M					**0**/*35*			
500 ppm	**A**			**0**/*33*					
	M			**1**/*33*					
	A+M			**1**/*33*					
1000 ppm	**A**	**1**/*22*		**1**/33				**1**/390	**1**/*4111*
	M	**1**/*22*		**2**/33				**2**/390	**2**/*4111*
	A+M	**1**/*22*		**2**/33				**3**/390	**3**/*4111*
10,000 ppm	**A**	**2**/*21*				**0**/*34*			
	M	**0**/*21*				**2**/*34*			
	A+M	**2**/*21*				**2**/*34*			
20,000 ppm	**A**			**1**/*35*					
	M			**0**/*35*					
	A+M			**1**/*35*					
50,000 ppm	**A**							**6**/383(+)	**6**/*4031*
	M							**4**/383	**4**/*4031*
	A+M							**10**/383(+)	**10**/*4031*
Historical control	**A**							**0**/350 to **3**/373 **	**0**/*3682* to **3**/3795 **
	M							**0**/350 to **8**/386 **	**0**/*3682* to **8**/*4123* **
	A+M	(**1**/*100-200*)	(**1**/*1000-2000*)*	(**1**/*100-200*)	(**1**/*1000-2000*)*	(**1**/*100-200*)*	(**1**/*1000-2000*)*	**0**/350 to **10**/386 **	**0**/*3682* to **10**/*4123* **

Number of anophthalmia + microphthalmia/ total number of foetuses per group (from ECETOC, 1989 and IPCS, 1991)

A Anophthalmia

M Microphthalmia

A+M Anophthalmia plus Microphthalmia

*approximately from 100-200 litters

** (over a 10 year period post chlorodifluoromethane experiment)

(+): statistically significant from control group (P<0.05), statistical analysis performed using litters only.

Human data

There were no data located on effects of chlorodifluoromethane on human reproduction.

4.1.2.9.3 Summary of toxicity for reproduction

Fertility was not affected by chlorodifluoromethane in male rats and mice. Developmental toxicity was not demonstrated in rabbits. The chlorodifluoromethane showed a significantly increased incidence of anophthalmia (1.6% in litters of treated group vs 0.16% in controls) and combined anophthalmia+microphthalmia (2.6% in litters treated group vs 0.5% in controls) in the offsprings of dams exposed to 50,000 ppm. The historical controls showed from 0 to 0.8% of incidence of anophthalmia and from 0 to 2.6% of incidence of anophthalmia+microphthalmia per litters. Therefore the incidence of anophthalmia in the large study is higher than in the historical controls and the incidence of anophthalmia+microphthalmia is comparable to the upper limit of historical controls. Maternal toxicity at 50,000 ppm is related only to slight reduction of body weight gain, in fact no other adverse effect was recorded. Due to the high specificity of this kind of malformations (anophthalmia and anophthalmia+microphthalmia) in laboratory animals, it is unlikely that they are related to maternal toxicity.
Therefore the NOAEC for developmental toxicity in the rat is considered 1000 ppm (3500 mg/m3).
Moreover, since a low rate of specific malformations was evident in presence of slight maternal toxicity, this could justify a classification of chlorodifluoromethane in cat 3 (harmful for reproduction) with the risk phrase R63.

Note: The use of the NOAEC of 1000 ppm from the Palmer study (Palmer, 1978b) has been considered as a very conservative approach. Indeed no adverse effects were observed in the study of Culik and Crowe (1978) up to 20,000 ppm. This will be taken into account in the risk characterisation section.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Because chlorodifluoromethane is a gas (boiling point -40.8ºC) and is only moderately soluble in water and has a high Henry's constant, its potential effects on mammalian health have been almost exclusively studied using the inhalation route. Although dermal penetration and oral ingestion cannot be totally excluded, they appear as minor routes of entry in the organism.
Exposure has been evaluated only for workers, since HCFC 22 is used only as a chemical intermediate and as a refrigerant mainly in large refrigeration units. Therefore, consumers' exposure is possible only in accidental cases.
The studies in animals show that chlorodifluoromethane is rapidly absorbed into the blood stream by the inhalation route of administration. It is not metabolised to any significant extent and is eliminated unchanged in the exhaled air. A similar profile is seen in humans.

