Joint Assessment of Commodity Chemicals

No. 17

CHLORODIFLUOROETHANE

(1-chloro-1,1,difluoroethane; HFA 142 b)

CAS : 75-68-3

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JACC Report No 17

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-chloro-1,1,difluoroethane 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

CHLORODIFLUOROETHANE (1-chloro-1,1,difluoroethane)

SUMMARY AND CONCLUSION

1-Chloro-1,1-difluoroethane is a moderately flammable, colourless gas at ambient temperature. It is used as a chemical intermediate in the production of highly specialized fluoropolymers and has been proposed as a substitute for fully halogenated chlorofluorocarbons.

Chlorodifluoroethane has a low calculated ozone depletion potential (ODP) of 0.05 - 0.06 compared to the fully halogenated chlorofluorocarbons. The reference compounds trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) have an ODP of 1.0. Chlorodifluoroethane has a global warming potential (GWP) of 0.34 - 0.39 compared to CFC-11 and CFC-12 which have a GWP of 1.0 and 3.1 respectively.

Chlorodifluoroethane has a low to moderate acute toxicity to Daphnia and fish.

Specific kinetic and metabolism studies of chlorodifluoroethane are lacking, but analysis of selected tissues and urine from rats and dogs exposed by inhalation for 13 weeks to 41,000 mg/m^3 did not indicate accumulation or that metabolic degradation takes place.

Chlorodifluoroethane has a low order of acute toxicity to mammals. Its 30 min LC_{50} in mice is at atmospheric concentrations of 1,230,000 mg/m^3. The primary effect at high exposure levels was central nervous system depression.

In repeated exposure studies, concentrations up to 82,000 mg/m^3 were tolerated by rats and up to 41,000 mg/m^3 by dogs without indication of toxicity.

Chlorodifluoroethane caused cardiac sensitisation at concentrations of 205,000 mg/m^3 or greater in dogs after challenge with exogenous adrenaline. The no effect level was 102,500 mg/m^3.

Compared to other chlorofluorocarbons, chlorodifluoroethane is of intermediate toxicity with respect to respiratory irritancy and cardiovascular sensitising ability.

No teratogenic and embryotoxic effects were detected when pregnant rats were exposed during the sensitive part of gestation to a concentration of 41,000 mg/m^3.

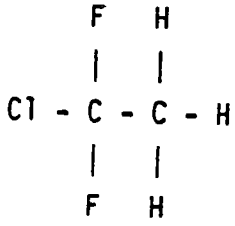
In the majority of bacterial mutagenicity tests, chlorodifluoroethane showed weakly positive effects at very high dose. Cell transformation tests gave equivocal results. Conversely using *in vivo* studies (Dominant Lethal assay and Bone Marrow Cytogenetics) chlorodifluoroethane was inactive indicating that chlorodifluoroethane does not present a genotoxic hazard *in vivo*.

Chlorodifluoroethane did not produce neoplastic changes in male and female rats exposed to concentrations as high as 82,000 mg/m^3 for two years.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical structure:



Chemical formula: $CClF_2\ CH_3$

Common name: Chlorodifluoroethane

Synonyms: 1-Chloro-1,1-difluoroethane
1,1-Difluoro-1-chloroethane
Difluoromonochloroethane
Ethane, Chlorodifluoro-
HCFC-142b HFA 142b*

CAS Registry No.: 75-68-3

Conversion factors: 1 ppm = 4.1 mg/m^3
1 mg/l = 243.28 ppm

*HFA 142b abbreviation means : Hydro Fluor Alkane $C_2H_3F_2Cl$

First figure	= Number of C-Atoms minus 1	1
Second figure	= Number of H-Atoms plus 1	4
Third figure	= Number of F-Atoms	2
b represents the isomer		HFA 142b

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

2.2 Physical and Chemical Properties

Chlorodifluoroethane is a colourless gas at ambient temperature. It is weakly soluble in water and is flammable. Some physical and chemical data for chlorodifluoroethane are given in Table 1.

