Joint Assessment

of Commodity Chemicals

No.14

1-CHLORO-2,2,2-TRIFLUOROETHANE (HFA-133a)

CAS: 75-88-7

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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 chlorotrifluoroethane is presented. Strictly this is not a commodity chemical, but in view of the interest that exists in alternatives to the fully halogenated 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

1-chloro-2,2,2-trifluoroethane (chlorotrifluoroethane) is a non-flammable, colourless and nearly odourless gas. It is manufactured on a small scale as a chemical intermediate primarily for the production of the anaesthetic halothane. The amount released into the atmosphere results from fugitive losses during manufacture and is, therefore, very small. It is assumed to have a short atmospheric lifetime and is essentially broken down in the troposphere.

The physical properties of chlorotrifluoroethane indicate a negligible potential for bioaccumulation. Similarly, contamination of water and food would not be expected.

Chlorotrifluoroethane has an extremely low order of acute toxicity which is characterised by central nervous system depression. An atmospheric concentration of 388,000 mg/m^3 for 10 min is required to produce anaesthesia in mice whilst 1,019,000 mg/m^3/10 min kills mice.

Repeated exposures for up to 13 weeks 6h/d 7d/week result in central nervous system depression, the no-effect levels for this being 2,400 mg/m^3 in the mouse and 24,000 mg/m^3 in the rat and dog. Testicular atrophy was found in rats exposed to 48,000 mg/m^3 but effects on fertility have not been investigated. Following exposure for 6h/d for 5 days, similar adverse effects on the testes were seen at 2,400 mg/m^3 and above in the mouse with damage to the germinal epithelium, an increased incidence of abnormal sperm and reduced fertility. The no-effect level for fertility in the mouse was 485 mg/m^3.

The teratogenic potential of chlorotrifluoroethane has not been unequivocally established but it is embryotoxic in rats at 2,400 mg/m^3 and embryolethal in rabbits at 24,000 mg/m^3.

Chlorotrifluoroethane is not mutagenic either *in vitro* (*Salmonella* reverse mutation test and cell transformation assay) or *in vivo* (cytogenetic and dominant lethal studies).

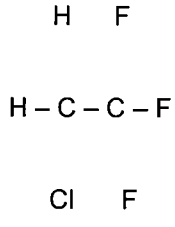
There are no inhalation studies longer than 13 weeks but an oral gavage study in which rats were dosed at 300 mg/kgbw, 5d/wk for 52 weeks has indicated that chlorotrifluoroethane is carcinogenic in the rat. Males showed an increased incidence of benign interstitial cell neoplasms of the testis, many of which were bilateral. All males, in addition, showed marked tubular atrophy of the testis even when tumours were not present. Females showed an increased incidence of uterine adenocarcinomas, many with transcoelomic metastatic deposits within the abdominal cavity.

There are no national permissible exposure limits for chlorotrifluoroethane but companies manufacturing hygiene standards from 5mg/m^3 to 24 mg/m^3 are applied in operations involving its use. No adverse health effects in man have been reported.

2. IDENTITY. PHYSICAL AND CHEMICAL PROPERTIES. ANALYTICAL METHODS

2.1 IDENTITY

Chemical Structure:



Chemical Formula: $CH_2Cl\text{-}CF_3$

Common Name: 1-chloro-2,2,2-trifluoroethane,
chlorotrifluoroethane.

Common Synonyms: 'Arcton' 133a; CFC 133a; HFA-133a*
2-chloro-1,1,1-trifluoroethane; FC 133a; R 133a;
1,1,1-trifluoro-2-chloroethane;
2,2,2-trifluorochloroethane;
1,1,1-trif1uoroethyl chloride.

CAS Registry Number: 75-88-7

Conversion Factors: 1ppm = 4.92 mg/m^3
1mg/l = 203ppm

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* HFA-133a abbreviation means: Hydrofluoroalkane : $C_2H_2F_3Cl$

First Figure	= Number of C-Atoms minus 1	1
Second Figure	= Number of H-Atoms plus 1	3
Third Figure	= Number of F-Atoms	3

a represents the isomer HFA133a

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

Chlorotrifluoroethane is nearly odourless, colourless, non-flammable gas. Its physical and chemical data are summarised in Table 1.