In over 50 years of use of chlorodifluoromethane, there have been only few reports on adverse health effects, all due to accidental exposure to extremely high inhaled levels. The results from extensive toxicity testing in animals lead to the definition of very high NO(A)ELs for some of the endpoints (table 4.15).

Table 4.15 Summary of effects

Substance name	Inhalation (N(L)OAEL)	Dermal (N(L)OAEL)	Oral (N(L)OAEL)
Acute toxicity	NOAEC: 25,000 ppm (87,500 mg/m^3) LOAEC: 50,000 ppm (175,000 mg/m^3)	NR	NR
Irritation / corrosivity	NR	NR	NR
Sensitization	NR	NR	NR
Repeated dose toxicity (local)	NR	NR	NR
Repeated dose toxicity (systemic)	NOAEC: 10,000 ppm (35,000 mg/m^3)	NR	NR
Mutagenicity	NR	NR	NR
Carcinogenicity	NOAEC: 1000 ppm (3500 mg/m^3)	NR	NR
Fertility impairment	NR	NR	NR
Developmental toxicity	NOAEC: 1000 ppm (3500 mg/m^3)	NR	NR

NR: not relevant

The human health section covers the health related effect from direct and indirect exposure to chlorodifluoromethane. As regulation concerning the ozone depleting potential of the substance is in place, it is not the intention of this risk assessment report to cover the indirect human health effects from increased UV-radiation caused by the stratospheric ozone layer depleting potential of the substance

4.1.3.2 Workers

It is estimated that a few hundred workers in the EU are potentially exposed to chlorodifluoromethane during its production, storage and transport. Exposure is possible only by the inhalation route.
The number of workers potentially in contact in the refrigeration sector, the main use of chlorodifluoromethane, is estimated to be around 10,000. Some measured data are available (4.1.1.2.3). Exposure levels in the use as chemical intermediate are similar to those in production (table 4.3).
Exposure levels have been defined for various scenarios with measured and modelled data, both for acute and for long term exposure (table 4.4). These values and the NO(A)EC for the relevant endpoints are used to derive a MOS.

4.1.3.2.1 Acute toxicity

Chlorodifluoromethane has a low order of acute toxicity in all animal species. The 4-hour inhalation LC50 in rats was found to be as high as 219000 ppm (766500 mg/m^3). The main toxic effect associated with inhalation exposure to chlorodifluoromethane is central nervous system depression. Animal exposure to very high concentrations causes narcosis, tremor, convulsions and shallow respiration. As with other halocarbons, the sensitivity of the heart to the arrhythmogenic effects of catecholamines (e.g. adrenaline released during the stress response) can be increased during exposure to high concentrations of chlorodifluoromethane. The threshold for this cardiac sensitising effect in dogs is about 50,000 ppm (175,000 mg/m^3) and the NOAEC is 25,000 ppm (87,500 mg/m^3 – NOAEC for cardiac sensitization in dog).

This 87,500 mg/m^3 value is retained as overall NOAEC and compared to short term exposure values available for the different scenarios (table 4.16).
Accidental human exposures to very high concentrations following a massive leak of chlorodifluoromethane gas from refrigeration facilities in confined areas have caused fatalities which have been attributed to asphyxiation.
Because very large concentrations of chlorodifluoromethane in air are necessary to induce acute adverse effects to health, potential risks are associated only with major accidental situations.