2.3 Analytical Methods

There are no published methods for the analysis of chlorodifluoroethane in air. The material has been measured routinely in inhalation toxicity studies using gas chromatography coupled with either thermal conductivity detectors or flame ionization detectors (Seckar et al, 1986; Hutton and Lieder, 1989).

3. PRODUCTION, STORAGE, TRANSPORT AND USE

There is no known natural source of chlorodifluoroethane. It is produced at the rate of several thousand tons each year, by liquid phase hydrofluorination of methylchloroform or vinylidene chloride.

Since chlorodifluoroethane is produced mainly as an intermediate, losses of product during production, transport and use are relatively small because of the completely closed system used.

All equipment used for transport and storage is designed to withstand high pressures. No information is available on accidental release. (See chapter 9.4).

Chlorodifluoroethane has a limited use, primarily as a chemical intermediate in the production of fluoropolymers, and is being developed as a substitute for some existing fully halogenated CFC's with comparable physical properties which may find applications as blowing agents and refrigerants.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Introduction

No information is available on the biodegradation of chlorodifluoroethane in the environment; a biodegradation study is in progress (Solvay, 1990).

4.2 Environmental Factors

The physical - chemical properties of chlorodifluoroethane suggest that it would mix rapidly in the troposphere. Reaction with naturally occuring hydroxyl radicals (OH) in the troposphere is expected to be the primary degradation route. The estimated atmospheric lifetime of this reaction is about 19.1 years (UNEP/WMO 1989).

The ozone depletion potential (ODP) is estimated to be 0.05 to 0.06 determined by one and two dimensional models respectively. This is compared with an ODP value of 1.0 for the fully halogenated trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12). The global warming potential (GWP) range for chlorodifluoroethane is reported by UNEP/WMO (1989) to be 0.34 to 0.39 as compared to CFC-11 and CFC-12 which have a GWP of 1.0 and 3.1 respectively. The range was determined by one dimensional models assuming a methylchloroform derived lifetime of 6.3 years.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Environmental levels and exposure of the general public are negligible since chlorodifluoroethane is produced as an intermediate. Occupational levels of 1,000 ppm = 8,200 mg/m^3 (t.w.a. 8h) and 4,000 ppm = 16,400 mg/m^3 (t.w.a. 15 min) have been proposed by WGD (1987).

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Tests with chlorodifluoroethane on environmental organisms have been carried out recently with aquatic organisms.

6.1 Fish Toxicity

The 96h -LC_{50} for guppies (Poecilia reticulata) was 220 mg/l tested in a static system according to OECD guidelines (Kuijpers and Groeneveld, 1990a).

6.2 Invertebrate Aquatic Species Toxicity

With Daphnia magna the 48h -EC_{50} was 160 mg/l tested in a static system according to OECD guidelines (Kuijpers and Groeneveld, 1990b). Hutton and Lieder (1989) found a static acute 48h - EC_{50} of chlorodifluoroethane to Daphnia magna > 190 mg/m^3.

7. KINETICS AND METABOLISM

7.1 Animal Studies

Specific kinetic and metabolic studies in vivo are not available, but analysis of selected tissues from rats and dogs exposed by inhalation for 13 weeks to 41,000 mg/m^3 did not reveal the presence of chlorodifluoroethane. No significant increase of inorganic fluoride in the urine was observed suggesting that no metabolism takes place (Kelly and Trochimowicz, 1976 see chapter 8.2). However, Van Dycke (1977) observed a slight dechlorination (0.6%) in vitro after incubation of chlorodifluoroethane with rat hepatic microsomes.

7.2 Human Studies

No data exist on absorption, distribution, metabolic transformation or elimination of chlorodifluoroethane in man.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 Single Exposures

As chlorodifluoroethane is a gas at room temperature, no information is available on acute oral and dermal toxicity.