2.3 ANALYTICAL METHODS

Methods using gas chromatography in toxicological studies have been described by Leuschner *et al* (1977), Kilmartin *et al* (1980) and Hodge *et al* (1980).

3. PRODUCTION. STORAGE. TRANSPORT AND USE

There is no known natural source of chlorotrifluoroethane. It is produced in small quantities from trichloroethylene (trichloroethene; $CHC1=CC1_2$) in a liquid-phase process involving an antimony halide catalyst. Chlorotrifluoroethane has a limited market primarily as a chemical intermediate in the manufacture of the inhalation anaesthetic halothane (1-bromo-chlorotrifluoroethane) (McNeill, 1979).

4. ENVIRONMENTAL TRANSPORT. DISTRIBUTION AND TRANSFORMATION

4.1 INTRODUCTION

Chlorotrifluoroethane release into the environment is low, resulting from fugitive losses during the manufacturing processes.

4.2 TRANSPORT. DISTRIBUTION AND TRANSFORMATION

Chlorotrifluoroethane has a relatively high Henry's Constant, logH = 0.04 (Nirmalakhandan and Speece, 1988). Because of this and the fact that its release is almost entirely into the atmosphere, entry into the aquatic environment or soil will be negligible. This suggests that chlorotrifluoroethane would mix rapidly in the troposphere where reaction with naturally occurring hydroxylradicals (OH) is expected to be the primary degradation route. The tropospheric lifetime for chlorotrifluoroethane is 4.8 years, based on a calculated rate of this reaction (Makida and Rowland, 1978; UNEP/WMO 1989). The estimates were made

assuming that the reference chemical methylchloroform has a tropospheric lifetime of 6.3 years. This lifetime allows a small percentage of the product to survive to reach thestratosphere. An ozone depletion potential (ODP) value has not been determined.

4.3 BIODEQRADATION

There is no information available on the biodegradation of chlorotrifluoroethane.

4.4 BIOCONCENTRATION AND BIOACCUMULATION

There is no information on the bioconcentration and bioaccumulation of chlorotrifluoroethane. However, they are not likely to occur to any measurable extent, as a result of the high Henry's constant and the consequent tendency for the product to partition into the atmosphere.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 ENVIRONMENTAL LEVELS

5.1.1 Air

Levels of chlorotrifluoroethane in ambient air have never been measured but are expected to be below detection because of the small scale of manufacture and the absence of any dispersive use.

5.1.2 Water

Because of its physicochemical properties and low production volumes, the levels of chlorotrifluoroethane in water are expected to be negligible.

5.2 HUMAN EXPOSURE

The only potential for human exposure is to the operatives employed on plants manufacturing chlorotrifluoroethane for the production of halothane. All operations involving this chemical adhere to internal hygiene standards between 5 mg/m^3 and 24 mg/m^3 for an 8h TWA.

6. EFFECT ON ORGANISMS IN THE ENVIRONMENT

No data available. The quantities present in the environment and effects on organisms in the

environment are expected to be negligible.

7. KINETICS AND METABOLISM

7.1 ANIMAL STUDIES

7.1.1 Absorption

There are no quantitative data on absorption of chlorotrifluoroethane. Shulman and Sadove (1965) indicate that absorption by inhalation is rapid in mice and dogs (see Section 8.1).

7.1.2 Distribution

There are no data on distribution of chlorotrifluoroethane in tissues.

7.1.3 Metabolic Transformation

Evidence for dechlorination of chlorotrifluoroethane has been reported by Salmon *et al* (1981) in an *in vitro* study utilising a microsomal preparation derived from Aroclor 1254 induced rat liver homogenates. There are no data on *in viva* metabolism of chlorotrifluoroethane.

7.1.4 Elimination

There are no quantitative data on elimination of chlorotrifluoroethane but Shulman and Sadove (1965) have indicated that rapid recovery follows cessation of exposure. (See Section 8.1).

7.2 HUMAN

No data are available on toxicokinetics and metabolism in man.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 SINGLE EXPOSURE

Inhalation of extremely high concentrations of chlorotrifluoroethane is characterised by signs of anaesthesia followed by death but recovery from non-lethal exposures is rapid.

