# JACC Report

# No 31

# 1,1,1,2-Tetrafluoroethane (HFC-134a)

# CAS No. 811-97-2

# February 1995

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# ECETOC

# Joint Assessment of Commodity Chemicals No. 31

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## (HFC-134a)

## CAS No. 811-97-2

February 1995

European Centre for Ecotoxicology
and Toxicology of Chemicals

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# THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals.

In the programme, commodity chemicals, that is those produced in large tonnage by several companies and having widespread and multiple uses, are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

ECETOC is not alone in producing such reviews. There are a number of organisations that have produced and are continuing to write reviews with the aim of ensuring that toxicological knowledge and other information are evaluated. Thus a Producer, Government Official or Consumer can be informed on the up-to-date position with regard to safety, information and standards. Within ECETOC we do not aim to duplicate the activities of others. When it is considered that a review is needed every effort is made to discover whether an adequate review exists already; if this is the case the review is checked, its conclusions summarised and the literature published subsequent to the review assessed. To assist ourselves and others working in this field we publish annually a summary of international activities incorporating work planned, in hand, or completed on the review of safety data for commodity chemicals. Interested readers should refer to our Technical Report No. 30 entitled "existing Chemicals: Literature Reviews and Evaluations".

This document presents a critical assessment of the toxicology and ecotoxicology of Tetrafluoroethane (HFC 134a; CAS No. 811-97-2).

# 1,1,1,2-Tetrafluoroethane (HFC-134a) CAS No. 811-97-2

## CONTENTS

# SECTION 1. SUMMARY AND CONCLUSIONS

Tetrafluoroethane is a non-flammable, colourless gas with a faint ethereal odour. It is being developed as a substitute for fully halogenated chlorofluorocabons and for partially halogenated hydrochlorofluorocarbons. Its main current applications are in refrigeration and air conditioning (domestic, automotive and industrial), in which it is used either alone or as a component of blends.

Tetrafluoroethane, when released to the environment, partitions almost exclusively into the atmosphere. Degradation of tetrafluoroethane will occur mainly in the troposphere by reaction with hydroxyl radicals leading to trifluoroacetic acid, formic acid, hydrofluoric acid and carbon dioxide as ultimate degradation products. The overall atmospheric lifetime is 14 years. Tetrafluoroethane has a Global Warming Potential (GWP) of 0.3 relative to a reference value of 1.0 for trichlorofluoromethane (CFC-11).

Acute toxicity to aquatic organisms is very low. Although no significant biodegradation has been observed, the high volatility and low bioaccumulation potency makes any impact of tetrafluoroethane on the aquatic environment highly unlikely.

Tetrafluoroethane is rapidly absorbed and equilibrated in tissues after inhalation and is eliminated from the blood in expired air with a half life of a few minutes. Metabolism to trifluoroacetic acid occurs only in minor amounts.

Tetrafluoroethane has an extremely low order of acute toxicity. Concentrations over 2,975,000 $mg/m^3$ (700,000 ppm) in the inhaled air are required to produce lethal effects. The symptoms of acute intoxication are characterised by central nervous effects due to narcotic properties seen only at extremely high exposure concentrations.

When tetrafluoroethane is in contact with cutaneous or ocular mucosal membranes it causes slight irritation possibly due to the test procedures. It is not a skin sensitiser.

Tetrafluoroethane can induce cardiac sensitisation in dogs at 340,000 $mg/m^3$ (80,000 ppm) and higher after an exogenous epinephrine challenge.

Tetrafluoroethane showed no adverse effects on fertility in a limited study in mice. It was not teratogenic in rats and rabbits. Only non-specific effects on foetal maturation in the form of delayed foetal ossification in the rat were observed at 212,500 $mg/m^3$ (50,000 ppm) and above.

Tetrafluoroethane was not genotoxic *in vitro* or *in vivo* as shown in a large variety of studies including all important end points.

The chronic toxicity of tetrafluoroethane was studied in rats with durations between 2-52 wk at inhalation exposure levels up to 212,500 mg/m$^3$ (50,000 ppm). No toxicologically significant effects were seen in these studies.

Two carcinogenicity studies were conducted. In a limited study in rats with daily oral administration of 300 mg/kg body weight tetrafluoroethane in corn oil over a period of 1 year, and a 16 month post-treatment observation phase, no tumorigenic effect was seen.

In a two year inhalation study with exposures up to 212,500 mg/m$^3$ (50,000 ppm), tetrafluoroethane did not produce neoplastic changes in female rats. In male rats at 212,500 mg/m$^3$ (50,000 ppm) a slight increase in the incidence of testicular Leydig cell hyperplasia and benign Leydig cell adenomas was observed. As tetrafluoroethane is not genotoxic these changes are considered to be non-genotoxic and are not of significance for human hazard at low exposure levels.

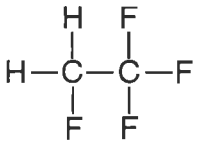
There are no reported effects of tetrafluoroethane in man.

An occupational exposure limit (8 h average) of 1,000 ppm (4,250 mg/m$^3$) is recommended by AIHA.

# SECTION 2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

## 2.1 IDENTITY

Chemical Structure:



Chemical formula: $C_2H_2F_4$

Common name: asymmetric tetrafluoroethane

IUPAC name: 1,1,1,2-tetrafluoroethane

Common synonyms: Fluorocarbon 134a, HFA-134a, HCFC 134a

CAS Registry Number: 811-97-2

EINECS: 212-377-0

Conversion factors: 1 ppm = 4.25 mg/m$^3$;
1 mg/m$^3$ = 0.24 ppm (20 °C)

## 2.2 PHYSICAL AND CHEMICAL PROPERTIES

Tetrafluoroethane is a non-flammable colourless gas with a faint ethereal odour. Some physical and chemical data are given in Table 1.

## 2.3 ANALYTICAL METHODS

A method for tetrafluoroethane analysis is described by Hext (1989) and is based on gas chromatography with flame ionisation detection.

**Table 1 Physical and chemical properties of tetrafluoroethane. (Based on Klea 134a; Product Information. ICI Chemicals and Polymers ICI (1993)).**

| | |
|---|---|
| Molecular weight: | 102.2 |
| Physical form: | Gas |
| Boiling point (°C) at 1013 hPa: | -26 |
| Melting point (C°) | -108 |
| Liquid density at 25 °C, g/ml: | 1.207 |
| Vapour density (air=1): | 3.52 |
| Vapour pressure at 20 °C: | 5.7 bar |
| Solubility in water at 25 °C, 1 bar (g/l): | 1.0 |
| Flammability: | Non flammable |
| Log $P_{ow}$: | 1.06 |
| Log $K_{oc}$: | 1.5 (estimated) |
| Henry's law constant at 25 °C, g/l.bar: | 1.0 |

# SECTION 3. PRODUCTION AND USE

There are many potential processes for the manufacture of tetrafluoroethane (see, for example, Webb and Winfield, 1992). From the published literature, the main commercial processes proposed are:

- hydrofluorination of trichloroethylene, via 1-chloro-1,1,1-trifluoroethane (HCFC-133a);
- isomerisation/hydrofluorination of 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113) to 1,1-dichloro-1,2,2,2-tetrafluoroethane (CFC-114a), followed by hydrodechlorination of the latter;
- hydrofluorination of tetrachloroethylene to 1-chloro-1,2,2,2-tetrafluoroethane (HCFC-124) and subsequent hydrodechlorination to tetrafluoroethane.

