Tetrafluoroethylene

(CAS No. 116-14-3)

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CONTENTS

EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of the toxicity and ecotoxicity data on tetrafluoroethylene (TFE) that could inform the hazard/risk assessment required under current OECD/EU schemes [a,b]. In the USA, TFE is included in the EPA Chemical Right-to-Know Initiative [c].

TFE is a colourless gas that is mainly used in the production of polytetrafluoroethylene and other fluorinated polymers. It is sparingly soluble in water. Any TFE released into the environment will be distributed to the atmosphere, where it will quickly degrade to carbon dioxide and hydrogen fluoride that is washed out by rain. TFE does not contribute directly to the greenhouse effect (global warming) and has no effect on the stratospheric ozone layer, but may enhance the formation of tropospheric ozone, more or less significantly, depending on the quantities emitted.

In the aquatic environment, no hydrolysis of TFE will occur and it is not prone to rapid biodegradation and bioaccumulation. TFE will not adsorb significantly to soils and sediments. Although experimental data are not available, model calculations predict that that TFE is not toxic to environmental organisms.

Short-term inhalation exposure of laboratory animals to high doses of TFE did not evoke cardiac sensitisation or anaesthetic effects that are typically found with other fluorinated compounds. With TFE, the primary effect was damage to the kidney, though overall the toxcity was judged to be low. Longer-term exposures also resulted in a low level of toxicity manifest as kidney effects and anaemia in rats and mice, and possibly testicular changes in hamsters. No specific study of the reproductive effects of TFE is available.

TFE is not genotoxic either *in vitro* or *in vivo*. The principal metabolic product (cysteine conjugate) of TFE, S 1,1,2,2-tetrafluoroethyl-L-cysteine, is also not mutagenic *in vitro*. In long-term carcinogenicity studies in rats and mice, repeated inhalation of high doses of TFE produced tumours of the kidney in rats and mice and in the liver of mice. These tumours were considered to have been caused by metabolites of TFE and *in vitro* studies of the comparative metabolism in different species suggest that following exposure to TFE the risk to humans of developing tumours of the kidney would be much lower than in rats or mice.

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[a] OECD Existing Chemicals Programme [http://www1.oecd.org/ehs/hazard.htm]

[b] EU Existing Chemicals Work Area [http://ecb.ei.jrc.it/existing-chemicals]

[c] US-EPA high production volume (HPV) challenge list [http://www.epa.gov/oppt/chemrtk/]

In mice, however, there were also more tumours of the haematopoietic system in some organs. The current lack of knowledge about the mechanisms involved in the development of these three tumours types precludes a full evaluation of the hazard to humans from exposure to TFE.

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 (i.e. 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.

This document presents a critical evaluation of the available toxicology and ecotoxicology of tetrafluoroethylene (CAS No. 116-14-3).

Where relevant, the Task Force has graded the (eco)toxicological studies by means of a "code of reliability" (CoR) to reflect the degree of confidence that can be placed on the reported results. The codes and criteria used to assess reliability are included in Appendix A.

1. SUMMARY AND CONCLUSIONS

Tetrafluoroethylene (TFE) is a colourless, odourless and flammable gas that is sparingly soluble in water.

TFE is produced mainly by the pyrolysis of chlorodifluoromethane. It is mainly used in the production of polytetrafluoroethylene homopolymer. TFE is also used as a co-monomer for the production of other fluorinated polymers.

Any TFE released into the environment is expected to partition almost entirely to the atmosphere, where it will quickly react with atmospheric hydroxyl radicals ($\cdot OH$), with an average atmospheric lifetime of less than 2 days. Subsequent decomposition yields carbonyl fluoride (COF_2) that is further hydrolysed in the presence of atmospheric water to form hydrogen fluoride (HF) and carbon dioxide (CO_2), the HF being washed out by rain.

TFE does not contribute directly to the greenhouse effect (global warming), but may enhance the formation of tropospheric ozone. TFE has no effect on the stratospheric ozone layer.

In the aquatic environment, no hydrolysis of TFE will occur. TFE is not expected to biodegrade easily and is not expected to bioaccumulate. TFE will not adsorb significantly to soil and sediment.