The concentrations and duration of exposure at which chlorotrifluoroethane causes anaesthesia and death in mice are shown in Table 2. The lethal concentration of chlorotrifluoroethane for a 10 min exposure period in mice was 1,213,000 mg/m^3 (Robbins, 1946) or 1,019,000 mg/m^3 (Shulman and Sadove, 1965). The lethal concentration for a 30 min exposure in mice was 728,000 mg/m^3 (Raventos and Lemon, 1965). The concentration causing anaesthesia in mice for a 10 min exposure period was 388,000 mg/m^3 (Robbins, 1946; Shulman and Sadove, 1965) and 209,000 mg/m^3 for a 30 min exposure period (Raventos and Lemon 1965). Robbins (1946) and Raventos and Lemon (1965) reported convulsions either during exposure or recovery. In contrast, Shulman and Sadove (1965) stated that convulsions were not seen and that induction of, and recovery from, anaesthesia was rapid. For example, 728,000 mg/m^3 produced anaesthesia in 45 sec and a return of the righting reflex after an anaesthetic period of 10 min was 30 sec.

Diggle and Gage (1956) reported that 2,400,000 mg/m^3 chlorotrifluoroethane caused death in rats after an exposure period of 8 min. Death was preceded by incoordination and anaesthesia (see Table 3).

Shulman and Sadove (1965) have investigated the effects of inhalation of chlorotrifluoroethane in dogs (Table 4). Ten dogs were exposed to chlorotrifluoroethane via an endotracheal catheter. Respiratory rate, pulse rate, arterial pressure, central venous pressure and ECG were recorded. Anaesthesia was seen at concentrations between 388,000 and 631,000 mg/m^3. Circulatory depression did not occur until relatively high concentrations (970,000 -2,910,000 mg/m^3) were attained and there was a wide range between respiratory and subsequent circulatory arrest concentrations. Dogs were easily resuscitated following concentrations which caused asystole (1,455,000- 3,880,000 mg/m^3) and the dogs appeared normal following resuscitation. Pathological studies on tissues were not reported in these single-exposure studies.

Thus, the primary toxic effect of acute inhalation of chlorotrifluoroethane was central nervous system depression and this occurred only at extremely high concentrations.

8.2 REPEATED EXDOSURE

Shulman and Sadove (1965) exposed mice to anaesthetic concentrations of chlorotrifluoroethane for 30 min/d on twelve consecutive days. They were killed for pathological evaluation after the last exposure by overdosage of chlorotrifluoroethane. None of the mice showed any ill effects as a result of the repeated exposures and no pathological changes were seen in the organs (heart, lung, liver, kidney, adrenal, spleen and pancreas) examined microscopically. The same authors reported that one dog which was anaesthetised for 1h, ten times within a 2 wk period showed no ill effects although pathological evaluation was not reported.

The effects of repeated exposures (duration approximately 6h/d) in groups of 2-3 female rats have been investigated by Diggle and Gage (1956) (Table 3). Concentrations of between 48,000 and 120,000 mg/m^3 caused incoordination and lethargy whilst at 240,000 or 480,000 mg/m^3 rats became comatose. They recovered between each exposure and no dose-related pathological changes were detected on histological examination. No effects were seen at 24,000 mg/m^3.

Leuschner *et al* (1977) exposed 20 male and 20 female Sprague-Dawley rats to 48,000 mg/m^3 chlorotrifluoroethane, 6 h/d, daily for 90 d. A control group of 20 male and 20 female rats were exposed to air only. Investigations were performed on clinical behaviour, body-weight, food consumption, haematology, blood clinical chemistry, urine clinical chemistry, urine sediments, ophthalmoscopy, auditory acuity, organ weights and histopathology. There were no deaths. The rats were sedated during each exposure but appeared normal before and after, although 17 out of 40 rats developed bloody and inflamed noses; this was associated with histological evidence of inflammatory changes in the nasal mucosa. Body-weight gain of the treated rats was reduced so that terminal body-weights were approximately 28% and 17% lower than controls for males and females respectively. Food consumption of the treated groups was also lower than controls. Haemoglobin, haematocrit, red blood cell counts and platelet counts were slightly reduced. Reductions in leucocyte counts of approximately 30% were seen and reticulocyte counts were increased by approximately 40%. There were reductions in plasma glucose levels of approximately 15% and in protein levels of approximately 10%. Bromsulphthalein retention time was increased approximately 35% and 62% in males and females respectively but there were no changes in plasma enzyme (GPT/AP/GOT) activity. Thymus weights relative to body-weight were reduced by approximately 50% and testis and ovary weights relative to body-weight by approximately 60 and 35% respectively. Atrophy was seen histologically in these organs. Thyroid weights relative to body-weight were increased by approximately 45% but only in males. Atrophy occurred of the spleen. Changes in the lungs included emphysema, oedema, bronchitis and pneumonia.