The nameplate capacity of existing and announced plants amounts to 175 kt/y (Roberts, 1993). The future world-wide demand for tetrafluoroethane has been estimated by McCulloch (1993) to be around 150 kt/y in 1995 and 300 kt/y in 2020.

Tetrafluoroethane is being developed as a substitute for fully halogenated chlorofluorocarbons and for partially halogenated hydrochlorofluorocarbons. Its main current applications are in refrigeration and air conditioning (domestic, automotive and industrial), in which it is used either alone or as a component of blends. Other applications still under development are as blowing agent for polyurethane foams and as propellant for medical aerosols ("metered-dose inhalers").

# SECTION 4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

The environmental fate and impact of tetrafluoroethane have recently been reviewed by Franklin (1993).

## 4.1 SOURCES

There is no known natural source of tetrafluoroethane.

McCulloch (1993) has estimated that the global man-made emissions of tetrafluoroethane will be around 100-150 kt/y in the first two decades of the next century.

## 4.2 ENVIRONMENTAL DISTRIBUTION

On the basis of its physical properties tetrafluoroethane may be expected, when released to the environment, to partition almost exclusively into the atmosphere as:

- it is a gas at room temperature and atmospheric pressure, with a normal boiling point of -26 °C and a vapour pressure at 20 °C of 5.7 bar;

- its Henry's Law constant for dissolution in water is only about 1.0 g/l.bar at 25 °C. For atmospheric concentrations of 100-200 pptv[1], i.e. the levels predicted by McCulloch (1993) for the year 2020, the equilibrium concentration in cloud and surface waters would thus be less than 0.2 pptw[2].

Any tetrafluoroethane which might be present in aqueous waste streams discharged directly into rivers or lakes would be expected, by analogy with similar compounds, to have a half-life with respect to volatilisation of days or a few weeks at the very most.

[1] pptv = parts per trillion (volume)

[2] pptw = parts per trillion (weight)

Moreover, any tetrafluoroethane present in surface or ground waters would have little tendency to partition onto biota or soil as:

- log $P_{ow}$ is 1.06, indicating the absence of any significant potential for passive bioaccumulation (PAFT, 1990);

- from various correlations, log $K_{oc}$ may be estimated to be approximately 1.5, which indicates that tetrafluoroethane has only a moderate sorption affinity to soil from aqueous media and would therefore be expected to be mobile in soil.

The atmospheric lifetime being much longer than either the intrahemispheric or interhemispheric mixing times, it results that tetrafluoroethane will become more or less uniformly distributed in the atmosphere on a global scale (Franklin 1993).

## 4.3 ATMOSPHERIC LIFETIME[1]

The atmospheric degradation of tetrafluoroethane will occur mainly in the troposphere, being initiated by attack by naturally occurring hydroxyl radicals. The overall lifetime is estimated to be 14 years (IPCC, 1994).

## 4.4 OZONE DEPLETING POTENTIAL

Since tetrafluoroethane contains neither chlorine nor bromine, it has generally been assumed that it has no effect on stratospheric ozone (WMO, 1989; WMO, 1991). The possibility of ozone depletion by $CF_3O_x$ radicals (x = 1 or 2), arising from the atmospheric degradation of tetrafluoroethane and other compounds, has been the subject of much recent debate. Evidence is now available to show that any contribution of $CF_3O_x$ to ozone depletion is insignificant (Ko *et al*, 1994; Ravishankara *et al*, 1994).

## 4.5 GLOBAL WARMING POTENTIAL

Global Warming Potentials (GWPs) express the radiative forcing (increase in earthward infra-red radiation flux) due to emission of a unit mass of a given compound, divided by the radiative forcing due to emission of the same mass of a reference compound.

[1] Life time is the time necessary for 63% degradation; it is equal to "half life" divided by Ln2 (= 0.69).

Based on the lifetimes quoted above, the Global Warming Potential (GWP) of tetrafluoroethane is 0.3 (AER, 1992) relative to a reference value of 1.0 for CFC-11. Relative to CFC-12, for which tetrafluoroethane is the main substitute, the GWP is 0.1.

GWPs may also be expressed relative to $CO_2$ as the reference substance, and assessed over a finite integration time horizon (ITH). For HFC-134a the corresponding GWP values are 3,100, 1,300 and 420 (relative to reference values of 1.0 for $CO_2$ taken at each ITH), for ITHs of 20, 100 and 500 years respectively (IPCC, 1994).

When the concentration of tetrafluoroethane in the atmosphere reaches 100 pptv (i.e. probably in the second decade of the next century) the contribution of this compound to radiative forcing will be only about 1 % of the total radiative forcing due to all anthropogenic pollutants added to the atmosphere from now until then, and still present at that time (or about 0.3 % of the forcing due to all pollutants ever emitted and still present) (Franklin, 1993).