No experimental data are available on the effects of TFE on environmental organisms. The predicted toxic concentrations of TFE to either aquatic or terrestrial organisms are considerably higher than the solubility level of TFE in water. Therefore, it can be assumed that TFE will not be toxic in the environment.

Data are available for a number of mammalian species on the acute toxicity of TFE by inhalation [a] . Lethal concentration (LC_{50}) values are relatively consistent across species and show no particular sex-related sensitivity. The 4-h LC_{50} in rats is approximately 30,000 ppm TFE (123 g/m^3). The primary toxic effect is kidney damage in rats exposed to concentrations around 3,700 ppm (15,100 mg/m^3) for 4 hours. TFE does not induce cardiac sensitisation up to 500,000 ppm (2,040 g/m^3) in dogs or cats. It does not present any significant anaesthetic potential at concentrations up to 700,000 ppm (2,860 g/m^3) in rats. This is in contrast to the findings with other fluorinated compounds.

The toxicity of TFE has been studied in rats, mice and hamsters following repeated exposure for up to 13 weeks. Proteinuria and renal tubular degeneration were seen in rats and renal tubular karyomegaly in both rats and mice. The no-observed-adverse effect level (NOAEL) for kidney toxicity was 625 ppm (2,555 mg/m^3) for mice.

[a] No data are available on the acute oral and dermal toxicity of TFE because it is a gas at room temperature.

In the rat, effects were seen at the lowest dose of 312 ppm (1,275 mg/m^3) (lowest-observed-effect level, LOEL). In addition, both species showed secondary hypoproliferative anaemia when exposed to TFE. Testicular atrophy was not seen in rats and mice. In hamsters, no evidence of kidney toxicity or anaemia was seen, but signs of testicular atrophy were found after 13 weeks of exposure to 600 ppm (2,450 mg/m^3) and above. The NOAEL for these effects was 200 ppm TFE (820 mg/m^3).

No signs of respiratory tract irritation were seen in the acute or repeated-dose animal studies.

TFE has been fully assessed for its genotoxic potential in a number of studies. It did not induce gene mutations in bacteria and mammalian cells *in vitro*, and was not clastogenic in Chinese hamster ovary (CHO) cells *in vitro* or in two micronucleus tests in mice. Hepatocytes isolated from mice exposed to TFE showed no evidence of unscheduled DNA synthesis (UDS). Therefore, TFE is not genotoxic both *in vitro* and *in vivo*. In mice exposed to TFE for 2 years, TFE induced hepatocellular neoplasms developed by pathways independent of ras mutations. A cysteine conjugate of TFE, S-1,1,2,2-tetrafluoroethyl-L-cysteine, a nephrotoxic metabolite activated by renal C-S lyases (β-lyases), is also without mutagenic activity.

TFE was found to be carcinogenic in rats and mice exposed by inhalation. Mice exposed to concentrations of 312, 625 or 1,250 ppm TFE (1,275, 2,555 or 5,110 mg/m^3) for 95 weeks showed a concentration-related increased incidence of liver tumours (hepatocellular adenoma and/or carcinoma and haemangiosarcoma) in both sexes, the effects in all exposed groups being statistically significantly different to controls. Increased incidences of histiocytic sarcoma were also observed in a number of organs.

In the rat, the kidney was the primary target organ. Male rats were exposed to 156, 312 or 625 ppm TFE (638, 1,275 or 2,555 mg/m^3) for 103 weeks and increased mortality occurred in those exposed to the highest concentration. Female rats were exposed to 312, 625 or 1,250 ppm TFE and increased mortality was seen in all exposed groups. In addition, absolute and relative liver weights were increased in both sexes. Exposure to TFE caused an increase in the incidence of renal tubular adenoma and adenocarcinoma, and combined adenoma-carcinoma in both sexes; there was also an increased incidence of haemangiosarcoma in the liver of female rats exposed to 625 ppm of TFE.

TFE is metabolised by glutathione conjugation and via the mercapturic acid pathway. The cysteine conjugate of TFE is also known to be a substrate for renal C-S lyase. Studies on the mode of action of TFE as a rodent carcinogen suggest that the hepatic and renal carcinogenicity of TFE in rodents is associated with its metabolism via the glutathione and C-S lyase pathways. In rats and mice, the highest C-S lyase activities are found in the target organs, the rat kidney and mouse liver.