Since only one exposure level was used in this study the significance of some of the findings is uncertain. Most of the changes may have been a consequence of the effect on body-weight although the testicular atrophy is consistent with the findings in three dominant lethal studies in mice (Hodge *et al*, 1979, 1980; Kilmartin *et al*, 1980) and a carcinogenicity study in rats (Longstaff *et al*, 1984).

Leuschner (1977) exposed six Beagle dogs to 24,000 mg/m^3 chlorotrifluoroethane 6h/d, daily for 3 months. Six control dogs were exposed to air only. No effects were seen on behaviour or external appearance, faeces, food and water consumption, body-weight gain, haematology, blood and urine clinical chemistry, urine sediments, electrocardiography, blood pressure, ophthalmoscopy, hearing and dentition. There were no macroscopic changes or effect's on organ weights at autopsy and no histological changes were seen on microscopic examination of the tissues.

The effects of repeated inhalation exposures (6h/d for 5d) in groups of 20 male CD-1 mice are also available from a series of dominant lethal studies. Hodge *et al* (1979) reported that 4,800 mg/m^3 had no clinical effects but at 48,000 mg/m^3 and 96,000 mg/m^3 (reduced to 24,000 mg/m^3 after 2 days due to high mortality rate) the mice were subdued. At 48,000 mg/m^3, 8/20 mice died whilst at 96,000/24,000 mg/m^3 concentrations 6/20 died. There was no pathological evaluation in this study.

A second study was conducted at 12,000 and 48,000 mg/m^3 6h/day for 5d (Hodge *et al*, 1980). The mice were subdued and 17/60 died at 12,000 mg/m^3 whilst 27/80 died at 48,000 mg/m^3. Body-weight gain at both exposure levels was reduced during the treatment period. Reductions in testis and epididymis weights were seen in mice killed at weekly intervals up to 9 wk after treatment and there was also an increased incidence of abnormal sperm in the treated groups. Histological examination of the testis revealed damage to the germinal epithelium affecting spermatogonia and spermatocytes but there was evidence of recovery after five weeks particularly at 12,000 mg/m^3.

A third study was conducted at exposure levels of 485, 2,400, 4,800 and 12,000 mg/m^3 (Kilmartin *et al*, 1980). All treated groups had slightly lower weight gains than controls and the mice were subdued at 4,800 and 12,000 mg/m^3; 18/60 mice died at 12,000 mg/m^3 and 4/60 died at 4800 mg/m^3; 1/59 mice died at 485 mg/m^3 but since there were no mortalities at 2,400 mg/m^3 this was probably incidental to treatment. Reductions in testis and epididymis weights were seen in mice killed at weekly intervals up to 9 wk after treatment at exposure levels of 2,400 mg/m^3 and above, whilst at 485 mg/m^3 testis and epididymis weights were reduced only in week 7. There was also an increased proportion of abnormal sperm in all treated groups although this was minimal at 485 mg/m^3. Microscopic examination of the testes showed that exposure levels of 2,400 mg/m^3 and above caused damage to the germinal epithelium which

affected the normal production of sperm. No histological changes were seen at 485 mg/m^3.

These three studies demonstrate that exposure for 6h/d for 5 days to chlorotrifluoroethane has an adverse effect on the mouse testis at 2,400 mg/m^3 and above. An isolated reduction in testis and epididymis weights and a minimal effect on sperm morphology were seen at 485 mg/m^3 but there were no histological changes. These studies are discussed further with respect to reproductive effects and mutagenicity in Sections 8.6 and 8.7.