Mice exposed to chlorodifluoroethane (isomer not specified) at concentrations above 1,800,000 mg/m^3 died after a few minutes and showed severe vascular disorders in the lungs and brain (plethora and perivascular edema); cells of the brain cortex were swollen. Concentrations between 1,300,000 and 1,800,000 mg/m^3 were fatal to mice exposed for 2h (Nikitenko and Tolgskaya, 1965). Davies et al, (1976) found the 30 min LC_{50} for chlorodifluoroethane in mice to be 1,230,000 mg/m^3.

Rats were exposed to chlorodifluoroethane concentrations of 615,000 mg/m^3 to 3,280,000 mg/m^3 for 30 min. Although slight intoxication was apparent on exposure to 615,000 mg/m^3, the postural reflex did not disappear until the concentration reached 820,000 mg/m^3. Unconsciousness occurred at 1,230,000 mg/m^3 and death at 2,050,000 mg/m^3. Effusion of fluid from the respiratory tract occurred on exposure to concentrations of 1,230,000 mg/m^3 (Lester and Greenberg, 1950).

Mecler and Knapinsky, (1978) exposed Charles River CD rats to 820,000 and 1,640,000 mg/m^3 of chlorodifluoroethane for 6h. Rapid and laboured breathing, lethargy and discharge from eyes and noses were observed only during exposure at the highest concentration. During exposure to 1,640,000 mg/m^3, there was 20% mortality after 5 - 5.5h. Necropsy of the surviving rats after 14 days observation revealed dark red mottling of the lungs and kidneys, especially in animals at the highest exposure level.

Carpenter et al (1949) classified chlorodifluoroethane as slightly toxic to Shermann rats. Deaths were observed in the range of 360,000 mg/m^3 to 740,000 mg/m^3.

The minimum (threshold) concentration of chlorodifluoroethane effecting the time and strength of the unconditioned reflex in rabbits was reported to be 49,200 to 90,036 mg/m^3 (Karpov, 1963).

In summary the primary toxic action of acute inhalation was central nervous system depression which only occurred at high exposure levels. Death from acute exposure was mainly due to the anaesthetic properties of chlorodifluoroethane.

8.2 Repeated Exposures

Rats and guinea pigs (number and strains not specified) were exposed 2h/d, 6d/w for 4 weeks to a concentration of 448,000 mg/m^3 chlorodifluoroethane (isomer not specified). Only at the end of the experiment was there a decrease in the rate of body weight gain, changes in the blood (lower haemoglobin and number of erythrocytes and moderate leucocytosis) and histopathological changes in the lungs (swelling of alveolar septa and peribronchitis). The authors considered these findings to be not significant (Nikitenko and Tolgskaya, 1965).

In another study ten adult white rats were exposed to 410,000 mg/m^3 of chlorodifluoroethane for 16 hours daily; all rats died within nine days. At autopsy, all rats had extensive consolidation of the lungs, indicative of irritation. The other organs appeared normal. Five additional rats were then exposed to a concentration of 41,000 mg/m^3 for 16 hours per day for two months. No signs of ill health were apparent at any time. Examination of the organs at autopsy revealed no pathological changes. Microscopic examination of the lungs showed mild, diffuse round cell infiltration in two of five rats suggesting chronic irritation of the lungs (Lester and Greenberg, 1950).

More recently ten male Charles River CD rats were exposed to chlorodifluoroethane by inhalation at a concentration of 82,000 mg/m^3 for 6h/d, 5d/w for two weeks. No clinical, haematological, blood chemical, urine analysis, or histopathological evidence of effects attributable to

repeated exposure to chlorodifluoroethane were found (Moore and Trochimowicz, 1976).

In a second study, Kelly and Trochimowicz (1976) exposed two groups of Charles River CD rats (27/sex/group) and two groups of male beagle dogs (4/group) were exposed to chlorodifluoroethane at levels of 4,100 mg/m^3, or 41,000 mg/m^3 for 6h/d, 5d/w for 90 days. There were no adverse clinical, haematological, urine analysis, blood chemistry, or histopathological effects attributable to chlorodifluoroethane exposure at either test level.

