Joint Assessment of Commodity Chemicals

No. 11

1,2-DICHLORO-1,1-DIFLUOROETHANE (HFA-132b)

CAS : 1649-08-7

Brussels, May 1990

ISSN-0773-6339-11

ISSN-0773-6339-12

JACC Report

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 1,2-dichloro-1,1-difluoroethane is presented. Strictly this is not a commodity chemical, but in view of the interest that exists in chlorinated fluorocarbons it was considered that an interim statement was needed on the state of knowledge that exists with respect to this chemical.

CONTENTS

1. SUMMARY AND CONCLUSIONS 1

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS 3

2.1 Identity 3
2.2 Physical and Chemical Properties 3
2.3 Analytical Methods 4

3. PRODUCTION, STORAGE, TRANSPORT AND USE 4

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION 4

4.1 Introduction 4
4.2 Environmental Factors 4

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE 5

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT 5

7. KINETICS AND METABOLISM 5

7.1 Animal Studies 5

7.1.1. Absorption 5
7.1.2. Distribution 5
7.1.3. Metabolic Transformation 6
7.1.4. Elimination 6

7.2. Human Studies 6

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS 6

8.1 Single Exposure 6
8.2 Repeated Exposure 7
8.3 Long-Term Exposure 8
8.4 Skin and Eye Irritation, Skin Sensitisation, Cardiac Sensitisation. 8
8.4.1 Skin Irrtiation 8
8.4.2 Eye Irritation 8
8.4.3 Allergic Sensitisation 8
8.4.4 Cardiac Sensitisation 9
8.5 Reproductive Effects 9
8.6 Embryotoxic and Teratogenic Effects 9
8.7 Mutagenicity 10
8.8 Carcinogenicity 10

9. EFFECTS ON MAN 10

BIBLIOGRAPHY.....11

TABLE.....12

APPENDICES.....13

1. SUMMARY AND CONCLUSIONS

1,2-Dichloro-1,1-difluoroethane (dichlorodifluoroethane) is a volatile, colourless, non-flammable liquid not produced in commerical quantities. Therefore, data on environmental behaviour are limited. Assuming a four-year tropospheric lifetime, a low ozone depletion potential (ODP) of about 0.025 would be expected, compared to the fully halogenated chlorofluorocarbons such as trichlorofluoromethane (CFC11) with an ODP of 1.0.

Dichlorodifluoroethane has a low toxicity. Its approximate oral lethal dose (ALD) in rats is 25,000 mg/kg. It is a mild eye and skin irritant but does not induce dermal sensitisation. By inhalation, its 4-hour approximate lethal concentration (ALC) in rats is 110,000 mg/m^3. The main action of dichlorodifluoroethane is weak anaesthesia at exposures at or near the lethal concentration. In addition, as with many halocarbons and hydrocarbons, dichlorodifluoroethane is capable of sensitising the mammalian heart (dog) to an adrenaline challenge at exposure concentrations of 27,500 mg/m^3 and above. Dichlorodifluoroethane is not mutagenic in Salmonella typhimurium bacteria, with or without metabolic activation.

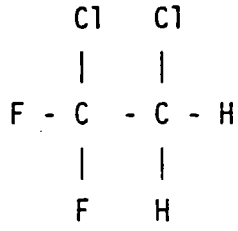
The toxicity of dichlorodifluoroethane has been evaluated on repeated exposures studies. Rats were exposed for 6 h/d, 5 d/w for 13 weeks at concentrations of 2,750, 11,000 and 27,500 mg/m^3. Bile duct proliferation, in the liver and elevated liver/body weight ratios were seen at all concentrations in male rats. At the two higher concentrations liver/body weight ratios were elevated in females, there was a depression in speramtogenesis in males and an elevation of serum ALP in both sexes. During exposure to 27,500 mg/m^3 CNS depression occurred as shown by decreased motor activity and low responsiveness to sound. In a pilot teratolology study, pregnant rats were exposed at concentrations of 2,750, 11,000, and 27,500 mg/m^3 dichlorodifluoroethane for 6 h/d on days 6 - 15 of gestation. Maternal toxicity and reduced foetal body weights were seen at all test concentrations and an increased incidence in resorption rate at the two highest exposure levels.