## 4.6 TROPOSPHERIC OZONE FORMATION

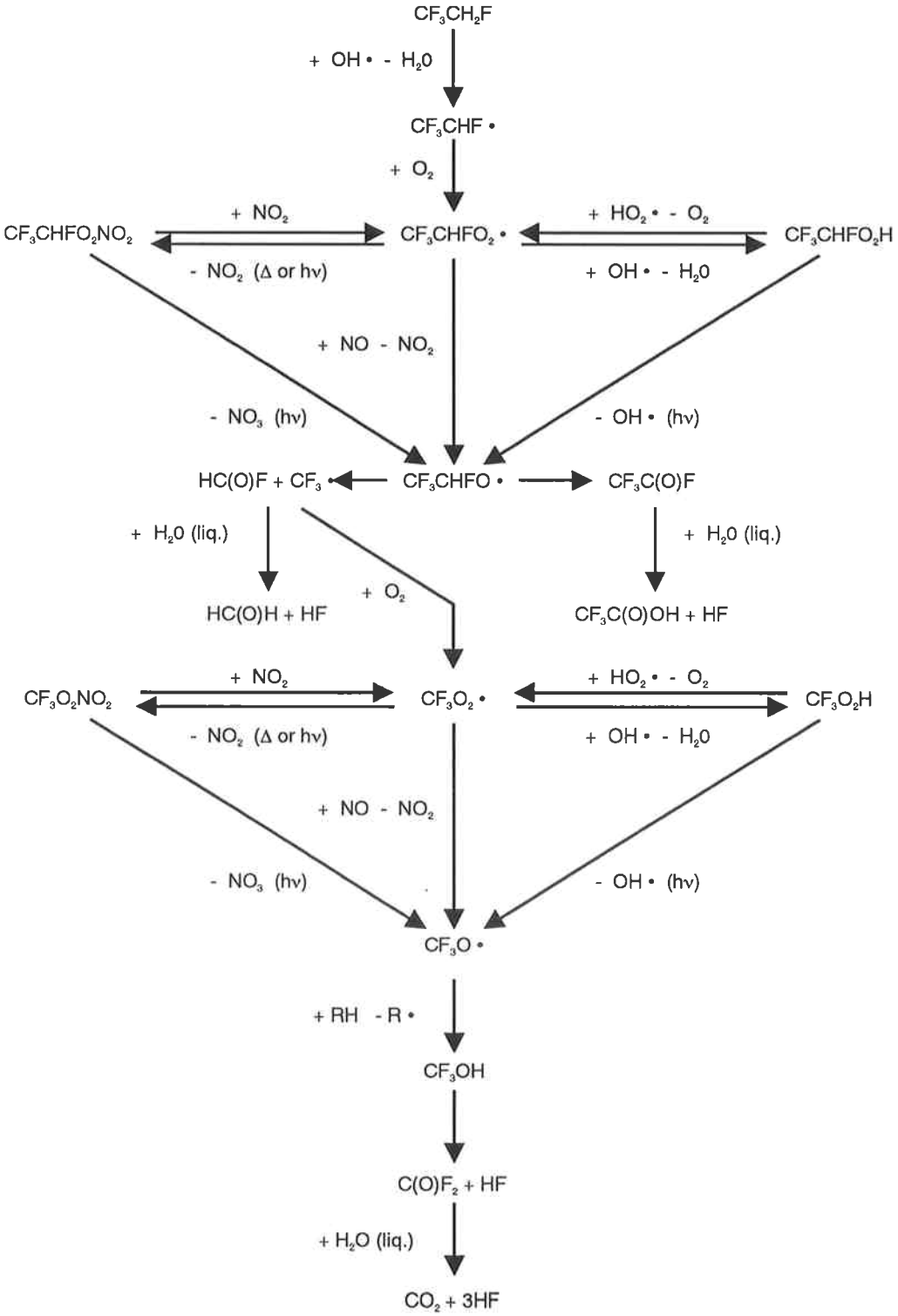
As discussed in WMO (1989), tetrafluoroethane is too unreactive in the atmosphere to make any significant contribution to local urban tropospheric ozone formation, and the related "photochemical smog", near the emission sources.

## 4.7 DEGRADATION MECHANISM AND PRODUCTS

The atmospheric degradation mechanism for tetrafluoroethane has recently been reviewed in detail by Franklin (1993). Support for the basic reaction scheme proposed in WMO (1989) has been provided by laboratory studies (see, for example : WMO, 1991; Edney and Driscoll, 1992; Tuazon and Atkinson, 1993; STEP/AFEAS, 1993). Breakdown of tetrafluoroethane in the troposphere will be initiated by the OH radical and will proceed via various intermediates to give the $CF_3CHFO$ radical, which can either react with oxygen to form trifluoroacetyl fluoride ($CF_3COF$) or undergo carbon-carbon cleavage to give formyl fluoride (HCOF) and the $CF_3$ radical. The latter will ultimately be converted to carbonyl fluoride ($COF_2$) and HF. Atmospheric modelling studies predict that, as an average over the whole troposphere, about 40 % of tetrafluoroethane will be converted to $CF_3COF$ and 60 % to HCOF + $COF_2$ + HF.

The degradation mechanism is represented in Figure 1.

**Figure 1 Tropospheric Degradation Mechanism for HFC-134a**



Although peroxynitrates ($CF_3CHFO_2NO_2$, $CF_3O_2NO_2$), hydroperoxides ($CF_3CHFO_2H$, $CF_3O_2H$) and trifluoromethanol ($CF_3OH$) may be formed during the degradation, they are not thought to play a significant role in the atmospheric chemistry of tetrafluoroethane, probably being rather short-lived intermediates.

The principal fate of the acid fluorides ($CF_3COF$, HCOF and $COF_2$) will be uptake by cloud water (with an estimated lifetime of a few days to a few months), followed by hydrolysis to trifluoroacetic acid (TFA) formic acid, $CO_2$ and HF. Dry deposition of the acid fluorides to ocean or land surfaces may occur to a limited extent; it will in any case be followed by hydrolysis (AFEAS, 1992; STEP/AFEAS, 1993).

## 4.8 CONTRIBUTION OF DEGRADATION PRODUCTS TO ENVIRONMENTAL FLUORIDE AND TO THE ACIDITY OF RAINWATER

Assuming: a) an atmospheric release (and degradation) rate of 100 kt tetrafluoroethane/y (equal to the expected releases in the early part of the next century), b) 40 % conversion of tetrafluoroethane to TFA and HF, 60 % conversion to HCOOH, $CO_2$ and 4HF, and c) uniform scavenging of the acids thus produced into the global average rainfall of $5 \times 10^{11}$ kt/y, the calculated resulting levels of fluoride and acidity are low compared with those arising from existing sources:

- $F^-$ production would be 50 kt/y, i.e. very small compared with the estimated atmospheric fluoride flux of 1,000-8,000 kt/y (WMO, 1989);

- the contribution of tetrafluoroethane to the fluoride concentration in rainwater would be 0.1 ppbw. This should be compared with typical fluoride concentrations in "background" rainwater of around 10 ppbw[1], i.e. 100 times greater, and with levels of about 1 ppmw[2] used for the fluoridation of drinking water, i.e. 10,000 times greater (WMO, 1989);

- the trifluoroacetic, formic and hydrofluoric acids formed from tetrafluoroethane and scavenged in rainwater would represent an acidity of close to $3 \times 10^9$ mol $H^+$/y, i.e. 3,000 times less than the acidity arising from natural and anthropogenic emissions of

[1] ppbw = parts per billion (weight)

[2] ppmw = parts per million (weight)

$SO_2$ and $NO_x$ (UKRGAR, 1990). Thus the contribution of tetrafluoroethane to acid rain would be negligible.

## 4.9 CONTRIBUTION OF TETRAFLUOROETHANE TO ENVIRONMENTAL TRIFLUOROACETATE (TFA)

No natural sources of trifluoroacetate are known. Making the same assumptions as in Section 4.8 for the emission and degradation rates of tetrafluoroethane, its conversion to TFA and the incorporation of the latter into rainwater, one can calculate that:

- the amount of TFA formed would be 45 kt/y;
- the global average concentration of TFA in precipitation would be about 0.1 ppbw;
- if all the TFA accumulated in the upper mixed layer of the oceans, there would be a resulting seawater TFA concentration increase of about 1.5 pptw per 100 kt tetrafluoroethane degraded.