Also after long term exposure of Sprague Dawley CD rats at 82,000 mg/m^3 no evidence of respiratory irritation based on clinical observation and histopathologic evaluation was observed (Seckar et al, 1986; see chapter 8.3).

These recent studies do not support the earlier findings of irritation to the lungs and given the length of the studies and number of animals involved, the recent work would seen to be more credible.

8.3 Long Term Exposures

In a combined chronic toxicity/carcinogenicity study, four groups of 130 M and 110 F Sprague Dawley CD rats were exposed to chlorodifluoroethane concentrations of 4,200, 41,000 and 82,000 mg/m^3 for 6h/d, 5d/w for 104 weeks. No treatment related effects were found on mortality or body weight, on haematological, clinical chemical, urine analytical and ophthalmological findings, on histopathological examination of organ tissues or on the incidence of neoplasms (Seckar et al, 1986).

8.4 Skin and Eye Irritation, Sensitisation

No ocular irritation was seen in rabbits when liquified chlorodifluoroethane was instilled in the conjunctival sac. Skin irritation does not occur due to rapid volatilization (Seckar, 1989).

No data are available on allergic sensitisation.

8.5 Special Studies

8.5.1 Cardiovascular Sensitisation

The ability of chlorodifluoroethane to sensitise the heart to adrenaline was studied in beagle dogs. No responses were noted in 6 animals exposed to a chlorodifluoroethane concentration of 102,500 mg/m^3 for five minutes and then challenged with adrenaline (iv). Of 12 animals exposed to 205,000 mg/m^3, 5 dogs showed marked responses, and of the 12 dogs exposed to 410,000 mg/m^3 all showed marked responses (Reinhardt et al, 1971).

The effect of endogenous adrenaline on the cardiac sensitisation potential was also studied in dogs. Groups of 12 beagle dogs were exposed to 3,280,000 mg/m^3 of chlorodifluoroethane (80% w/w + 20% oxygen) for 30 seconds. An amplified sound-effect tape recording was played immediately after the exposure to stimulate the release of endogenous adrenaline. In combination with exposure to 3,280,000 mg/m^3 chlorodifluoroethane, the noise stimulus resulted in 5 out of 12 animals showing marked responses (5/12) compared with 1 out of 12 with the compound alone and none with the noise alone (Reinhardt et al, 1971).

8.5.2 Cardiovascular and Respiratory Function

Groups of 3 Rhesus monkeys (Macaca mulatta) were anaesthetised by iv injection of sodium pentobarbital and exposed for periods of 5 minutes to concentrations of 205,000 and 410,000 mg/m^3 (Belej et al, 1974). Chlorodifluoroethane did not produce arrythmia or tachycardia, the most characteristic effect being depression of myocardial contractility and a fall in aortic blood pressure.

Three anaesthetised Rhesus monkeys (Macaca mulatta) were exposed to 205,000 mg/m^3 and four to 410,000 mg/m^3 chlorodifluoroethane for five minutes. There was no effect on pulmonary resistance or compliance but respiratory stimulation was noted (Aviado and Smith, 1975).

Dogs were exposed from 102,500 mg/m^3 to 820,000 mg/m^3 chlorodifluoroethane for five minutes. At the high concentration hypotension, tachycardia, an increase in pulmonary resistance and a decrease in pulmonary compliance were observed (Belej and Aviado, 1975).

Aviado (1975) reviewed the available toxicity data from exposure of mice, rats, dogs and monkeys to aerosol propellants for the respiratory and circulatory systems of aerosol propellants and proposed a classification scheme. Chlorodifluoroethane was classed as a low pressure propellant of intermediate toxicity. Many other propellants displayed a higher potential to cause cardiac arrythmia (with and without adrenaline administration).