A plausible mode of action has been established to explain the development of kidney tumours in rats exposed to TFE. Metabolic processing of the glutathione conjugate of TFE results in the formation of S-(1,1,2,2,-tetrafluoroethyl)-L-cysteine, a nephrotoxic metabolite activated by renal C-S lyases. The reactive intermediates formed are known to alkylate proteins resulting in cytotoxicity and reparative hyperplasia, which, over the duration of a lifetime study, is believed to lead to the development of renal tumours. There is no evidence to suggest that chemically induced genotoxicity plays a role in the development of these tumours.

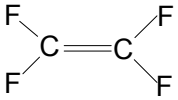
While there is evidence for extensive metabolism of S-(1,1,2,2-tetrafluoroethyl)-L-cysteine by hepatic C-S lyases in mouse liver, there is no evidence for cellular damage and the increases in cell replication rates following exposure to TFE were minimal and transient. Consequently, a mode of action has not yet been established for the development of the mouse liver tumours. The mechanisms underlying the development of mouse histiocytic sarcomas is also unknown.

Comparison of the metabolism of TFE in liver and kidney fractions from mice, rats and humans has identified quantitative differences between rodents and humans. These findings, suggest that the risk to humans of developing kidney tumours following exposure to TFE is significantly less than that in rats. However, although an excellent correlation exists between the metabolism of TFE and liver cancer in mice, lack of knowledge about the mechanisms involved in the development of these tumours and the mouse histiocytic sarcomas precludes a full evaluation of the hazard to humans from exposure to TFE.

No specific studies are available on the reproductive and developmental toxicity of TFE. Some evidence of testicular atrophy associated with focal hypocellularity of the germinal epithelium of the seminiferous tubules has been seen in 14-d and 13-wk studies in hamsters. It is unclear whether this effect is related to TFE exposure because the interpretation is confounded by the testicular immaturity of the exposed hamsters.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name:	Tetrafluoroethylene
IUPAC name:	1,1,2,2-Tetrafluoroethylene
Synonyms:	Ethene, tetrafluoro- Ethylene, tetrafluoro- FC-1114 K-1114 Perfluoroethene Perfluoroethylene TFE TFE monomer
Danish:	Tetrafluoroetylen
Dutch:	Tetrafluoroethyleen
Finnish:	Tetrafluorieteeni
French:	Tétrafluoroéthylène
German:	Tetrafluorethylen
Greek:	Τετραφλυοροαιθυλενιο
Italian:	Tetrafluoroetilene
Norwegian:	Tetrafluoroeten
Portuguese:	Tetrafluoretileno
Spanish:	Tetrafluóretileno
Swedish:	Tetrafluorethylen
CAS name:	Ethene, tetrafluoro-
CAS registry No.:	116-14-3
EC (EINECS) No.:	204-126-9
Formula:	C_2F_4
Molecular mass:	100.02
Structural formula:	

2.2 EU classification and labelling

There is currently no official EU classification.

TFE should be classified and labelled provisionally in accordance with the Dangerous Substances Directive 67/548/EEC and its subsequent amendments (EC, 2001) as follows.

Classification:		Xn, Harmful
		F+, Extremely flammable
Labelling:	R- phrases	R 40 : Limited evidence of a carcinogenic effect [a]
		R 12 : Extremely flammable
	S-Phrases	S 16 : Keep away from sources of ignition - No smoking
		S 23 : Do not breathe gas
		S 33 : Take precautionary measures against static discharges

2.3 Physical and chemical properties

At normal (ambient) temperature and pressure, tetrafluoroethylene (TFE) is a colourless, odourless, flammable gas that is only slightly soluble in water. Data on physical and chemical properties are listed in Table 1.

