Joint Assessment of Commodity Chemicals

No. 16

DICHLOROFLUOROMETHANE (HCFC-21)

CAS : 75-43-4

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JACC Report No. 16

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THE ECETOC SCHEME FOR THE

"JOINT ASSESSMENT OF COMMODITY CHEMICALS" (JACC)

This report has been produced as part of a programme for reviewing critically the toxicity and environmental hazards of selected industrial chemicals. A number of organisations world-wide produce such reviews so that, based on up-to-date knowledge, existing chemicals can continue to be produced and used safely. ECETOC is contributing to this with its JACC reviews.

In general, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are reviewed. Every effort is made to discover whether an adequate review exists already, but when this is not so a review is produced jointly by experts from a number of companies with interests in the chemical. Whenever good scientific reviews on certain toxicological or ecotoxicological aspects exist, their conclusions are summarised and only the subsequent literature is assessed. Only the uses of the chemical as such are considered; its occurrence as an impurity in other products is not normally taken into account.

In this document a critical assessment of the toxicology and ecotoxicology of dichlorofluoromethane is presented. Strictly this is not a commodity chemical, but in view of the interest that exists in chlorinated fluorocarbons it is considered that an interim statement is needed on the state of knowledge that exists with respect to this group of chemicals.

CONTENTS

1.SUMMARY AND CONCLUSIONS

Dichlorofluoromethane is a non flammable colourless gas under normal conditions and has been produced only in low quantities.

No information on biodegradation, bioconcentration and bioaccumulation is available.

Most dichlorofluoromethane, which might eventually be released into the atmosphere would be destroyed before reaching the stratosphere. The estimated tropospheric lifetime of dichlorofluoromethane related to the reaction with naturally occurring hydroxylradicals is about 2 years.

Dichlorofluoromethane is rapidly absorbed by animals. Studies in rats indicate a considerable degree of metabolic transformation.

The acute inhalation toxicity is low, with an LC_{50} value of 213,070 mg/m^3 for a four-hour exposure in rats. Exposure at 427,000 mg/m^3 was fatal to rats and guinea pigs within one hour; this concentration caused loss of coordination, tremors and narcosis. Other tests with guinea pigs and mice have shown that concentrations > 213,070 mg/m^3 can cause unconsciousness or death.

In repeated exposures studies the main target organ is the liver. Rats exposed to 42,700 mg/m^3 of dichlorofluoromethane, 6h/d, 5d/w for two weeks survived but an increased serum transaminase level was observed. Histopathological examination indicated liver cell degeneration. In a 90-day study exposure to 4,270 and 21,350 mg/m^3 produced excessive mortality in rats. This was accompanied by liver cirrhosis. Four dogs exposed at the same dose levels lost weight, but histopathological changes in the liver were mild and evident only at 21,350 mg/m^3.

In cardiac sensitisation screening studies, the minimal concentration of dichlorofluoromethane inducing cardiac arrhythmia was 42,700 mg/m^3 in the dog and 106,750 mg/m^3 in the monkey. On rats and mice such effects were induced at concentrations of 811,300 mg/m^3 and 427,000 mg/m^3 respectively. Bronchoconstriction was noted at 106,750 mg/m^3 in dogs and tachycardia with hypotension was observed in anaesthetised monkeys and dogs exposed to 213,500 and 427,000 mg/m^3 of dichlorofluoromethane.

Dichlorofluoromethane produced pre-implantation loss in pregnant rats exposed at 42,700 mg/m^3. After exposure for 6h/d on days 6 - 15 of gestation, 15 of 25 pregnant females had no viable foetuses or implantation sites on the uterine wall. Pregnancy outcome and foetal development in the other ten rats were unaffected.

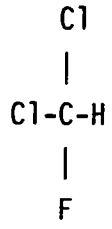
No information is available on its carcinogenic potential. Dichlorofluoromethane is not mutagenic in the Ames Salmonella test and in Saccharomyces cerevisiae.