The physico-chemical properties of TFA indicate that it will partition into the aqueous compartments of the environment, where it will be completely ionised, showing no appreciable tendency to adsorb onto soils or to accumulate passively in biota. Possible chemical or microbial sinks for TFA in the environment were discussed by Franklin (1993). Very recent information indicates that TFA under anoxic sediment conditions can be degraded to trifluoromethane, inorganic fluoride, methane and $CO_2$ (Visscher *et al*, 1994)

## 4.10 BIODEGRADATION

In the closed bottle assay with activated sludge the percentage of transformation of tetrafluoroethane after 28 days was only 2 - 3 % (Tobeta, 1989).

Under laboratory conditions, aerobic degradation by the methanotropic bacterium *Methylosinus trichosporium* OB3b was also unsuccessful (DeFlaun *et al*, 1992).

# SECTION 5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

The production of tetrafluoroethane is so recent, and the amounts emitted still so small, that no observations of this compound in the background atmosphere or other environmental compartments have yet been reported in the literature.

# SECTION 6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Environmental testing of tetrafluoroethane has only been carried out on aquatic organisms. As tetrafluoroethane is a gas special procedures were employed to obtain solutions of the test substance and to prevent losses occurring during the test. All exposure concentrations were analytically verified.

## 6.1 BACTERIA

The 6-h EC10 for growth inhibition for bacterium *Pseudomonas putida* was > 730 mg/l (Coleman and Thompson, 1990).

## 6.2 INVERTEBRATE AQUATIC SPECIES

With the freshwater crustacean *Daphnia magna*, the 48-hour EC50 under static conditions was 980 mg/l (Stewart and Thompson 1990).

## 6.3 FISH

The 96 h $LC_{50}$ of tetrafluoroethane for rainbow trout (*Salmo gairdneri*) was 450 mg/l under semi-static conditions. No mortality was observed below 300 mg/l, whilst no symptoms of toxicity were evidenced at 87 mg/l (Thompson, 1990).

From these experiments it can be concluded that tetrafluoroethane has a very low acute toxicity to aquatic organisms.

The low octanol/water partition coefficient (log $P_{ow}$ <3; see Table 1) makes bioaccumulation of tetrafluoroethane unlikely.

# SECTION 7. ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION

Male and female Wistar rats were exposed once to atmospheres containing 42,500 mg/m$^3$ (10,000 ppm) $^{14}$C-labelled tetrafluoroethane for a period of 1 hour. On cessation of exposure the animals were removed from the inhalation chambers and housed individually in glass metabolism cages. Urine and faeces were collected as well as expired organic material. Total radioactivity in expired air, urine and faeces amounted to approximately 1 % of the inhaled dose[1] in both male and female rats. Of this 1 %, two thirds were exhaled within one hour after cessation of exposure as unchanged tetrafluoroethane. The remaining radioactivity was excreted as carbon dioxide in exhaled air and in urine as trifluoroacetic acid (TFA) and in faeces as unidentified metabolites. The bulk was excreted in the first 24 hours after exposure. Carbon dioxide was the major metabolite accounting for 0.22 % of the dose for male and 0.27 % for female rats. Urinary excretion accounted for 0.09 % of the dose in both sexes and faecal excretion being 0.04 %. In urine only one metabolite could be detected by F-19 NMR and this was identified as TFA. Total metabolism measured as the sum of radioactivities in urine, faeces and as carbon dioxide was 0.34 % and 0.40 % of the inhaled dose in males and females respectively. Analyses of a range of tissues at the end of the study showed a relatively uniform distribution of radioactivity. There was no evidence for specific accumulation in any organ or tissue, including fat (Ellis, 1993).

Other studies on the metabolism of tetrafluoroethane in isolated rat hepatocytes demonstrate also that the molecule undergoes limited metabolism as measured by the release of inorganic fluoride. Tetrafluoroethane defluorination is proportional to the head space concentration. With a 50 % tetrafluoroethane concentration in the head space, fluoride release amounted to 12 mmol fluor/mg protein in 2 hours. The microsomal metabolism was inhibited by carbon monoxide, was decreased in the presence of low oxygen concentration, and was increased in the presence of hepatic microsomes isolated from Arochlor-treated rats. These results indicate that tetrafluoroethane undergoes a cytochrome P-450-catalysed defluorination reaction (Reidy *et al*, 1990). Olson *et al* (1990) conclude that the Cytochrome P-450-dependent oxidation of tetrafluoroethane is catalysed primarily by P-450IIE1. *In vitro* oxidative defluorination was demonstrated in rat, rabbit and human liver microsomes resulting in inorganic fluoride and TFA. Specific activity of cytochrome P-450IIE1 in man is similar to animals.

[1] Inhaled dose defined as : equivalent to the amount of fluorcarbon available for absorption in the respiratory tract over the exposure period of one hour.

Harris *et al* (1992) found no evidence of trifluoroacetylated proteins in rats exposed to 42,500 mg/m$^3$ (10,000 ppm) tetrafluoroethane for 6 hours, indicating that metabolism does not involve a trifluoroacetyl halide.

Ellis *et al* (1993) have determined the elimination of volatile organic material following exposure to tetrafluoroethane by inhalation in the rat with a half life of approximately 20 minutes.

# SECTION 8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

## 8.1 SINGLE EXPOSURE

Tetrafluoroethane is of low acute toxicity by the inhalation route. In the rat a 15 min $LC_{50}$ 3,400,000 mg/m$^3$ (> 800,000 ppm), a 4 hour $LC_{50}$ 2,125,000 mg/m$^3$ (> 500,000 ppm) are reported (Collins, 1984). An approximate 4 hour lethal concentration of 2,409,750 mg/m$^3$ (567,000 ppm) is reported in the rat (Kennedy, 1979a).

During the exposure the rats showed incoordination, pumping respiration, unresponsiveness, cyanosis, convulsion and death. The surviving rats regained their coordination within 5 minutes after exposure and appeared normal.

Tetrafluoroethane was not lethal to dogs exposed during 3 to 5 h to 2,975,000 and 3,400,000 mg/m$^3$ (700,000 and 800,000 ppm) (Shulman and Sadove, 1967). Rats exposed to 871,250 mg/m$^3$ (205,000 ppm) were lethargic and showed an increased respiratory rate. No effect was observed at 344,250 mg/m$^3$ (81,000 ppm) (Kennedy, 1979a). A 10 min-$EC_{50}$ for anaesthetic effects measured by the loss of the righting reflex was 1,190,000 mg/m$^3$ (280,000 ppm) in the rat (Collins, 1984) and 1,147,500 mg/m$^3$ (270,000 ppm) in the mouse (Shulman and Sadove, 1967).