[a] Previously "Possible risk of irreversible effects"

Table 1: Physical and chemical properties

Parameter	Value, unit	Reference
Melting point	-131.15°C	Lide, 2002a
Freezing point	-142.5°C[a]	Ruff and Bretschneider, 1933
	-131.15°C[b]	Furukawa *et al*, 1953
Boiling point at 1,013 hPa	-75.95°C	Lide, 2002b
Relative density D_4^{20} (density of water at 4°C is 1,000 kg/m^3)	Not applicable	
Viscosity, mPa·s at 20°C	Not applicable	
Refractive index n_D at 20°C	Not applicable	
Vapour pressure at 20°C	30,200 hPa[c]	Ausimont, 2000
Vapour density at 25°C (air=1)	3.4	ICI, 1996
	3.53	Du Pont, 1999
Threshold odour concentration, ppm (mg/m^3)	Not applicable	
Surface tension, mN/m at 20°C	Not applicable	
Solubility in water at 28°C	110 mg/l [d]	Ausimont, 2001
Partition coefficient, log K_{ow} (octanol/water) at 20°C	1.21	Lyman *et al*, 1990
Partition coefficient, log K_{oc} (organic carbon/water) at 20°C	2.03 [e]	US-EPA, 2000
Henry's Law constant at 25°C	63,700 Pa·m^3/mol [f]	SRC, 2001
	83,900 Pa·m^3/mol [g]	US-EPA, 2000
Flash point (closed cup)	Not applicable	
Flammability limits at 20 - 25°C	Not available	
Explosion limits in air at 1,013 hPa, at ambient temperature	6.5 - 45% (v/v)	Ausimont, 2000
Auto-flammability, ignition temperature	183°C	Ausimont, 2000

[a] Triple point, reported as 130.65 K

[b] Triple point, reported as 142.00 K

[c] Reported as 30.2 bar (1 bar = 1,000 hPa)

[d] In equilibrium with gaseous TFE (with partial pressure of 1,013 hPa)

[e] Calculated, reported as K_{oc} = 106.8

[f] Calculated, reported as 0.629 atm·m^3/mol, implies solubility of 157 mg TFE/l at 1 bar

[g] Calculated, reported as 0.828 atm·m^3/mol, implies solubility of 119 mg TFE/l at 1 bar

Commercial TFE typically has a purity of ≥ 99.7%. Common impurities are various other fluorocarbons, depending on the conditions of the production process (Section 3.1).

TFE can decompose explosively, in the absence of air, to CF_4 and carbon. This reaction can be initiated by exposure of TFE vapour to high temperatures or other ignition sources and its susceptibility increases with increasing pressure. Van Bramer *et al* (1994) indicate that a saturated TFE vapour can explode at temperatures of -16°C or greater when under a pressure of at least 10,320 hPa, while an unsaturated TFE vapour can explode at 25°C and 7,900 hPa. TFE is also flammable in air, within certain concentration limits. Furthermore, it can undergo explosive autopolymerisation in the presence of oxygen (Van Bramer *et al*, 1994).

2.4 Conversion factors

Conversion factors for TFE concentrations in air at standard conditions (25°C and 1,013 hPa) are:

- 1 mg/m^3 = 0.245 ppm
- 1 ppm = 4.088 mg/m^3

In this report, converted values are given in parentheses. The generic formula is given in Appendix B.

(Conversion factors at 20°C and 1,013 hPa would be: 1 mg/m^3 = 0.241 ppm and 1 ppm = 4.158 mg/m^3.)

2.5 Analytical methods

The general analytical method used for the determination of TFE is gas chromatography (GC) with Flame Ionisation Detector (FID). The detection limit is 0.18 ppm by volume (0.74 mg/m^3) of TFE in air (SPI, 1998a).

TFE-based polymers have been analysed for residual TFE content by GC analysis of the headspace of a sample equilibrated in a solvent such as dimethylacetamide. The lowest detection limits were 0.08 mg/kg (Rijk and De Kruijf, 1997) or 0.01 mg/kg (SPI, 1998b).

There are no standard methods for analysis of TFE in water, sediments and soil.

2.5.1 Biological media

No standard method of analysis is available. Fluorine-19 Nuclear Magnetic Resonance (F-19 NMR) is frequently used as a highly selective and sensitive means of detecting TFE and its metabolites in biological media. Alternatively, the presence of fluoride ion, measured with a fluoride specific electrode, may be used to indicate exposure to TFE or its metabolites (Odum and Green, 1984; Hayden *et al*, 1991; Hargus and Anders, 1991; Chen *et al*, 1992; Harris *et al*, 1992; Bruschi *et al*, 1993, 1998; Fisher *et al*, 1993).