For technical and toxicological reasons dichlorofluoromethane is not being actively developed as an alternative fluorocarbon.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical structure:



Chemical formula: $HCCl_2F$

Common name : Dichlorofluoromethane

Common synonyms : Methane, dichlorofluoro-;
fluorodichloromethane;
F-21; R-21; HCFC-21*

CAS registry No: 75-43-4

Conversion factors: 1(ppm) = 4.276 mg/m^3
1 mg/l = 233 ppm

*HCFC-21 abbreviation means: Hydro chlorofluorocarbon $CHCL_2F$
first figure = Number of C - Atoms minus 1 0
second figure = Number of H - Atoms plus 1 2
third figure = Number of F - Atoms 1
= HCFC 21

The number of Cl-Atoms is not included in the abbreviation, but represents the rest to the total saturation of the formula.

2.2 Physical and Chemical Properties

Dichlorofluoromethane is a non flammable, volatile colourless gas at normal temperatures and pressures. Some physical and chemical data are given in Table 1.

2.3 Analytical Methods

A method for analysis has been described for dichlorofluorethane which involves gas chromatography with dual flame ionisation detection (FID) (Lindberg, 1979)

3. PRODUCTION, STORAGE, TRANSPORT AND USE

There is no natural source of dichlorofluoromethane. It has been produced in small quantities only by a single producer as a refrigerant.

4. ENVIRONMENTAL, TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Introduction

Dichlorofluoromethane has been produced only in small quantities. Information on biodegradation, bioconcentration and bioaccumulation has not therefore been developed.

4.2 Environmental Factors

The physical-chemical properties of dichlorofluoromethane suggest that normal climatic conditions would allow it to mix rapidly within the lower region of the troposphere. Reaction with naturally occurring hydrogen radicals (OH) is predicted to be the primary degradation route. The atmospheric lifetime related to this reaction is estimated to be about 2 years. The estimates were made assuming that the reference chemical, methylchloroform, has an inferred lifetime of 6.3 years (UNEP/WMO, 1989).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Environmental levels and human exposure are negligible since dichlorofluoromethane is not in commercial production.

6. EFFECT ON ORGANISMS IN THE ENVIRONMENT

No data are available.

7. KINETICS AND METABOLISM

7.1 Animal Studies

There are no quantitative data on absorption of dichlorofluoromethane, but the increased fluoride levels observed in 90 day inhalation toxicity studies (see section 8.2) and the metabolism data (see section 7.1.2) indicate that absorption by inhalation is rapid and that some metabolic transformation takes place in laboratory animals.

7.1.2 Metabolic Transformation and Elimination

The pharmacokinetics of dichlorofluoromethane was investigated in rats. Male Wistar-rats were placed in a desiccator containing soda lime and connected to a pressureless oxygen supply. Animals were injected intraperitoneally with a dose equivalent to a concentration of 3,250 nl gas/kgbw dichlorofluoromethane and placed in the closed chamber. Exhaled dichlorofluoromethane was monitored in the gas phase by gas chromatography. Kinetic parameters of metabolic transformation after inhalation were calculated based on a two compartment open pharmacokinetic model. Only part of the injected dichlorofluoromethane was exhaled and it was assumed that the remainder was metabolised. Total clearance values were calculated to be 4,400 ml/h/kg (Peter et al, 1986).

Increased urinary elimination of fluoride in rats and dogs exposed to dichlorofluoromethane in 90 day studies also indicates that metabolic transformation takes place (see section 8.2)

7.2 Human

No data are available on human absorption, distribution, metabolic transformation and elimination of dichlorofluoromethane.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 Single Exposure

The signs of acute intoxication indicate that the CNS is the major target organ when animals are exposed to high concentrations. Levels higher than 427,000 mg/m^3 are lethal in the rat and guinea pig within a few minutes (Booth and Bixby, 1932).

Animals exposed to concentrations between 42,700 and 427,000 mg/m^3 for five minutes to 6 hours exhibit signs typical of various stages of anaesthesia (Booth and Bixby, 1932; Nuckolls, 1935; Caujolle, 1964; Weigand, 1971; Graham 1985).

The 4h LC_{50} in rats was 213,070 mg/m^3. In addition to central nervous depression, increased lacrimation, piloerection and mydriasis were observed (Tappan and Waritz, 1964).

Detailed information on acute effects in various animal species is given in Table 2.

8.2 Repeated Exposure

Two young dogs were exposed for five minutes twice daily, over a period of 14 days to 1,714 mg/kgbw of mixture containing 60% difluorochloromethane and 40% dichlorofluoromethane. After two to three minutes the puppies became sedated and ataxic but recovered within a few minutes after removal from the test chamber. No other effects were noted and the dogs gained weight in a normal manner (Smith and Case, 1973).