The minimal MOS is derived taking into account the following Assessment Factor:

1. a factor of 3 for interspecies variations
2. a factor of 3 for intraspecies variations

Hence the calculated minimal MOS is 9 (3 x 3)

Conclusion ii for acute toxicity

Table 4.16 Occupational risk assessment for acute toxicity

Minimal MOS	Inhalation				Dermal				Combined			
9	**Exposure**	**NOAEC**	**MOS**	**Conclusion**	**Exposure**	**NOAEC**	**MOS**	**Conclusion**	**Exposure**	**NOAEC**	**MOS**	**Conclusion**
Production												
Subscenario 1 Normal activity	NR				NR				NR			
Subscenario 2 Maintenance	126. 7 mg/m^3	87,500 mg/m^3	690	ii	NR				NR			
Subscenario 3 Packaging/filling	126.7 mg/m^3	87,500 mg/m^3	690	ii	NR				NR			
Subscenario 4 Sampling/lab	49.7 mg/m^3	87,500 mg/m^3	1760	ii	NR				NR			
Formulation												
Subscenario 1	NR				NR				NR			
Uses												
Subscenario 1 Use as a refrigerant	2027 mg/m^3	87,500 mg/m^3	43.2	ii	NR				NR			
Subscenario 2 Use as an intermediate	NR				NR				NR			

NR: not relevant

4.1.3.2.2 Irritation and corrosivity

Chlorodifluoromethane gas induces very weak or no irritating effects on skin and eyes in experimental testings. However contact with the liquefied gas may cause frost-bite due to local freezing induced by the rapid evaporation of the material.

4.1.3.2.3 Sensitisation

Skin

Chlorodifluoromethane is not reported as a skin sensitizer.

Respiratory tract

It is very unlikely that chlorodifluoromethane has any respiratory sensitising potential.

4.1.3.2.4 Repeated dose toxicity

Experience with human repeated exposure and the single epidemiology study available do not report consistent findings either on the heart or on the nervous system. In experimental animals there was no specific organ toxicity identified in relation to repeated exposure to several animal species. High concentrations tended to induce narcotic effects. These effects were confined to the inhalation exposure periods and were reversible after the animals were removed from the exposure chambers.
By the inhalation route a NOAEC of 10,000 ppm (35,000 mg/m^3) was established in rats exposed for 2 years and mice exposed for 1½ year (5h/day, 5d/week).
By the oral route chlorodifluoromethane dissolved in corn oil, dosed by gavage to rats at the dose of 300 mg/kg administered 5d/week during 1 year resulted in no adverse effects.

The NOAEC of 35,000 mg/m^3 for inhalation route is compared to the long term exposure levels for the different scenarios in table 4.17.

The minimal MOS is derived taking into account the following Assessment Factor:

3. a factor of 3 for interspecies variations
4. a factor of 3 for intraspecies variations

Hence the calculated minimal MOS is 9 (3 x 3)

Conclusion,ii for repeated dose toxicity

Table 4.17 Occupational risk assessment for repeated dose toxicity

Minimal MOS	Inhalation				Dermal				Combined			
9	Exposure	NOAEC	MOS	Conclusion	Exposure	NOAEC	MOS	Conclusion	Exposure	NOAEC	MOS	Conclusion
Production												
Subscenario 1 Normal activity	3.8 mg/m^3	35,000 mg/m^3	9210	ii	NR				NR			
Subscenario 2 Maintenance	3.8 mg/m^3	35,000 mg/m^3	9210	ii	NR				NR			
Subscenario 3 Packaging/filling	30.5 mg/m^3	35,000 mg/m^3	1147	ii	NR				NR			
Subscenario 4 Sampling/laboratory	3 mg/m^3	35,000 mg/m^3	11666	ii	NR				NR			
Formulation												
Subscenario 1	NR				NR				NR			
Uses												
Subscenario 1 Use as a refrigerant	235 mg/m^3	35,000 mg/m^3	150	ii	NR				NR			
Subscenario 2 Use as a chemical intermediate	3.8 mg/m^3	35,000 mg/m^3	9210	ii	NR				NR			