For technical and toxicological reasons dichlorodifluoroethane is not being actively developed as an alternative fluorocarbon at present.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical Structure :



Chemical Formula :	$CClF_2CH_2Cl$
Common Name :	Dichlorodifluoroethane
Common Synonyms :	HCFC-132b; 1,2-dichloro-1,1-difluoroethane; HFA-132b*
CAS Registry Number :	1649-08-7
Conversion Factors :	1 ppm = 5.5 mg/m^3
	1 mg/l = 181 ppm

2.2 Physical and Chemical Properties

Dichlorodifluoroethane is a volatile, colourless, non-flammable liquid at room temperature and normal atmospheric pressure. It is practically odourless, slightly soluble in water, and miscible in most organic solvents. Selected physical and chemical properties are given in Table 1.

* HFA-132b abbreviation means : Hydro-Fluor Alkane : $C_2H_2F_2Cl_2$

First figure = Number of C - Atoms minus 1	1
Second figure = Number of H - Atoms plus 1	3
Third figure = Number of F - Atoms	2
b represents the isomer	132b

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

2.3 Analytical Methods

There are no published methods for the analysis of dichlorodifluorethane in air. The material has routinely been measured in inhalation toxicity studies using gas chromatography coupled with either thermal conductivity detectors or flame ionization detectors (DuPont, 1988a).

3. PRODUCTION, STORAGE, TRANSPORT AND USE

There is no known natural source of dichlorodifluoroethane.

Dichlorodifluoroethane has only been produced in research quantities and has never been available commercially. Therefore, there is no information relative to production levels, disposal, transport, storage, or use patterns.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Introduction

Dichlorodifluoroethane is not available in commercial quantities; no information is available on the biodegradation or the bioaccumulation potential of dichlorodifluoroethane.

4.2 Environmental Factors

The physical and chemical properties of dichlorodifluoroethane suggest that it would mix rapidly in the troposphere. Reaction with naturally occurring hydroxyl radicals (OH^-) in the trosposphere is expected to be the primary degradation route. The atmospheric half-lifetime estimate of this reaction is about four years (UNEP/WHO, 1989).

Based on a four-year tropospheric lifetime, the ozone-depleting potential (ODP) of dichlorodifluoroethane would be expected to be about 0.025, one-third the value for dichlorofluoroethane (HCFC-141b, ODP = 0.08) and much lower than fully halogenated chlorofluorocarbons such as trichlorofluoromethane (CFC 11) with an ODP of 1.0 (MacFarland, 1989).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Since it has not been made in commercial quantities, no data are available on the amounts of dichlorodifluoroethane in air, water or food. There is no information on human exposure.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

No data are available on the effects of dichlorodifluoroethane on environmental organisms.

7. KINETICS AND METABOLISM

7.1 Animal Studies

7.1.1 Absorption

There are no specific quantitative data on the absorption of dichlorodifluoroethane. Acute and repeated-dose toxicity studies suggest that the material is rapidly absorbed by inhalation and quickly achieves an equilibrium in blood and tissues. (See chapters 8.1 and 8.2)

7.1.2 Distribution

There are no data on distribution of dichlorodifluoroethane in tissues.

7.1.3 Metabolic Transformation

There are no data on the *in vitro* or *in vivo* metabolism of dichlorodifluoroethane.

7.1.4 Elimination

There are no quantitative data on the elimination of dichlorodifluoroethane in animals. However, based on results from acute and repeated dose studies, removal from exposure would be expected to lead to a decrease in blood levels of dichlorodifluoroethane within a few minutes (see chapter 8.1 and 8.2) although specific studies to confirm this have not been carried out.

7.2 Human Studies

No information is available on the absorption, distribution, metabolic transformation and elimination of dichlorodifluoroethane in man.