A group of ten male rats was exposed 6h/d, 5d/w for 2 weeks to 42,700 mg/m^3 of dichlorofluoromethane. There were no deaths but the rats lost weight and exhibited marked anaemia and increased serum transaminase levels indicating liver damage. Pathological examination immediately after the last exposure indicated liver necrosis which had not recovered after 14-days postexposure (Trochimowicz et al, 1977).

Five rats, five guinea pigs, two beagle dogs and two cats were exposed to 42,700 mg/m^3 of dichlorofluoromethane for 3.5 h/d, 5d/w for 4 weeks. The behaviour of all animals remained normal throughout the experiment. The increase in body weight of rats was somewhat retarded and the guinea pigs lost weight. The blood and urine analysis were normal. Gross pathologic examination revealed alterations in the livers of all the guinea pigs and cats and one of the dogs but not of rats. Histopathological examination revealed increased hepatic single cell necrosis and fatty degeneration in all exposed animals (Weigand, 1971).

Groups of 27 male and 27 female Ch.R. albino rats and four male beagle dogs were exposed 6h/d 5d/w, for 90 days to 4,270 mg/m^3 or 21,350 mg/m^3 dichlorofluoromethane. Rats were severely affected; between days 59 and 90, 37 % of the rats exposed to the low concentration and 28% exposed to the high concentration died. Clinical chemistry and histopathological examination of test rats revealed extensive liver cirrhosis. In the dog experiments no fatalities were observed; the only significant effects occurred at 21,350 mg/m^3 and consisted of slight weight loss during

exposure and minimal unspecified morphological changes in the liver (Trochimowicz et al, 1977).

A 90 day inhalation study was conducted in 4 groups Ch.R. albino rats 35 males and 35 females in each group with concentrations of 0, 213, 640 and 2,130 mg/m^3 (6 h/d, 5 d/w). At 2,130 mg/m^3 the body weight gain was lower than in controls during the early phase of the experiment. Leucocyte counts were increased in animals exposed to 2,130 mg/m^3 as were serum alkaline phosphatase and alanine amino transferase. Urine volumes showed a tendency to an increase after exposure to 2,130 mg/m^3. A dose related increase in urine fluoride was observed in both sexes after 45 days treatment. A similar increase in urinary fluoride was observed at 90 days, but there was essentially no difference between rats exposed to 640 and 2,130 mg/m^3. This suggests that saturation of the metabolic transformations occurs at dose levels at or below 640 mg/m^3. Histopathological evaluation of tissues revealed portal cirrhosis of the liver, interstitial oedema of the pancreas and degeneration of the seminiferous epithelium in all treatment groups (Lindberg, 1979).

8.3 Long-term Exposure

No data are available.

8.4 Skin and Eye Irritation, Skin Sensitisation

Dichlorofluoromethane produced mild irritation when applied at concentrations higher than 25% in propylene glycol to the shaved, intact skin of guinea pigs. No irritation was observed at concentration of 2.5% in propylene glycol. No evidence of sensitisation was seen (Graham, 1985).

Undiluted liquid dichlorofluoromethane, chilled to the temperature of dry ice, was placed into the right conjunctival sacs of two rabbits. After 20 seconds, the treated eye of one rabbit was washed with 0.9 % saline for one minute. Dichlorofluoromethane produced slight corneal opacity, transient congestion of the iris and moderate conjunctival irritation in

an unwashed eye. The washed eye had very slight corneal opacity, moderate conjunctival irritation and no iris involvement. Both eyes were normal within five days (Graham, 1985).

Dichlorofluoromethane was sprayed directly into the eyes of each of six rabbits from a distance of two inches. No corneal or iris injury was seen. Mild lacrimation was seen in four rabbits when examined one and four hours after exposure (Graham, 1985).

8.5 Special Studies

Early studies on the toxicity of certain hydrocarbons and halocarbons showed that they could render the mammalian heart abnormally reactive or sensitive to adrenaline, resulting in cardiac arrhythmias. Halocarbons have been screened for this effect and for acute effects on acute bronchopulmonary function. (Results of relevant studies in different animal species are summarised in Table 3).