Deep narcosis in dogs, cats and monkeys was induced after 2,125,000 mg/m$^3$ (500,000 ppm) within 1 minute and the recovery period from narcosis lasted approximately 2 minutes (Shulman and Sadove, 1967).

## 8.2 REPEATED EXPOSURES

Groups of 10 male rats were exposed to 0 or 425,000 mg/m$^3$ (0 or 100,000 ppm) tetrafluoroethane (6 h/d), 5 d/wk, in a 14 day period. At the end of the 10th exposure period 5 treated and 5 control rats were randomly selected and sacrificed for pathological evaluation. The remaining 5 rats per group were held for a 14 day recovery period. During the exposure the animals showed an increased respiratory rate. No treatment related abnormalities were observed with respect to body weight gain, haematology or blood chemistry. Analysis of the urine samples collected after the 9th exposure resulted in a significant increase in fluoride excretion in the treated rats suggesting tetrafluoroethane metabolism. Organ weights of treated and control rats exhibited no significant

differences and no compound-related pathological changes were observed in any of the test rats (Kennedy, 1979b).

In a subacute inhalation study, groups of 16 male and 16 female rats were exposed to 0, 4,250, 42,500 or 212,000 mg/m$^3$ (0, 1,000, 10,000 or 50,000 ppm) tetrafluoroethane for 6 h/d for 20 days in a 28 day period; evidence that the gas was absorbed into the blood during exposure was obtained. No treatment-related abnormalities were observed with respect to body weight, clinical signs, food intake and food utilisation, haematology, blood chemistry, urine composition and ophthalmoscopy. Changes in liver, kidney and gonad weights were noted. These changes were confined to male rats at 50,000 ppm except for an increase in liver weight which was also seen at 10,000 ppm. There were no pathological changes in these tissues and the liver and kidney weight increases are considered to be due to a physiological adaptation to treatment and not considered to constitute toxic responses to treatment. The reduced testicular weights are interpreted in the same manner and are in the absence of morphological changes not of toxicological significance. A slight focal interstitial pneumonia was the only pathological change noted in males exposed at 50,000 ppm which was possibly related to treatment (Riley *et al*, 1979). These effects have not been seen in subsequent studies.

Groups of 20 male and 20 female SD rats were exposed to concentrations of 0, 8,500, 42,500 or 212,000 mg/m$^3$ (0, 2,000, 10,000 or 50,000 ppm) tetrafluoroethane (6 h/d, 5 d/wk) for 13 weeks. Ten males and 10 females from each group were killed in week 14 following their last exposure, and the remaining animals were killed in week 18 following a 4 week recovery phase. Small differences in body weight gain and food consumption were noted between treated and control animals but these are considered to be due to minor environmental differences in the holding chambers. There were no significant differences on blood or urine clinical chemistry parameters, haematology parameters, ophthalmoscopy or organ weights and no treatment related macroscopic or microscopic pathology findings (Hext, 1989).

A combined chronic toxicity/carcinogenicity study in rats with exposure levels with vapours of tetrafluoroethane ranging from 10,625, 42,500 and 212,500 mg/m$^3$ (2,500, 10,000 and 50,000 ppm) was conducted. A description of the study and detailed results are given in Section 8.8.

## 8.3 SKIN AND EYE IRRITATION, SENSITISATION

### 8.3.1 Skin irritation

Liquefied tetrafluoroethane (0.5 ml per application site) was applied on to a square of 8 layers thick gauze pads. The gauze pads were placed on scarified and intact skin areas of rabbits, covered with an occlusive polypropylene film and fixed with an adhesive tape. Slight irritation to intact skin possibly due to local freezing appeared after 24 hours of contact (Mercier, 1990a).

### 8.3.2 Eye irritation

Administration of tetrafluoroethane as a gas (either a 5-seconds or 15-seconds spray from a distance of 10 cm) to the eyes of rabbits resulted in only very slight irritation (Mercier, 1990b). This effect is possibly a consequence of the test procedure.

### 8.3.3 Skin sensitisation

Guinea pigs received one single intradermal injection of Freund's complete adjuvant followed by 7 consecutive (occlusive) epicutaneous administrations of liquefied tetrafluoroethane. After a period of 12 days without treatment the challenge administration was performed by occlusive epicutaneous treatment with liquefied tetrafluoroethane. The test compound did not produce evidence of skin sensitisation (Mercier, 1990c).

## 8.4 SPECIAL STUDIES CARDIOVASCULAR AND RESPIRATORY FUNCTIONS

Early studies on the toxicity of certain hydrocarbons, especially anaesthetics, showed, that they could render the mammalian heart abnormally reactive or sensitive to adrenaline (epinephrine) resulting in cardiac arrhythmias. Tetrafluoroethane has also been screened for this effect. Male Beagle dogs were exposed to nominal tetrafluoroethane concentrations of 212,000, 318,750 and 425,000 mg/m$^3$ (50,000 ppm, 75,000 ppm and 100,000 ppm) and given a bolus injection of 8 μg/kg epinephrine. Two of 10 dogs exposed to 75,000 ppm and 2 of 4 dogs exposed to 100,000 ppm exhibited a marked response (multiple ventricular beats). One dog exposed to 100,000 ppm developed ventricular fibrillation and cardiac arrest. None of the 10 dogs exposed to 50,000 ppm tetrafluoroethane exhibited a cardiac sensitisation response (Mullin, 1979).

In another study in Beagle dogs the cardiac sensitisation potential of tetrafluoroethane was evaluated at concentrations of 170,000, 340,000, 680,000 and 1,456,000 mg/m$^3$ (40,000 ppm,

80,000 ppm, 160,000 ppm and 320,000 ppm) until equilibrium concentrations in the blood were established (approximately after 5 min of exposure). The dogs were then given an intravenous injection of epinephrine (8 μg/kg) and monitored for cardiac arrhythmias. Three of 10 dogs developed cardiac arrhythmias after a concentration of 80,000 ppm, 4 out of 10 dogs after 160,000 ppm and 3 out of 4 dogs after an exposure concentration of 320,000 ppm. Concentrations of 40,000 ppm tetrafluoroethane were tolerated without any signs for cardiac arrhythmias. The reference compound in this study, CFC-12 (dichlorodi-fluoroethane), showed a comparable cardiac sensitisation potential (Hardy *et al*, 1991).

## 8.5 REPRODUCTIVE EFFECTS, EMBRYOTOXICITY AND TERATOLOGY

### 8.5.1 Fertility

Male CD-1 mice were exposed 6 h/d for 5 days to levels of tetrafluoroethane up to 212,000 mg/m$^3$ (50,000 ppm) and mated with unexposed female mice. No effects on fertility were observed, as shown by investigating the parameters for reproductive performance (Hodge *et al*, 1979).