8. EFFECTS ON EXPERIMENTAL AMIMALS AND IN VITRO TEST SYSTEMS

8.1 Single Exposure

Dichlorodifluoroethane is of low acute toxicity. The approximate oral lethal dose in the rat is 25,000 mg/kg (Du Pont, 1975). By the inhalation route, its main action is one of weak anaesthesia at high exposure levels. The 4-hour approximate lethal concentration in rats was 110,000 mg/m^3; rats appeared unsteady, weak and slightly drowsy during exposure at this concentration (Torkelson, 1971). In mice, the 30-minute LC_{50} was 269,000 mg/m^3 dichlorodifluoroethane with anaesthesia occurring at exposure levels of 71,500 mg/m^3 and higher (Raventos and Lemon, 1965).

8.2 Repeated Exposure

Groups of 10 male Crl:CD^{R} BR rats was exposed to either 0 (control) or 55,000 mg/m^{3} dichlorodifluoroethane for 6 h/d, 5 d/w for two weeks. Signs of toxicity included a reduction in body weight gain, irregular respiration and CNS depression as shown by lethargy, poor coordination, occasional tremors and prostration; the CNS effects disappeared within 30 minutes post-exposure. Pathological examination of rats sacrified immediately after the tenth exposure showed thymic atrophy and aspermatogenesis in the tests. These changes were not present in rats sacrificed 14 days after exposure ceased (Du Pont, 1976a).

Groups of 20 male and 20 female Crl:CD^{R} BR rats were exposed by inhalation to dichlorodifluoroethane for 6 h/d, 5 d/w for 13 weeks at concentrations of 0, 2,750, 11,000 and 27,500 mg/m^{3}. Male rats exposed at all concentrations showed bile duct proliferation in the liver and disruption of spermatogenesis with cell debris in the epididymides occurring at the two higher concentrations. Other effects included elevations in liver/body weight ratios in males at all concentrations and in females exposed at the two highest concentrations. Elevation of serum alkaline phosphatase activity was seen in both sexes exposed to 11,000 or 27,500 mg/m^{3}. During exposure all groups exposed to dichlorodifluoroethane showed reduced food consumption and body weight depression. In the two highest exposure groups there was depression in the absolute but not relative brain and testes weights. Other organ weight changes (slight increases in heart, lung and kidney) were seen but based on the absence of histological findings in these organs, the biological significance of these organ weight changes is not known.

During exposure to 27,500 mg/m^{3} of dichlorodifluoroethane, rats showed CNS depression as indicated by decreased activity and low responsiveness to sound (Du Pont, 1988b).

8.3 Long-Term Exposure

No data are available.

8.4 Skin and Eye Irritation, Skin Sensitisation and Cardiac Sensitisation

8.4.1 Skin Irritation

In a test for primary irritation, one drop (approximately 0.05 ml) each of 100% material and a 10% solution of the test material in propylene glycol was applied and lightly rubbed into the shaved intact shoulder skin of 10 male albino guinea pigs; the area was not occluded. Dichlorodifluoroethane at a 100% concentration produced only mild irritation; no irritation was seen with the 10% solution (Du Pont, 1976b).

8.4.2 Eye Irritation

In an eye irritation study, 0.1 ml of undiluted dichlorodifluoroethane was placed into the right conjunctival sac of each of two ablino rabbits. After 20 seconds, one treated eye was washed with water for one minute; the treated eye of the other rabbit was not washed. Observations of the cornea, iris and conjunctival were made after one and four hours, and one, two, three and seven days after dosing. The undiluted material produced a slight corneal opacity and mild to moderate conjunctival irritation in both rabbits which was present up to three days after dosing, but disappeared by seven days after dosing (Du Pont 1976c).