In conclusion, repeated exposures to chlorotrifluoroethane for up to 13 weeks resulted in central nervous system depression, the no-effect level being 2,400 mg/m^3 in the mouse and 24,000 mg/m^3 in the rat and dog. Testicular atrophy was seen in rats at 48,000 mg/m^3 but the no effect level has not been determined. Repeated exposure over 5 days had an adverse effect in the testis at 2,400 mg/m^3 and above in the mouse; minimal changes were seen at 485 mg/m^3.

8.3 LONG TERM EXPOSURE

There are no data on the inhalation toxicity of chlorotrifluoroethane for a duration of longer than 90 days.

8.4 SKIN AND EYE IRRITATION DERMAL AND RESPIRATORY SENSITISATION

There are no data on the potential irritancy or allergenic properties of chlorotrifluoroethane. In the liquid state, local freezing of tissues is likely due to a reduction in temperature during evaporation.

8.5 CARDIOVASCULAR AND RESPIRATORY EFFECTS

The only reported data on cardiovascular and respiratory effects of chlorotrifluoroethane is that of Shulman and Sadove (1965) (see Section 8.1). An increased sensitivity of the heart to adrenaline (cardiac sensitisation) during inhalation of high concentrations of chlorotrifluoroethane may be anticipated since it occurs with several other halogenated ethanes (Clark and Tinston, 1973; Reinhardt *et al*, 1971).

8.6 REPRODUCTIVE EFFECTS, EMBRYOTOXICITY AND TERATOGENICITY

8.6.1 Effects on Fertility:

The effects of exposure to chlorotrifluoroethane on the fertility of male mice are available from three dominant lethal studies (Hodge *et al*, 1979, 1980; Kilmartin *et al*, 1980) in which male CD-1 mice were exposed to various concentrations of chlorotrifluoroethane for 6h/d for 5 d (see Section 8.7 and Table 5).

Each treated male was then serially mated with two virgin females over four days at weekly intervals for 8 or 9 weeks. The females were killed 15d later and their uteri examined for numbers of live implantations, early deaths and late deaths. The major finding from these studies was a reduction in the number of pregnancies at concentrations of 2,400 mg/m^3 and above. This is consistent with a reduced fertility of the males resulting from an adverse effect of chlorotrifluoroethane on the testis (see Section 8.2). No effects on male fertility were seen at 485 mg/m^3.

8.6.2 Embryotoxic and Teratogenic Effects

Culik and Kelly (1979) investigated the potential embryotoxic and teratogenic effects of chlorotrjfluoroethane in Charles River-CD rats. Rats were exposed to 0 (controls), 2,400, 9,600, 24,000 or 96,000 mg/m^3, 6h/d, on days 6 to 15 of gestation (the day on which sperm were found in the vaginal smear was considered to be day 1 of gestation) and were subjected to autopsy on day 21 of gestation. Evidence of embryotoxicity was seen at all exposure levels. In the control and the 2,400 mg/m^3 groups, there were no foetal deaths nor total litter resorptions. Foetal weights and crown-rump length were lower in the 2,400 mg/m^3 group than in controls. At 9,600 mg/m^3, 4/21 pregnant females had total resorptions and only 67 foetuses were alive in the other females. At 24,000 mg/m^3, 37/41 pregnant females had total resorptions and only 7 foetuses were alive in the other females. At 96,000 mg/m^3. 22/23 pregnant females had total resorptions and only one foetus was alive in the other female. Foetal weights and crown-rump length were also lower than controls in the groups exposed to 9,600 mg/m^3 and above. Thus, the no-effect level for embryo-lethality was 2,400 mg/m^3 but in view of the reduced foetal size and weight also seen at this dose level the no-effect level for embryotoxicity was not established.

In the same experiment, treatment related increases in the incidence of number of runts and delayed ossification in several bone structures were seen at exposure levels of 2,400 mg/m^3 and above. These were considered to be reflections of embryotoxicity and consequent retarded foetal development.

An increased incidence of hydronephrosis was reported in all treated groups. However, during the late part of gestation, there is a transient disparity in the growth rates of the renal papilla and parenchyma which results temporary in an enlargement of the renal pelvis. This apparently increased incidence of hydronephrosis was therefore consistent with interference by chlorotrifluoroethane with timely organ development.