8.6 Reproductive Effects, Embryotoxicity and Teratology

8.6.1 Developmental Toxicity Potential

Two groups of 25 pregnant Sprague Dawley rats were exposed to 4,100 and 41,000 mg/m^3 chlorodifluoroethane for 6h/d from day 3-15 of gestation. The exposure had no effect on the body weight gain of the mothers. No clinical signs of toxicity were observed in any of the treated animals. The outcome of pregnancy (as measured by the number of implantations, early or late resorptions and number of live foetuses per litter) was not affected by the exposure. Chlorodifluoroethane was not embryotoxic. The exposure did not effect the embryonal development as measured by the weight and crown-rump length of the foetuses. The morphological examination of the foetuses provided no evidence of a teratogenic effect (Culik and Kelly, 1976).

No evidence of a teratogenic response was observed when groups of 20 pregnant Sprague Dawley CD rats were exposed to 8,200 or 41,000 mg/m^3 of chlorodifluoroethane, 6h/d during day 6 through day 15 of gestation (Danske et al, 1978).

8.6.2 Other Reproduction Studies

No data are available.

8.7 Mutagenicity and Genetic Toxicity

8.7.1 In vitro Studies

Salmonella typhimurium, strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, were exposed to chlorodifluoroethane at levels of 820,000 mg/m^3 and 1,640,000 mg/m^3 over 6 hours. No mutagenic response was seen in the presence or absence of a rat liver homogenate preparation (Barsky and Butterworth, 1976).

Chlorodifluoroethane was tested in Salmonella typhimurium, strains TA 1535, TA 1537, TA 98, and TA 100, in atmospheres that contained up to 2,050,000 mg/m^3 of the compound. A 48 hour exposure period was used. The gas was weakly mutagenic in strain TA 1535 both in the activated and non activated system (Koops and Krahn, 1977).

Jagannath and Brusick (1977) tested chlorodifluoroethane (concentration not specified) directly and in the presence of a rat liver microsomal homogenate preparation (S-9) with the same strains as described above and TA 1538, using exposure times of 1, 24, 48 and 72 hours. Chlorodifluoroethane exhibited genetic activity with the strains TA 1535 and TA 100 in the activated and non-activated assays.

Chlorodifluoroethane was positive in the Salmonella Reverse Mutation (Ames) Test in TA 1535 and TA 100 strains in presence of rat liver microsomal preparation (S9 mix) using an incubation period of 24 hours and concentrations up to 2,050,000 mg/m^3. Chlorodifluoroethane was also positive in the Cell Transformation (Styles) Assay with baby hamster kidney fibroblasts (BHK21) exposed in liquid phase (concentration not specified) in the presence of S-9 mix (Longstaff et al, 1984).

In contrast a negative result was found in a cell transformation test with mouse BALB/3T3/cells exposed to chlorodifluoroethane in gas phase (concentration not specified) for 1, 2, 4, 6 and 24 hours (Matheson and Brusick, 1978).

8.7.2 In vivo Studies

The mutagenic potential of chlorodifluoroethane was evaluated in a dominant lethal assay using Sprague Dawley CD rats. Groups of 10 male rats were exposed by inhalation to levels of 4,100, 41,000, or 82,000 mg/m^3, 6h/d, 5d/w for 15 weeks. The mutagenicity was evaluated using an 8 week post-treatment mating period on the basis of pregnancy rates (corporea lutea and implantation sites) in non-exposed females. Chlorodifluoroethane showed no activity in this test system. The body weight gain in the males exposed to 82,000 mg/m^3 was decreased (Seckar et al, 1986).

In a cytogenetic study groups of 10 male Sprague Dawley CD rats were exposed to 4,100, 41,000 or 82,000 mg/m^3 of chlorodifluoroethane 6h/d, 5d/w for 13 weeks. The animals were then killed and their bone marrow isolated, processed, and examined. A slight but statistically non-significant, increase in the mitotic index was observed in the mid- and high-level exposure groups. This was not attributed to the treatment by the authors. There were no increases in numbers of chromosome gaps at any exposure level. Increased numbers of chromosome breaks were observed in all dose groups when compared to the control group. The intergroup differences were neither statistically significant nor dose related. Retrospective analysis showed that some rats with increased numbers of chromosome breaks displayed evidence of a respiratory infection which could have contributed to the effect (Seckar et al, 1986).