NR: not relevant

4.1.3.2.5 Mutagenicity

In vitro, chlorodifluoromethane has some mutagenic activity on some bacterial strains. Chlorodifluoromethane is not active in several tests using mammalian cells and yeast.
In vivo, the overall responses of all the tests conducted with chlorodifluoromethane on rats and mice do not indicate genotoxic activity. The overall weight of evidence suggests that chlorodifluoromethane poses no genotoxic hazard to humans.
According to the criteria in the twelfth adaptation to technical progress of the Dangerous Substances Directive (93/21/EC), chlorodifluoromethane is not classified as mutagenic.

4.1.3.2.6 Carcinogenicity

The limited epidemiological investigation available does not show evidence of an increase in the cancer incidence in people occupationally exposed to chlorodifluoromethane in the refrigeration industry.
The animal studies provide limited evidence for the carcinogenicity of chlorodifluoromethane in rats only.
A clear **NOAEC** of **1000 ppm** (**3500 mg/m^3**) was demonstrated in the male rats. No increased tumor incidence attributable to chlorodifluoromethane exposure was diagnosed in female rats or in mice of either sex.

The NOAEC of 3500 mg/m^3 for inhalation route is compared to the long term exposure levels for the different scenarios, MOS values are reported in table 4.18

The minimal MOS is derived taking into account the following Assessment Factor:

5. a factor of 3 for interspecies variations
6. a factor of 3 for intraspecies variations

Hence the calculated minimal MOS is 9 (3 x 3)

Conlusion (ii) for carcinogenicity

Table 4.18 Occupational risk assessment for carcinogenicity

Minimal MOS	Inhalation				Dermal				Combined			
9	Exposure	NOAEC	MOS	Conclusion	Exposure	NOAEC	MOS	Conclusion	Exposure	NOAEC	MOS	Conclusion
Production												
Subscenario 1 Normal activity	3.8 mg/m³	3500 mg/m³	921	ii	NR				NR			
Subscenario 2 Maintenance	3.8 mg/m³	3500 mg/m³	921	ii	NR				NR			
Subscenario 3 Packaging/filling	30.5 mg/m³	3500 mg/m³	114.7	ii	NR				NR			
Subscenario 4 Sampling/laboratory	3 mg/m³	3500 mg/m³	1166.6	ii	NR				NR			
Formulation												
Subscenario 1	NR				NR				NR			
Uses												
Subscenario 1 Use as a refrigerant	235 mg/m³	3500 mg/m³	15	ii	NR				NR			
Subscenario 2 Use as a chemical intermediate	3.8 mg/m³	3500 mg/m³	921	ii	NR				NR			

NR: not relevant

4.1.3.2.7 Toxicity for reproduction

The NOAEC for developmental toxicity in the rat is considered 1000 ppm (3500 mg/m3).
Moreover, since a low rate of specific malformations was evident in presence of slight maternal toxicity, this could justify a classification of chlorodifluoromethane, according to the criteria in the twelfth adaptation to technical progress of the Dangerous Substances Directive (93/21/EC), in cat 3 (harmful for reproduction) with the risk phrase R63.

Effects on fertility

Male reproduction in rat was not affected but for a slight effect on sex accessory gland at 50,000 ppm; since a single dose was used, a NOEC can not be derived. The dose level of 50,000 consequently may be therefore considered as a marginal LOEC.
No data available on female reproduction.
No adverse effects of chlorodifluoromethane on male fertility were seen in inhalation studies at concentrations up to 50,000 ppm (175,000 mg/m^3) in rats and 100,000 ppm (350,000 mg/m^3) in mice.