### 8.5.2 Embryotoxicity and teratology

Tetrafluoroethane was tested at 0, 4,250, 42,500 or 212,000 mg/m$^3$ (0, 1,000, 10,000 and 50,000 ppm). Groups of 29 or 30 pregnant Alpk/APfSD, Wistar derived rats were exposed 6 h/d to tetrafluoroethane from day 6 to 15 of pregnancy. The exposure to tetrafluoroethane produced abnormal clinical signs in animals but did not affect the maternal body weights. Mean foetal weights were slightly but significantly lower in the 50,000 ppm group. Embryonic and foetal survival were unaffected by the treatment. There was no evidence for teratogenicity but skeletal ossification was slightly retarded in the top dose group (50,000 ppm). It is therefore concluded that tetrafluoroethane is neither teratogenic nor embryotoxic at levels up to and including 50,000 ppm, but at this highest level tetrafluoroethane may be slightly foetotoxic (Hodge *et al*, 1980).

In another study using similar exposure conditions to the above, groups of 7 pregnant Sprague Dawley rats were tested at concentrations of 0, 127,500, 425,000 or 1,275,000 mg/m$^3$ (0, 30,000, 100,000 or 300,000 ppm) tetrafluoroethane. No teratogenic effects were observed although some maternal growth and foetal development retardation in the form of delayed ossification occurred. The minimum maternal effect dose was demonstrated to be 100,000 ppm, and the minimum embryo foetal effect dose was demonstrated to be 300,000 ppm (Lu, 1981).

Groups of 28 female New Zealand White rabbits were exposed by inhalation to target atmospheric concentrations of 0, 10,650, 42,500 and 170,000 mg/m$^3$ (0, 2,500, 10,000 and 40,000 ppm) tetrafluoroethane for 6 h/d from days 7 to 19 of gestation. Exposure levels of 40,000 and 10,000 ppm tetrafluoroethane were associated with slight maternal toxicity manifest as reduced body weight gain and food consumption. There was no evidence for maternal toxicity at the exposure level of 2,500 ppm. There was no evidence of embryotoxicity or foetotoxicity at any dose levels (Collins *et al*, 1994).

## 8.6 GENOTOXICITY

The data from *in vitro* and *in vivo* studies are summarised in Table 2.

***Gene mutation in Bacteria and yeast***

Tetrafluoroethane has been tested for bacterial mutagenesis in four separate Ames assays in different *Salmonella* strains TA 1535, TA 1537, TA 1538, TA98 and TA 100 and *Escherichia coli* WP 2 UVrA. In all cases tetrafluoroethane was shown to be non-mutagenic both in absence or presence of induced rat liver enzymes (S-9) (Brusick 1976; Longstaff *et al*, 1984; Callander and Priestley 1990; Araki, 1991).

Tetrafluoroethane was not mutagenic to *Saccharomyces cerevisiae* strain D 4 either in the presence or absence of an activating liver enzyme system (Brusick, 1976).

***Chromosome aberrations in cultured mammalian cells***

An *in vitro* cytogenetic assay was conducted in human lymphocytes with maximum exposure concentrations of 3,187,500 mg/m$^3$ (750,000 ppm). No statistically or biologically significant increases in chromosomal aberration frequencies were seen in any of the dose levels tested, either in the presence or absence of S-9 mix (Mackay, 1990).

Chinese hamster lung cells (CHL) were exposed to concentrations between 1,700,000 mg/m$^3$ (400,000 ppm = 40% in air) and 100% tetrafluoroethane vapour to investigate clastogenic effects. No induction of chromosomal aberrations was observed either with or without metabolic activation (Asakura, 1991).

**Table 2 The Genetic Toxicology of Tetrafluoroethane *in vitro***

| Assay | Strain | Test conditions | Result | Reference |
|---|---|---|---|---|
| *Salmonella typhimurium* | TA1535, TA1537, TA1538, TA98, TA100 | Plate suspension; +/- S9. Test conc. : 100% Expos. up to 1 h (suspension) or 24 h (plate); incub. 48 h | Negative | Brusick, 1976 |
| *Salmonella typhimurium* | TA1535, TA1538, TA98, TA100 | Plate; +/- S9 Test conc. up to 50% expos./incub. 72 h | Negative | Longstaff *et al*, 1984 |
| *Salmonella typhimurium* | TA1535, TA1537, TA1538, TA98, TA100 | Plate; +/- S9 Test conc. up to 100% expos./incub 24 and 48 h | Negative | Callander and Priestley, 1990 |
| *Salmonella typhimurium* | TA1535, TA1537, TA98, TA100 | Plate; +/- S9 Test conc. up to 60% expos./incub. 24 and 48 h | Negative | Araki, 1991 |
| *Escherichia coli* | WP2 UV rA | Plate; +/-S9 Test conc. up to 60% expos./incub. 24 and 48 h | Negative | Araki, 1991 |
| *Saccharomyces cerevisiae* | D4 | Plate and supspension;, +/-S9 Test conc. up to 1 h (suspension) or 24 h (plate); incub. 48 h | Negative | Brusick, 1976 |
| Chromosome aberrations | Human Lymhocytes | 2 donors; +/- S9 Test conc. up to 100% Expos. 3 h; Incub. :72 and 96 h | Negative | Mackay, 1990 |
| Chromosome aberration | Chinese Hamster Lung Cells (CHL) | +/- S9 Test conc. up to 100% Expos. 6 h (+S9) or 24 and 48 h (-S9); incub. 24 and 48 h | Negative | Asakura, 1991 |
| Micronucleus | Mouse; NMRI Polychromatic erythrocytes | Inhalation 6 h Test conc. 0, 50,000, 150,000 and 500,000 ppm; 5 m + 5 f/group | Negative | Müller and Hofmann, 1989 |
| Dominant lethal | Mouse CD1 | Inhalation (males): 6 h x 5 d; 15 m + 30-40 f/group Test conc.: 0,1,000, 10,000 and 50,000 ppm | Negative | Hodge *et al*, 1979 |
| Chromosome aberration | Rat; Alpk/APfSD (Wistar-derived) | Inhalation: 6 h x 5 d; 8 m/group Test conc.: 0,1,000, 10,000 and 50,000 ppm | Negative | Anderson and Richardson, 1979 |
| Unscheduled DNA Synthesis | Rat; Alpk/APfSD (Wistar-derived) Hepatocytes | Inhalation: 6 h;4-5 m/group Test conc.: 0,10,000, 50,000 and 100,000 ppm | Negative | Trueman, 1990 |

***Chromosomal mutation in vivo***

In an *in vivo* micronucleus assay NMRI mice were exposed for 6 hours to concentrations of 0, 212,500, 675,000 or 2,125,000 mg/m$^3$ (0, 50,000, 150,000 or 500,000 ppm). The incidence of micronucleated polychromatic erythrocytes in the bone marrow of the animals did not differ

statistically significant from the air controls. The ratio of polychromatic/normochromatic cells remained unaffected by the treatment with tetrafluoroethane (Müller and Hofmann, 1989).