8.7.3 Conclusion on Mutagenicity and Genetic Toxicity Data

Chlorodifluoroethane has shown weak positive results in the Ames-Test and equivocal results in cell transformation assays. Two negative *in vivo* assays (Dominant Lethal and Bone Marrow Cytogenetics), however suggest that chlorodifluoroethane does not present a genotoxic hazard for man.

8.8 Carcinogenicity

In a combined chronic toxicity/carcinogenicity study, 110 rats/sex/exposure level were exposed to chlorodifluoroethane at atmospheres up to 82,000 mg/m^3 for 6h/d, 5d/w for 104 weeks. No treatment related effects were seen relating to mortality, body weight, haematology, clinical chemistry, urinalysis, ophthalmoscopic findings, histopathological evaluation of tissues, or incidence of neoplasia (Seckar *et al*, 1986).

9. EFFECTS ON MAN

9.1 General Population Exposure

No data are available.

9.2 Occupational Exposure

There is no reliable information on workplace exposure to chlorodifluoroethane. Filicheva (1975) investigated 196 male and female workers (aged 20 - 40 years) involved in the production of chlorodifluoroethane (isomer not specified). The concentration exceeded the maximum acceptable concentrations on 10 or more times during the first three years of work and up to 10 times in the subsequent year; the actual concentrations were not specified. Functional disorders of the nervous system were found in 67% of cases. Changes included autonomic dysfunction often in combination with neurasthenic polyneuritis of the upper limbs. There were also changes in the peripheral blood, (reduced haemoglobin content, a moderately expressed

leukocytosis, and reduced erythrocyte sedimentation rate). The symptoms showed a persistence over several years. The authors considered the findings to be signs of chronic poisoning with fluorinated aliphatic hydrocarbons. This study is poorly reported and of limited value. Workers were exposed to high concentrations of a variety of other chemicals in addition to chlorodifluoroethane. There was no control of variables (such as alcohol consumption and tobacco), and no verifiable analytical methods were reported. Therefore, no causal relationship between chlorodifluoroethane exposure and any of the reported effect can be established.

9.3 Epidemiology

No data are available.

9.4 Safe Handling, First Aid, Medical Treatment and Transport.

Data has been supplied by Solvay et Cie (1989) and Du Pont de Nemours and Company (1990).

Handling : Earth all equipment and cylinders before use. Use explosive proof electrical equipment. No respiratory protection is required when using this product under normal conditions, but breathing high concentrations of vapours and liquid contact should be avoided. The use of lined neoprene gloves, chemical splash goggles and normal ventilation for standard manufacturing procedures are recommended for handling chlorodifluoroethane.

In case of accident it is recommended to remove persons to fresh air, to flush skin and eyes with plenty of water. In case of excessive skin/eye contact and difficult breathing, call a physician.

Notes to physician: Because of possible disturbances of cardiac rhythm, catecholamine drugs, such as epinephrine, should be used with special caution only in situations of emergency life support.

Transport: Use tank trucks, ton tanks and cylinders as shipping containers.

Hazard class : Flammable Cas.
UN/NA no. (no. ONU): 2517

Waste disposal: Reclaim the product by distillation, incinerate or remove to a permitted waste facility.

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Table 1: Physical and Chemical Properties of Chlorodifluoroethane

Molecular weight	: 100.5
Physical form	: gas
Colour	: colourless
Boiling point, °C at 1030HPa	: -9.2
Melting point, °C	: -130.8
Liquid density at 20°C, g/ml	: 1,123
Vapour density in air	: 3.5
Vapour pressure, psia at 20°c	: 42.0
Solubility in water at 25°g/l	: 1,9
Solubility in organic solvents	: soluble in acetone esters alcohol, etc
Flammability	: flammable (6 - 18 %)

Solvay & Cie Safety data sheet no 424 (1989)

APPENDIX 1

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