Five malformations were seen affecting five foetuses in five different litters. One control foetus had scoliosis; in the 9,600 mg/m^3 group one foetus showed *situs inversus* together with generalised oedema, one a hydrocephalus-like syndrome and one with anophthalmia. One foetus with microphthalmia Occurred in each of the 9,600 and 24,000 mg/m^{3}groups.

Weigand *et al* (1977) further investigated the potential embryotoxic and teratogenic effects of chlorotrifluoroethane in Wistar rats and Himalayan rabbits and also examined the effects of pre-treatment with progesterone to determine whether there was any disturbance of hormonal status in early pregnancy. Twenty four pregnant Wistar rats, of which twelve were injected s.c. with progesterone (6 mg/d) prior to exposure, were exposed to 24,000 mg/m^3 chlorotrifluoroethane 6h/d on days 7 to 16 of gestation (the day on which sperm were found in the vaginal smear was considered to be day 1 of gestation). Twelve Himalayan pregnant rabbits were exposed to the same concentration 6h/d on days 7 to 19 of gestation (the day of mating was designated day 0 of gestation). Since this was intended to be a preliminary study, no controls were used and data were compared with historical control data.

In rats, mild transient sedation, piloerection, reduced bodyweight gain and reduced food consumption were seen. At autopsy on day 21 of gestation, no macroscopic changes were seen. A prenatal mortality of 77% was seen in the rats which were not pre-treated with progesterone and of 82% in rats pre-treated with progesterone. Placental weight, foetal weight and crown-rump length were reduced and some of the surviving foetuses showed generalised oedema (8/53) and external anomalies of the limbs and tail (5/53). There was no significant difference between the rats pre-treated with progesterone and those not pre-treated.

In rabbits, there was a reduction in body-weight gain and food consumption. All animals showed vaginal bleeding during the last three days of the exposure, and four out of twelve animals aborted. By autopsy on day 29, all foetuses had died.

This study shows that chlorotrifluoroethane is embryotoxic in rats and rabbits at a concentration of 24,000 mg/m^3 but the high embryolethality, precluded the study from providing evidence teratogenic potential.

8.6.3 Evaluation

The studies described above show that chlorotrifluoroethane has an adverse effect on the

fertility of male mice at a concentration of 2,400 mg/m^3 and above, the no-effect level being 485 mg/m^3. In addition, a concentration of 2,400 mg/m^3 and above is embryotoxic in rats but a no-effect level has not been established. In rabbits, 24,000 mg/m^3 is embryolethal and lower concentrations have not been tested in this species. The teratogenic potential of chlorotrifluoroethane has not been unequivocally established.

8.7 MUTAGENICITY

The data from *in vivo and in vitro* studies are summarised in Tables 5 and 6.

Chlorotrifluoroethane was non-mutagenic in the *Salmonella typhimurium* TA98, TA100 reverse mutation (Ames) test (McGregor, 1976; Edmunds *et al*, 1979; Waskell, 1979) and gave negative results in the cell transformation (Styles) assay (Longstaff *et al*, 1984).

Anderson and Richardson (1979) performed a cytogenetic study in Alpk/Ap(Wistar-derived) male rats exposed to 4,800, 24,000 or 96,000 mg/m^3 chlorotrifluoroethane for 6h only or for 6h/d for 5d. Bone marrow samples were assessed for chromosomal abnormalities. A statistically significant increase in chromosomal abnormalities was seen at 24,000 mg/m^3 but only if gaps were excluded. In the multiple exposure group there was a severe effect on mitosis and the increase was made significant by the Occurrence of one break in one rat in which only two cells were examined. In the single exposure group, the increase was due to the unusually low rate of breaks in the control group. It was concluded that chlorotrifluoroethane was not clastogenic in rat bone marrow cells.

Three dominant lethal studies on chlorotrifluoroethane have been performed in male CD-1 mice via the inhalation route. Hodge *et al* (1979) reported that treatment with 48,000 or 96,000 mg/m^3 (the top dose level was reduced to 24,000 mg/m^3 after 2 days) caused a statistically significant increase in the incidence of early deaths in the animals mated in weeks 6-8. No effects were seen at 4,800 mg/m^3. Nevertheless, in week 6, the number of males mating was low and in weeks 7 and 8 the incidence of early foetal deaths was particularly low in the controls. This together with high dose levels and the change in exposure levels at the top dose makes the findings of doubtful value.