Developmental toxicity

The NOAEC for developmental toxicity in the rat is considered 1000 ppm (3500 mg/m^3) due to a significantly increased incidence of anophthalmia (1.6% in litters of treated group vs 0.16% in controls) and combined anophthalmia+microphthalmia (2.6% in litters treated group vs 0.5% in controls) in the offsprings of dams exposed to 50,000 ppm.
A low rate of specific malformations evident in presence of slight maternal toxicity could justify a classification of chlorodifluoromethane in cat 3 (harmful for reproduction) with the risk phrase R63.
The very large rat study from which the NOEL of 1000 ppm (3500 mg/m^3) was derived was designed to examine effects at low (1000 ppm (350 and 3500 mg/m^3)) and very high concentrations (50,000 ppm (175,000 mg/m^3)) rather than to establish a no effect concentration. Even at 50,000 ppm (175,000 mg/m^3), where a significant increase was seen in anophthalmia (6/383 litters) and combined anophthalmia/microphthalmia (10/383 litters), this increase would have been too small for detection in a conventional study (1 in 64 and 1 in 38 litters respectively). The three conventional rat studies and rabbit study showed no significant increase at any concentration up to 20,000 ppm (70,000 mg/m^3). The NOEL of 1000 ppm (3500 mg/m^3) used is therefore a very conservative value.
This NOAEC of 3500 mg/m^3 is compared to long term exposure values for the different scenarios in table 4.19.

The minimal MOS is derived taking into account the following Assessment Factor:

7. a factor of 3 for interspecies variations
8. a factor of 3 for intraspecies variations

Hence the calculated minimal MOS is 9 (3 x 3)

Note: The use of the NOAEC of 1000 ppm from the Palmer study (Palmer, 1978b) has been considered as a very conservative approach. Indeed no adverse effects were observed in the study of Culik and Crowe (1978) up to 20,000 ppm. For this reason there is no need for an additional Assessment Factor in the derivation of the minimal MOS (see section 4.1.2.9.3)

Conclusion ii for toxicity for the reproduction

Table 4.19 Occupational risk assessment for toxicity for reproduction

Minimal MOS	Inhalation				Dermal				Combined			
9	Exposure	NOAEC	MOS	Conclusion	Exposure	NOAEC	MOS	Conclusion	Exposure	NOAEC	MOS	Conclusion
Production												
Subscenario 1 Normal activity	3.8 mg/m³	3500 mg/m³	921	ii	NR				NR			
Subscenario 2 Maintenance	3.8 mg/m³	3500 mg/m³	921	ii	NR				NR			
Subscenario 3 Packaging/filling	30.5 mg/m³	3500 mg/m³	114	ii	NR				NR			
Subscenario 4 Sampling/laboratory	3 mg/m³	3500 mg/m³	1166	ii	NR				NR			
Formulation												
Subscenario 1	NR				NR				NR			
Uses												
Subscenario 1 Use as a refrigerant	235 mg/m³	3500 mg/m³	15	ii	NR				NR			
Subscenario 2 Use as a chemical intermediate	3.8 mg/m³	3500 mg/m³	921	ii	NR				NR			

NR: not relevant

Table 4.20 Overview of the conclusions with respect to occupational risk characterisation

		Acute toxicity (Minimal MOS = 9)		Local toxicity after single or repeated exposure			Sensitisation	Repeated dose toxicity Systemic (Minimal MOS = 9)			Mutagenicity	Carcinogenicity (Minimal MOS = 9)	Reproductive toxicity (Minimal MOS = 9)
		Dermal	Inhalation	Dermal	Inhalation	Eye		Dermal	Inhalation	Combined			
Production													
Subscenario 1	MOS	NR	NR	NR	NR	NR	NR	NR	9210	NR	NR	921	921
Normal activity	Concl.								ii			ii	ii
Subscenario 2	MOS	NR	690	NR	NR	NR	NR	NR	9210	NR	NR	921	921
Maintenance	Concl.		ii						ii			ii	ii
Subscenario 3	MOS	NR	690	NR	NR	NR	NR	NR	1147	NR	NR	114	114
Packaging/filling	Concl.		ii						ii			ii	ii
Subscenario 4	MOS	NR	1760	NR	NR	NR	NR	NR	11666	NR	NR	1166	1166
Sampling/lab	Concl.		ii						ii			ii	ii
Formulation													
Subscenario 1	MOS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Concl.												
Uses													
Subscenario 1 Use as a refrigerant	MOS	NR	43.2	NR	NR	NR	NR	NR	150	NR	NR	15	15
	Concl.		ii						ii			ii	ii
Subscenario 2 Use as an intermediate	MOS	NR	NR	NR	NR	NR	NR	NR	9210	NR	NR	921	921
	Concl.		ii						ii			ii	ii