In a dominant lethal assay 15 male CD1 mice per group were exposed to 0, 4,250, 42,500 or 212,000 mg/m$^3$ (0, 1,000, 10,000 or 50,000 ppm) tetrafluoroethane for 6 h/d for 5 consecutive days. After the last exposure each male was housed with 2 virgin females for 4 consecutive nights. Further matings with new females were done at weekly intervals for a total of 8 times. The study indicated that tetrafluoroethane did not affect the fertility or cause mutagenic effects (Hodge *et al*, 1979).

Tetrafluoroethane has also been tested in a cytogenetic study in groups of 8 male Alpk/APfSD Wistar derived rats *in vivo*. The test material was administered by inhalation at concentrations of 0, 4,250, 42,500 or 212,000 mg/m$^3$ (0, 1,000, 10,000 and 50,000 ppm) for 6 hours either as a single exposure or on 5 consecutive days. After exposure animals were killed and slides of bone marrow prepared and examined for chromosomal abnormalities. There were no statistically significant differences between tetrafluoroethane treated groups and the negative control group when total chromosomal aberrations were considered. When abnormalities other than chromosomal gaps were examined, a statistically significant increase was found in the group treated with 50,000 ppm for a single exposure only. This increase in the mean value was attributable to 1 animal and the result was not considered as an event of biological significance. The authors concluded that tetrafluoroethane did not induce chromosomal aberrations in the bone marrow cells of rats (Anderson and Richardson, 1979).

***Unscheduled DNA Synthesis: Primary rat hepatocytes***

Tetrafluoroethane was tested for the ability to induce Unscheduled DNA Synthesis (UDS) in an *in vivo* assay in rat hepatocytes. Male Alpk/APfSD Wistar derived rats were exposed for 6 hours to tetrafluoroethane concentrations of 0, 42,500, 212,000 and 425,000 mg/m$^3$ (0, 10,000, 50,000 and 100,000 ppm). There was no increase in DNA repair activity (Trueman, 1990).

***Cell transformation in vitro***

Tetrafluoroethane was also tested for its cell transforming capacity using the Styles cell transformation assay. In this assay, which makes use of a cell line derived from baby hamster kidney fibroblasts, tetrafluoroethane was shown to be negative (Longstaff *et al,* 1984).

In summary, tetrafluoroethane is not mutagenic and does not induce primary DNA damage or cell transformation.

## 8.7 CARCINOGENICITY

Groups of 36 male and 36 female Alpk/APfSD Wistar derived rats received 300 mg/kgbw tetrafluoroethane in corn oil by gavage 5 d /wk for 52 weeks and were then maintained for life. Two similar sized control groups were dosed with corn oil only and one control group received no treatment. The study was terminated after 125 weeks. Tetrafluoroethane did not increase the incidence of tumours in any of the organs from the treated group when compared with the control groups (Longstaff *et al*, 1984).

A combined chronic toxicity/carcinogenicity study was conducted by whole body inhalation exposures in groups of 85 male and 85 female Alpk/APfSD Wistar derived rats to target concentrations of 0, 10,625, 42,500 or 212,000 mg/m$^3$ (0, 2 500, 10,000 or 50,000 ppm tetrafluoroethane for 6 h/d, 5 d/wk. Ten rats of each sex from each group were designated for interim kill after 52 weeks and the remainder continuing to terminal kill after 104 weeks. The top dose was chosen as the limit dose (5% in air). All groups had a similar survival rate. The differences in body weight and food consumption noted reflected only biological variation and were not compound related. There was no evidence of toxicity effects at any exposure level in the clinical chemistry and haematology parameters investigated. Small increases in urinary fluoride levels were seen on occasion in groups exposed to 10,000 and 50,000 ppm, but were considered to be of no biological significance. The only treatment related effect of toxicological significance was confined to the testes of male rats exposed to 50,000 ppm. There was a statistically significant increase in the weight of the testes of controls and there was an increased incidence of Leydig cell hyperplasia and benign Leydig cell tumours (see Table 3). The no-effect level was considered to be 10,000 ppm tetrafluoroethane (Hext and Parr-Dobrzanski, 1993).

***Discussion***

The benign tumours of the testicular interstitial cells (Leydig cell adenoma) are common in the ageing rat. The spontaneous incidence of this tumour type is variable from one strain to another, ranging from a few percent in Sprague Dawley rats up to 100% in some Wistar derived and in Fisher 344 rats (Bär, 1992). These tumours do not usually progress to malignancy in the rat (e.g. no malignant Leydig cells tumours found in several thousands of control Fisher rats) (Boorman *et al*, 1990, Iawata *et al*, 1991). Benign Leydig cell tumours appear late in life and are not life-threatening to rats. They are associated with the senescence process. Leydig cells secrete sex hormones

**Table 3 Effect of HFC 134a on the pathology of the rat testis**

| Numbers of animals with[b] (n = 85) | Exposure concentration (ppm)[a] | | | |
|---|---|---|---|---|
| | 0 | 2,500 | 10,000 | 50,000 |
| Leydig cell hyperplasia | 27 | 25[c] | 31 | 40 |
| Leydig cell adenoma | 9 | 7[c] | 12 | 23** |

a Exposures were for 6 h/d, 5 d/wk for up to 104 weeks
b Data includes all animals from interim, intercurrent and terminal killings
c Data from 79 animals
** Significantly different from control values $p < 0,01$ (Fisher's exact test)

(e.g. testosterone, dihydroandosterone, oestradiol). The high incidence of hyperplasia and tumours of these testicular cells in old rats is thought to be related to senile endocrine disturbance (Mostofi and Price, 1973).

Various conditions have been shown to increase Leydig cell hyperplasia or tumour incidence in the rat including senility *per se*, and oestrogenic treatments (Mostofi and Bresler, 1976). In addition, an increased incidence of Leydig cell tumours has been described with a large number of substances covering a wide variety of chemical structures e.g. isradipine (Roberts *et al*, 1989), mesulargine (Prentice *et al*, 1992), cimetidine (Leslie *et al*, 1992), hydralazine, carbamazepine (Griffith, 1988) and even such a common dietary component as lactose (Bär, 1992).

Tetrafluoroethane (as well as the substances mentioned above), does not demonstrate mutagenic activity (see Section 8.6). This leads to the conclusion that the increased incidence of Leydig cell tumours observed in the long-term rat study with tetrafluoroethane is attributable to a non-genotoxic mechanism. Non-genotoxic mechanisms have been frequently associated with hormonal imbalances, especially in imbalance of sex hormones (Neuman, 1991). At present, a detailed understanding of the non-genotoxic mechanism has not been established for tetrafluoroethane.

Findings of the 2-year inhalation study with tetrafluoroethane indicate that Leydig cell hyperplasia and tumours occurred late in life and were not associated with increased mortality. Thus, the basic characteristics of the spontaneous appearance of this type of neoplasm in the rat were not changed by tetrafluoroethane, suggesting that the chemical simply tends to exaggerate the hormonal disturbances linked with senility.