A second study was conducted at 12,000 and 48,000 mg/m^3 (Hodge *et al*, 1980). The number of early foeta7 deaths was statistically significantly increased in the treated groups in week 7 but there was no evidence of a dose-response relationship. Evaluation of this study is also difficult in view of the high dose levels used.

In a third study conducted at 485, 2,400, 4,800 and 12,000 mg/m^3 (Kilmartin *et al*, 1980) there was no evidence for any mutagenic activity based on the incidence of early death. These three

dominant lethal studies provide no consistent evidence of mutagenicity.

In conclusion chlorotrifluoroethane has not been demonstrated to be mutagenic either *in vitro* (Ames. test and Styles assay) or *in vivo* (cytogenetic and dominant lethal studies).

8.8 CARCINOQENICITY

8.8.1 Experimental Data

The carcinogenic potential of chlorotrifluoroethane has been assessed in Alpk/AP (Wistar derived) rats (Longstaff *et al*, 1984). The groups consisted of one undosed control (32 male and 32 female), two vehicle dosed controls (one containing 40 male and 40 female and one containing 36 male and 36 female) and one treated with chlorotrifluoroethane (36 male and 36 female). The chlorotrifluoroethane was dissolved in corn oil to give a 3% solution and dosed by gavage at 300 mg/kgbw 5d/wk. Dosed controls were given corn oil at 1 ml/kgbw. The dosing period was 52 weeks and the study was terminated at week 125. All animals found dead or killed during the study and those killed at termination were subjected to a full post mortem examination. Reductions in body-weight gain and decreased testicular size were seen in males receiving chlorotrifluoroethane. Aggressive behaviour occurred, particularly in males. Body-weight gain in females was similar to controls and mortality in both sexes was not affected by treatment. Females receiving chlorotrifluoroethane had an increased incidence of uterine carcinomas (15/35) in comparison with controls (1/104). The first of these carcinomas was seen at week 84. The carcinomas had metastasised transcoelomically to the abdomen in a large proportion of animals. A small proportion also showed lung metasteses. Histologically the neoplasms were actively infiltrating adenocarcinomas. Males dosed with chlorotrifluoroethane showed an increased incidence of benign interstitial cell neoplasms of the testis (29/36) compared with controls (4/28, 9/36, 3/40). In many animals the neoplasms were bilateral. The first interstitial cell tumour was seen at week 64. The testes of all males dosed with chlorotrifluoroethane (including those with no evidence of neoplasms) showed arrest of spermatogenesis and atrophy of the seminiferous tubules. This change was first seen at week 37.

8.8.2 Evaluation

Chlorotrifluoroethane is carcinogenic in rats when administered by the oral route by gavage. This method of exposure is inappropriate to the form of exposure expected from normal use of the substance. Only one dose level was used so that there is no indication whether lower doses or whether exposure by inhalation would have similar effects. Since chlorotrifluoroethane is not genotoxic, it is likely that its carcinogenic activity is the result of an epigenetic mechanism, for instance by disturbance of hormonal balance of the male and female animals.

IARC (1986) concluded from the same data that there is limited evidence for the carcinogenicity of chlorotrifluoroethane to experimental animals.

EFFECTS ON MAN

There are no reported adverse health effects of chlorotrifluoroethane from occupational exposures.

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Table 1

PHYSICAL ANO CHEMICAL DATA OF
1-CHLORO-2,2,2 -TRIFLUOROETHANE (Weast, 1989)

Formula	$CH_2Cl\text{-}CF_3$
Molecular weight	118.49
Physical form	gas
Colour	colourless
Boiling point °C at 1013HPa	6.93
Freezing point °C	-105.5
Relative density at 0°C	1.39
Refractive index at 0°C	1.309
Henry's constant logH	0.04 (Nirmalakhandan and Speece, 1988)

Table 2.