8.4.3 Allergic Sensitisation

The skin sensitising potential of dichlorodifluoroethane has been tested in groups of 9 male albino guinea pigs. A series of four sacral intradermal injections were given once/week at 7 day intervals over a 3 week period (0.1ml of a 1.0 % solution of dichlorodifluoroethane in dimethyl phthalate). 14 days after the last application the

test animals were challenged with either one drop (~0.05 ml) of undiluted liquid or a 10% solution of test material in propylene glycol on the shaved skin. A group of seven unexposed guinea pigs received similar applications of the undiluted and diluted material at the time of challenge and served as age-matched controls. No evidence of allergic sensitisation was observed (Du Pont, 1976b).

8.4.4 Cardiac Sensitisation

Dichlorodifluoroethane, like many other halocarbons and hydrocarbons, can produce cardiac sensitisation in beagle dogs in response to an intravenous adrenaline challenge (Reinhardt, 1971). In screening tests with dogs, exposure concentrations of 27,500 mg/m^3 or greater were capable of sensitising the beagle heart to an injection of adrenaline (Du Pont, 1976d). These results are similar to those reported previously for trichlorofluoromethane (CFC 11) (Reinhardt, 1971).

8.5 Reproductive Effects

No toxicity studies have been conducted to evaluate the reproductive performance of male and female rats exposed to dichlorodifluoroethane.

8.6 Embryotoxic and Teratogenic Effects

In a developmental screening test (Du Pont, 1986) using Hydra, the ratio of the minimum dose toxic for the adult and the minimum dose toxic to the conceptus (A/D ratio) was near unity in each of several tests suggesting that the material is not an embryotoxin.

In a pilot study (Du Pont, 1988b), groups of 7 or 8 pregnant rats were exposed to 2,750, 11,000, or 27,500 mg/m^3 dichlorodifluoroethane for 6 h/d on days 6 - 15 of gestation. Maternal and foetal body weights were reduced at all exposure levels. The number of resorptions were increased in the 11,000 and 27,500 mg/m^3 groups.

These results indicate that dichlorodifluoroethane has a slight maternal and possible embryotoxic effect at high exposure levels.

8.7 Mutagenicity

Dichlorodifluoroethane was not mutagenic in the Ames Salmonella typhimurium assay (Strains TA1535, TA100, TA1537, TA1538 and TA98) in the presence or absence of a rat liver metabolic activation system. A 48-hour incubation period was used (Du Pont, 1976e). Even when incubated for 72 hours under anaerobic conditions, this material was not found to be mutagenic (Waskell, 1979).

8.8 Carcinogenicity

No data are available.

9. EFFECTS ON MAN

No adverse health effects have been ascribed to dichlorodifluoroethane.

BIBLIOGRAPHY

- DU PONT COMPANY, (1975). Unpublished Data. "Acute Oral Test." HLR680-75.

- DU PONT COMPANY, (1976a), Unpublished Data. "Two-Week Inhalation Toxicity Study." HLR 727-76.

- DU PONT COMPANY, (1976b). Unpublished Data. "Primary Skin Irritation and Sensitisation Test in Guinea Pigs." HLR 14-76.

- DU PONT COMPANY, (1976c). Unpublished Data. "Eye Irritation Test in Rabbits." HLR 14-76.

- DU PONT COMPANY, (1976d), Unpublished Data. "Cardiac Sensitisation." HLR 113-76.

- DU PONT COMPANY, (1976e). Unpublished Data. "In Vitro Microbial Mutagenicity Studies of Ethane, 1,2-Dichloro-1,1-Difluoro-", HLR 90-76.

- DU PONT COMPANY, (1986). Unpublished Data. "An In Vitro Evaluation of the Developmental Hazard Potential of Du Pont Compound H-16,469." HL0-743-86.

- DU PONT COMPANY, (1988a). Unpublished Data. "90-Day Inhalation Toxicity Study." HLR 20-88.

- DU PONT COMPANY, (1988b). Unpublished Data. "Pilot Teratogenicity Study of FC-132b in Rats." HLR 50-88.

- MACFARLAND, I.M., DU PONT COMPANY, (1989). Unpublished Data. Personal Communication

- RAVENTOS, J. and LEMON, P.G. (1965). The impurities in Fluothane: Their biological properties. Brit.J. Anaesth. 37:716-737.