NR: not relevant

4.1.3.2.8 Summary of risk characterisation for workers

Based on the dataset for the various effect endpoints and on the exposure data for the different scenarios, it can be concluded that there is no concern for occupational exposure to HCFC-22 (conclusion ii for all scenarios).

Conclusion (ii)

4.1.3.3 Consumers

Consumers' exposure to HCFC-22 is not expected. Some domestic refrigeration equipment contain HCFC-22 (either in the refrigeration system or in the insulating foams). The maintenance and servicing of the equipment are always made by professionals. In addition, under the provision of EC Regulation 2037/2000, the use of HCFC-22 for new refrigeration systems and foam blowing will be banned from 1st January 2004.

Conclusion (ii)

4.1.3.4 Humans exposed via the environment

HCFC-22 does not bioaccumulate, therefore no human exposure via the environment is expected. According to EUSES modelling, indirect exposure of humans to HCFC-22 via food, air and drinking water is negligible (see 4.1.1.4).

Conclusion (ii)

4.1.3.5 Combined exposure

There is no concern for consumers combined exposure to HCFC-22.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

4.2.1.1 Workers

HCFC 22 does not present a physico-chemical hazard in the normal conditions of use. Frostbite may occur on skin contact with accidental released liquid or pressurized gas.

4.2.1.2 Consumers

Consumers are normally not exposed to HCFC-22.

4.2.1.3 Humans exposed via the environment

Humans are not exposed to HCFC-22 via the environment.

4.2.2 Effects assessment: Hazard identification

4.2.2.1 Explosivity

HCFC-22 has no explosion potential.

4.2.2.2 Flammability

HCFC-22 is not flammable.

4.2.2.3 Oxidizing potential

HCFC-22 is not an oxidising agent.

4.2.3 Risk characterisation

There is no risk of physico-chemical hazard for the population and workers due to HCFC-22.

5 RESULTS

5.1 INTRODUCTION

5.2 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

5.3 HUMAN HEALTH

5.3.1 Human health (toxicity)

5.3.1.1 Workers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

5.3.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

5.3.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

5.3.1.4 Combined exposure

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

5.3.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to production, use as a chemical intermediate and use as a refrigerant scenarios.

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abbreviations

ADI	Acceptable Daily Intake
AF	Assessment Factor
AGAGE	Advanced Global Atmospheric Gases Experiment
ALT	alanine transaminase
AST	aspartate transaminase
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw, b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation

E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECD	Electron Capture Detection
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
FTIR	Fourier Transform Infrared Spectroscopy
FSH	Follicle Stimulating Hormone
GC	Gas Chromatography
GLP	Good Laboratory Practice
GWP	Global warming potential
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration

ILO	International Labour Organisation
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LH	Luteinizing Hormone
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MAK	Maximale Arbeitsplatzkonzentration (Maximum Concentrations at the Workplace)
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MS	Mass Spectroscopy
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)

O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
ODP	Ozone depleting potential
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
pKa	negative log of the acid dissociation constant
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant

T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document [1]
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
TWA	Time Weighted Average
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

The report provides the comprehensive risk assessment of the substance Chlorodifluoromethane. It has been prepared by Italy in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. The environmental risk assessment concludes that there is no concern for any of the environmental compartments.

For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified. The human health risk assessment concludes that there is no concern for any of these populations.