ANAESTHETIC CONCENTRATIONS AND LETHAL CONCENTRATIONS OF 1-CHLORO-2,2,2-TRIFLUOROETHANE AFTER SINGLE EXPOSURE IN MICE

AC50 (mg/m^3)	LC50 (mg/m^3)	LC50/AC50	Duration (min)	Comments	Reference
388,000	1,213,000	3	10	Convulsions on recovery	Robbins (1946)
209,000	728,000	3.5	30	Convulsions	Raventos and Lemon (1965)
388,000	1,019,000	2.6	10	No convulsions	Shulman and Sadove (1965)

Table 3:

EFFECTS OF REPREATED INHALATION EXPOSURE OF 1-CHLORO-2,2,2-TRIFLUOROETHANE IN FEMALE RATS.

From Diggle and Gage (1956) – (strains not specified)

Concn. mg/m^3	Exposure Regimen	Comments
2,400,000		Incoordination 3 min.
		Anaesthesia 4 min. Death 8 min.
480,000	2 x 6 hr	Comatose/staggering gait
	1 x 3 hr	Recovered between exposures. Thickening of alveolar walls of lungs.
240,000	1 x 6.5 hr	Lethargy. Thickening of alveolar walls of lungs.
	5 x 6.5 hr	Incoordination 30-40 min. Comatose Recovered between exposures. No hostological changes
120,000	8 x 6 hr	Hunched/uncoordinated. Dilation of unvoluted tubules of kidneys
48,000	7 x 5.5 hr	Signs of discomfort/lethargy. Recovery between exposures. No histological changes
24,000	7 x 6 hr	No ill effects.

Table 4.

MEAN AND EXTREME CONCENTRATIONS OF 1-CHLORO-2,2,2-TRIFLUOROETHANE WHICH PRODUCED SPECIFIC EFFECTS IN 10 DOGS. From Shulman and Sadove (1965) (strains not specified)

	Concn. for anaesthesia	Concn. for noticeable respiratory depression	Concn. for respiratory arrest	Concn. to lover systolic arterial pressure below 100mm/Hg	Concn. for asystole
Minimum (mg/m^3)	388,000	824,500	1,115,500	970,000	1,455,000
Maximum (mg/m^3)	631,000	1,552,000	1,988,500	2,988,500	3,880,000

Table 5.

THE GENETIC TOXICOLOGU OF 1-CHLORO-2,2,2-TRIFLUOROETHANE IN VIVO STUDIES

SPECIES/STRAINS	ASSAY	EXPOSURE	RESULT	REFERENCE
Male Rat (Alpk/ap Wistar-derived)	Cytogenetics bone marrow	4,800, 24,000, 96,000 mg/m^3 1 x 6h or 5 x 6 h	-ve	Anderson and Richardson (1979)
Mouse (CD-1)	Dominant lethal	4,800, 24,000, 96,000 mg/m^3 5 x 6 h	-ve	Hodge et al (1979)
Mouse (CD-1)	Dominant lethal	12,000, 48,000 mg/m^3 5 x 6 h	-ve	Hodge et al (1980)
Mouse (CD-1)	Dominant lethal	485, 2,400, 4,800, 12,000 mg/m^3 5 x 6 h	-ve	Kilmartin et al (1980)

Table 6.

THE GENETIC TOXICOLOGY OF 1-CHLORO-2,2,2-TRIFLUOROETHANE IN VIVO STUDIES

ASSAY	STRAIN/TYPE	METABOLIC ACTVATION	EXPOSURE	RESULTS	REFERENCE
Salmonella typhimurium	TA98, TA100	+/- Aroclor included rat liver s-9	24,000 – 480,000 mg/m^3 8h	-ve	Edmunds et al (1979)
Salmonella typhimurium	TA98, TA100	+/- Aroclor included rat liver s-9	4,800 – 2,400,000 mg/m^3 48h	-ve	Waskell (1979)
Salmonella typhimurium	TA98, TA 100 TA1535, TA1538	+/- Aroclor included rat liver s-9	48,000 – 2,400,000 mg/m^3 24h	-ve	McGregor (1976)
Salmonella typhimurium	BHK21	Aroclor included rat liver s-9	Gas or liquid 3h	-ve	Longstaff et all (1984)

APPENDIX 1

MEMBERSHIP OF THE ECETOC TASK FORCE HFA133A

D. Mayer	Hoechst AG D
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C. Stevens	ISC Chemcial Ltd GB
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Appendix 2

Members of the Scientific Committee

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