The lowest concentration levels causing cardiac effects are 42,700 mg/m^3 in dogs (with exogenous adrenaline) and 106,750 mg/m^3 in monkeys, but rats and mice have a lower sensitivity degree to these effects (811,300 mg/m^3 and 427,00 mg/m^3 respectively).

8.5.1 Acute Bronchopulmonary Function

The following changes occurred in various animal species exposed to dichlorofluoromethane (Aviado, 1975a):

Monkey: dose 213,500 mg/m^3 = bronchodilation with depression of respiration,

Dog: dose 106,750 mg/m^3 = bronchoconstriction,

Rat: dose 811,300 mg/m^3 = no bronchopulmonary effects were observed.

8.5.2 Cardiovascular Function

The concentration causing cardiac sensitisation in 50% of dogs following five-minute exposure (EC_{50}) was 106,750 mg/m^3 (Clark and Tinston, 1973). Sensitisation of the beagle heart to exogenous adrenaline occurred at concentrations greater than 42,700 mg/m^3 (Graham, 1985).

The effects of dichlorofluoromethane on the circulatory and respiratory systems have been studied in the monkey, dog, rat and mouse.

In anaesthetised monkeys, 106,750 and 213,500 mg/m^3 of dichlorofluoromethane produced tachycardia and hypotension. It also significantly reduced respiratory minute volume (Aviado and Smith, 1975). At the same dose levels cardiac arrhythmia, myocardial depression and tachycardia were reported (Belej et al, 1974). In anaesthetised dogs, 106,750 mg/m^3 of dichlorofluoromethane elicited a rise in pulmonary resistance, a decrease in pulmonary compliance and tachycardia. At 427,000 mg/m^3 and 852,000 mg/m^3, hypotension was observed (Belej and Aviado, 1975b).

The minimal concentration of dichlorofluoromethane which induced cardiac arrhythmia, tachycardia, myocardial depression and hypotension in the monkey was 106,750 mg/m^3. In the dog the tachycardia inducing dose was 106,750 mg/m^3 and the hypotensive dose was 427,000 mg/m^3. The effects of dichlorofluoromethane are opposite in the monkey and dog, the former showing bronchodilation, no decrease in compliance and early respiratory depression, and the latter bronchoconstriction, reduced compliance but no respiratory depression (Aviado, 1975).

In the anaesthetised rat, dichlorofluoromethane did not increase pulmonary resistance. Apnea occurred in four minutes at a concentration of 811,300 mg/m^3 and cardiac arrest nine minutes later. Bradycardia, slowing of the respiratory rate and reduction in tidal

volume were also observed (Friedman et al, 1973). In anaesthetised mice, 427,000 mg/m^3 of dichlorofluoromethane produced arrhythmias. When adrenaline was administered while the mice were exposed to dichlorofluoromethane, the number developing arrhythmias increased from one to six (Aviado and Belej, 1974).

8.6. Reproductive Performance, Embryotoxicity and Teratology

8.6.1 Reproductive Effects

No data on effects on fertility are available.

8.6.2 Embryotoxic and Teratogenic Effects

Pregnant rats were exposed to 42,700 mg/m^3 of dichlorofluoromethane 6h/d on days 6-15 of gestation. No adverse clinical signs of toxicity were seen but the rats gained substantially less weight than the control animals. Dichlorofluoromethane interfered with the process of implantation; 15 of 25 mated rats had no implants or viable foetuses. The outcome of pregnancy and the foetal development in the other ten rats were not affected. No teratogenic activity was seen (Kelly et al, 1978).

Exposure of female rats to dichlorofluoromethane at 153 mg/m^3 or 303 mg/m^3 for the whole gestation period caused a decrease in the levels of DNA and total nucleic acids in the liver, brain, ovaries and placenta (Aran'ina, 1972).

8.7 Mutagenicity

Dichlorofluoromethane was not mutagenic when incubated for 72 hours with Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA1538) with or without metabolic activation (Brusick, 1976).

Dichlorofluoromethane was not mutagenic for Salmonella typhimurium or Saccharomyces cerevisiae D4 (Brusick, 1976).

8.8 Carcinogenicity

No data are available on carcinogenicity studies.

9. EFFECTS ON MAN

Ten healthy volunteers and ten patients suffering from a pronounced arterial hypoxaemia due to bronchopulmonary diseases were exposed to an aerosol mixture of 60% dichlorofluoromethane and 40% trichlorofluoromethane by inhalation. The individuals inspired a dose of 202 ml of the aerosol within 2.5 hours or a dose of 126 ml during 10 successive breaths. Electrocardiography did not reveal any changes due to inspiration of the compounds (Fabel et al, 1972).