- REINHARDT, C.F., (1971). "Cardiac Arrhythmia and Aerosol Sniffing." Arch. Environ. Hlth. 22:265-279.

- TORKELSON, T.R.,(1971) "Single Exposures of Rats to the Vapours of Trace Substances in Methoxyflurane." Toxicol. Appl.Pharmacol. 19: 1-9, 1971

- UNEP/WMO. (1989) Scientific assessment of stratospheric ozone: 1989, Section 111, Ch. 4 Halogenated ozone depletion and global warming potentials. Report dated 21 August 1989, prepared for the the meeting of : Open-ended working group of the parties to the Montreal Protocol to integrate the four reports of the assessment panels into one synthesis report and to make recommendations on amendments to the Montreal Protocol. Sponsored by the United Environment Programme, World Meteorological Organization and held in Nairobi, Kenya on August 28 - September 5, 1989.

- WASKELL, M.D., (1979).Lack of Mutagenicity of Two Possible Metabolites. Anesthesiology 50 (1):9-12.

- WEAST, R.C. ED. (1989) CRC Handbook of Chemistry and Physics 69th, ed. Boca Raton FL, CRC Press.

TABLE 1

SELECTED PHYSICAL AND CHEMICAL PROPERTIES OF HFA-132b

			Ref
Molecular Weight	:	134.92	1
Physical Form	:	colourless liquid	1
Boiling Point °C at 1013hPA	:	46.8	1
Freezing Point °C	:	-101.2	1
Liquid Density 20°C g/ml	:	1.4163	1
Refractive index 20°C	:	1.3619	1
Vapour Pressure psia at 25°C	:	6.1	2
Solubility in H_2O g/L at 20°C 1013hPA	:	4.9	2
Solubility in organic solvents	:	miscible in acetone, ethanol, petroleum solvents, and vegetable oil	2
Flammability/Flash	:	non flammable	2

1) Weast (1989)

2) E.I. du Pont de Nemours and Co., Inc. Unpublished data.

APPENDIX 1

MEMBERSHIP OF THE ECETOC TASK FORCE HFA132b

D. Mayer	Hoechst D
S. Magda	Kali-Chemie D
R.J. Millischer	Atochem F
G. Malinverno	Montedison, Inst. Guido Donegani I
G.M. Rusch	Allied Corporation USA
C. Stevens	ISC Chemcial GB
H.J. Trochimowicz	E.I. Du Pont De Nemours USA
D. Tinston	ICI GB
W. Haebler	ECETOC B

APPENDIX 2

Members of the Scientific Committee

I.F.H. PURCHASE (Chairman), Director Central Toxicology Laboratory	ICI, Alderley Park, UK
M. SHARRATT*, (Vice-Chairman), Group Toxicology Advisor	BP, Guildford, UK
B. BROECKER, Coordinator, Product-related Environmental Problems	HOECHST, Frankfurt, D
H. DE HENAU, Professional and Regulatory Services	PROCTER AND GAMBLE, Brussels, B
H.O. ESSER, Vice- Director Produc Safety	CIBA-GEIGY, Basel CH
P.A. GILBERT*, Head of Environmental Relations Department	UNILEVER, Port Sunlight, UK
I.J. GRAHAM-BRYCE, Head of Environmental Affairs Division	SHELL, The Hague, NL
B. HILDERBRAND, Deputy Head, Department of Toxicology	BASF, Ludwigshafen, D
J.R. JACKSON, Director, Medicine and Health Science	MONSANTO EUROPE, Brussels, B
R. MILLISCHER, Chief Toxicologist	ATOCHEM, Paris F
W.F. TORDOIR, Head of Occupational Health and Toxicology Division	SHELL, The Hague, NL
H. VERSCHUUREN, Head, Department of Toxicology	DOW CHEMICAL, Horgen CH

* indicates Steward responsibility

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

D-1990-3001-63