Moreover, in contrast to the rat, the Leydig cell tumour occurrence in man is extremely low, representing less than 3% of all testicular neoplasms (Mostofi and Price, 1973). The rarity of

Leydig cell tumours in human beings as compared to the high spontaneous incidence in the rat make the relevance of the rat findings to man highly questionable.

Consequently the increased frequency of the benign Leydig cell tumours observed in rats exposed to tetrafluoroethane at the high concentration of 212,500 mg/m$^3$ (50,000 ppm) is considered not to indicate a tumourigenic risk to man.

## 8.8 OTHER INFORMATION

The working group is aware of an additional toxicology programme for the pharmaceutical application of tetrafluoroethane. The results of this programme were not available to the working group.

# SECTION 9. EFFECTS ON MAN

No adverse health effects from exposure to tetrafluoroethane have been reported.

The American Industrial Hygiene Association's Workplace Environmental Exposure Level (WEEL) Commitee assigned tetrafluoroethane an occupational exposure limit (8-hour time weighted average) of 1,000 ppm (4,250 mg/m$^3$) (AIHA, 1991).

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### JACC REPORTS

| No. | Title |
|---|---|
| No. 1 | Joint Assessment of Commodity Chemicals, Melamine. Feb 83 |
| No. 2 | Joint Assessment of Commodity Chemicals, 1,4-Dioxane. Feb 83 |
| No. 3 | Joint Assessment of Commodity Chemicals, Methyl Ethyl Ketone. Feb 83 |
| No. 4 | Joint Assessment of Commodity Chemicals, Methylene Chloride. Jan 84 |
| No. 5 | Joint Assessment of Commodity Chemicals, Vinylidene Chloride. Aug 85 |
| No. 6 | Joint Assessment of Commodity Chemicals, Xylenes. Jun 86 |
| No. 7 | Joint Assessment of Commodity Chemicals, Ethylbenzene. Aug 86 |
| No. 8 | Joint Assessment of Commodity Chemicals, Methyl Isobutyl Ketone. May 87 |
| No. 9 | Joint Assessment of Commodity Chemicals, Chlorodifluoromethane. Oct 89 |
| No. 10 | Joint Assessment of Commodity Chemicals, Isophorone. Sep 89 |
| No. 11 | Joint Assessment of Commodity Chemicals, (HFA-132b) 1,2-Dichloro-1,1-Difluoroethane. May 90 |
| No. 12 | Joint Assessment of Commodity Chemicals, (HFA-124) 1-Chloro-1,2,2,2-Tetrafluoroethane. May 90 |
| No. 13 | Joint Assessment of Commodity Chemicals, (HFA-123) 1,1-Dichloro-2,2,2-Trifluoroethane. May 90 |
| No. 14 | Joint Assessment of Commodity Chemicals, (HFA-133a) 1-Chloro-2,2,2-Trifluoromethane. Aug 90 |
| No. 15 | Joint Assessment of Commodity Chemicals, (HFA-141B) 1-Fluoro 1,1-Dichloroethane. Aug 90 |
| No. 16 | Joint Assessment of Commodity Chemicals, (HCFC-21) Dichlorofluoromethane. Aug 90 |
| No. 17 | Joint Assessment of Commodity Chemicals, (HFA-142b) 1-Chloro-1,1,Difluoroethane. Feb 91 |
| No. 18 | Joint Assessment of Commodity Chemicals, Vinylacetate. Feb 91 |
| No. 19 | Joint Assessment of Commodity Chemicals, Dicyclopentadiene. Jul 91 |
| No. 20 | Joint Assessment of Commodity Chemicals, Tris-/Bis-/Mono-(2-ethylhexyl)phosphate. May 92 |
| No. 21 | Joint Assessment of Commodity Chemicals, Tris-(2-butoxyethyl)-phosphate. Mar 92 |
| No. 22 | Joint Assessment of Commodity Chemicals, Hydrogen Peroxide. Jan 93 |
| No. 23 | Joint Assessment of Commodity Chemicals, Polycarboxylate Polymers as Used in Detergents. Nov 93 |
| No. 24 | Joint Assessment of Commodity Chemicals, (HFC-125) Pentafluoroethane. May 94 |
| No. 25 | Joint Assessment of Commodity Chemicals, (HCFC-124) 1-Chloro-1,2,2,2-Tetrafluoroethane. Jul 94 |
| No. 26 | Joint Assessment of Commodity Chemicals, Linear Polydimethylsiloxanes (viscosity 10-100,000 centisokes). Sep 94 |
| No. 27 | Joint Assessment of Commodity Chemicals, *n*-Butyl Acrylate. CAS No. 141-32-2. Aug 94 |
| No. 28 | Joint Assessment of Commodity Chemicals, Ethyl Acrylate. CAS No. 140-88-5. Sep 94 |
| No. 29 | Joint Assessment of Commodity Chemicals, 1,1-Dichloro-1-Fluoroethane (HCFC-141b) CAS No 1717-00-6. Feb 95 |
| No. 30 | Joint Assessment of Commodity Chemicals, Methyl Methacrylate. CAS No. 80-62-6. In Press |
| No. 31 | Joint Assessment of Commodity Chemicals, 1,1,1,2-Tetrafluoroethane (HFC-134a) CAS No. 811-97-2. Feb 95 |

## TECHNICAL REPORTS

### No. Title

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No. 2 The Mutagenic and Carcinogenic Potential of Formaldehyde. May 81
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No. 14 The EEC 6th Amendment : A Guide to Risk Evaluation for Effects on Human Health. Mar 94
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No. 22 Classification of Dangerous Substances and Pesticides in the EEC Directives. A Proposed Revision of Criteria for Inhalational Toxicity. 87
No. 23 Evaluation of the Toxicity of Substances to be Assessed for Biodegradability. Nov 86
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No. 30(5) Existing Chemicals : Literature Reviews and Evaluations. 94
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No. 47 EC 7th Amendment: 'Toxic to Reproduction' - Guidance on Classification. Aug 92
No. 48 Eye Irritation: Reference Chemicals Data Bank. Aug 92
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No. 51 Environmental Hazard Assessment of Substances. Jan 93
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No. 53 DHTDMAC: Aquatic and Terrestrial Hazard Assessment. CAS No. 61789-80-8. Feb 93
No. 54 Assessment of the Biodegradation of Chemicals in the Marine Environment. Aug 93
No. 55 Pulmonary Toxicity of Polyalkylene Glycols. (in preparation)
No. 56 Aquatic Toxicity Data Evaluation. Dec 93
No. 57 Polypropylene Production and Colorectal Cancer. Feb 94
No. 58 Assessment of Non-Occupational Exposure to Chemicals. May 94
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