10. OCCUPATIONAL EXPOSURE LIMITS

The recommended occupational exposure limit of dichlorofluoromethane is 10ppm = 42,8 mg/m^3 (t.w.a. 8h). (WGD, 1987; ACGIH, 1989; DFG, 1989).

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TABLE 1

Physical and chemical properties of dichlorofluoromethane (Weast 1989)

Formula	:	$CHCL_2F$
Molecular Weight	:	102,92
Physical Form	:	Gas
Colour	:	Colourless
Boiling Point °C at 1030 HPg	:	8.9
Freezing Point °C	:	-135
Critical temp °C	:	178.5
Density/Specific Gravity g/l at 9°C	:	1.405
Density of saturated vapour at B.P. g/l	:	4.57
Flash point/ flammability	:	Nonflammable
Solubility in water at 25°C and 1HPa:wt%	:	0.95
Solubility in alcohol glycol and ether	:	soluble
Refractive index of liquid 25 °C	:	1.354

TABLE 2

ACUTE EFFECTS IN VARIOUS ANIMAL SPECIES

Species	Concentration (mg/m^3)	Time of exposure	Symptoms	Authors
guinea pig	1,708,000	6 min.	tremors, death	Booth and Bixby 1932
guinea pig	854,000	< 11 min.	tremors, death	Booth and Bixby 1932
guinea pig	435,540	35-65 min.	death	Nuckolls, 1935
rat and guinea pig	427,000	15-50 min.	unconsciousness death	Weigand, 1971
guinea pig	256,200	5 min.	unconsciousness	Booth and Bixby 1932
guinea pig	213,500 222,040	2 hours	loss of coordination unconsciousness	Nuckolls, 1935
guinea pig	213,500	< 2 hours	death within 2h	Caujolle, 1964
rat and guinea pig	213,500	2 hours	disequilibrium narcosis	Weigand, 1971
guinea pig	128,100	6 hours	dyspnoea	Graham, 1985
rat and guinea pig	106,750	2 hours	disequilibrium, tremors, excitation	Weigand, 1971
guinea pig	98,210 106,750	2 hours	disequilibrium, seizures	Nuckolls, 1935
guinea pig	51,240	2 hours	dyspnoea, stupor	Nuckolls, 1935
mouse	42,700	30-100 min.	hyperactivity	Booth and Bixby 1932
rat and guinea pig	10,000	2 hours	no changes	Weigand, 1971

Table 3. CARDIOVASCULAR FUNCTION STUDIES OF DICHLOROFLUOROMETHANE IN DIFFERENT ANIMAL SPECIES

SPECIES	CONC. (mg/m3)	EFFECT	REFERENCE
Dog	42,700	lowest conc. causing cardiac sensitisation (with exogenous adrenaline)	Graham, 1985
	106,750	EC50 for cardiac sensitisation (without exogenous adrenaline)	Clark and Tinston, 1973
		tachycardia	Aviado, 1975a
		bronchoconstriction	Aviado, 1975a
		rise in pulmonary resistance decrease in pulmonary compliance	Belej and Aviado, 1975
	427,000 852,000	hypotension	Belej and Aviado, 1975

Table 2. CARDIOVASCULAR FUNCTION STUDIES OF DICHLOROFLUOROMETHANE IN DIFFERENT ANIMAL SPECIES (cont)

SPECIES	CONC. (mg/m3)	EFFECT	REFERENCE
Monkey	106,750	minimal concentration for induction of cardiac arrhythmia, tachycardia myocardial depression and hypotension	Aviado, 1975b Belej et al, 1974
	106,750 213,500	reduction of respiratory minute volume	Aviado and Smith, 1975
	213,500	bronchodilation with depression of respiration	Aviado, 1975a
Rat	811,300	Apnea, cardiac arrest	Friedman et al, 1973
Mice	427,000	Arrhythmia (without and with exogenous adrenaline)	Aviado and Belej, 1974

APPENDIX 1

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Responsible editor : D.A. Stringer, ECETOC
Avenue Louise, 250, Bte 63
B-1050 Brussels, Belgium

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