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

It is estimated that the world-wide production of TFE is of the order of 100 kt/y (Asahi Glass, 2001).

The sole industrial manufacturing process for TFE is the pyrolysis of chlorodifluoromethane (HCFC-22) at elevated temperature (≥ 650°C).

$$2\ CHClF_2 \longrightarrow CF_2 = CF_2 + 2\ HCl \qquad \text{(Eq. 1)}$$

Apart from the main reaction, minor side reactions, mostly originating with the action of HCl, lead to the formation of numerous other by-products. The majority of impurities are various chlorofluoro-derivatives boiling in the range from -84.4 to +77 °C. TFE for making fluoropolymers needs to be extremely pure, usually containing only 1 - 10 ppm (w/w) (1 - 10 mg/kg) as impurities (SRI International, 1983). An update on process conditions is given in SRI International (1992).

3.2 Storage

Most TFE is used immediately on-site for polymerisation.

Otherwise, TFE is stored as a gas, in a pressure vessel in cool well-ventilated areas, sheltered from sunrays and away from ignition sources and combustible, explosive and incompatible materials such as oxygen and oxidising substances.

3.3 Transport

Transportation of TFE in bulk is generally not permitted (UN code 1081) (Ministero dei Trasporti e della Navigazione, 1966). Limited quantities of TFE can be transported as liquefied compressed gas in metal pressure resistant containers (cylinders, tubes, pressure drums and tanks), subject to International Maritime Dangerous Goods (IMDG, 2000), International Carriage of Dangerous Goods by Rail (RID, 2003) European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR, 2003) and Dangerous Goods Regulation of the International Air Transport Association (IATA, 2003) regulations. In Italy, by derogation from ADR provisions, the road transportation in the gaseous state in bulk is permitted up to a maximum filling degree of 19 g/l and a minimum pressure of 1 MPa at 20°C (Multilateral Agreement M128, 2002.)

3.4 Use

TFE is used mainly in the production of polytetrafluoroethylene (PTFE) homopolymer. TFE is also copolymerised with hexafluoropropylene and other fluorinated monomers such as ethylene, perfluoroalkyl vinyl ether, isobutylene to produce a variety of fluoropolymers and fluororubbers (Kroschwitz and Howe-Grant, 1992). It is also used as an intermediate in the synthesis of other fluorinated compounds, e.g. agrochemicals.

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Emissions

4.1.1 Natural sources

TFE is not known to occur as a natural product.

4.1.2 Emissions during production and use

TFE is normally manufactured in a closed system. TFE vapours from vented equipment and tanks are destroyed by thermal oxidation. The use of TFE in fluoropolymer synthesis, nitroso-rubbers and low molecular mass compounded intermediates may result in its release to the environment through various waste streams. Quantitative data are not available.

Residual Levels in Polymers and Polymer Dispersions

In TFE based polymer powders or granules, residual TFE monomer is not detectable (limit of detection 0.01 - 1 mg/kg). Due to its water solubility (Table 1), TFE monomer is always present in aqueous TFE polymer dispersions at concentrations up to 1 mg/kg, typically around 0.5 mg/kg (SPI, 1998b).

No residual TFE monomer (analytical detection limit 0.05 - 0.01 ppm, w/w) (0.05 - 0.01 mg/kg) was found in PTFE at temperatures below 260°C, the maximum recommended "continuous service temperature" (SPI, 1998b).

No TFE (residual monomer) has been detected in products or articles made from TFE based polymer (Rijk and De Kruijf, 1997; SPI, 1998b).

4.2 Environmental distribution

The theoretical distribution of TFE into different compartments of the environment has been estimated using the Mackay Level 1 fugacity model (Mackay and Paterson, 1981) and physico-chemical parameters listed in Table 1. The results are given in Table 2.

Table 2: Partitioning (%) into the environment (Franklin, 2003)

Air	99.99
Water	0.005
Soil	< 0.001
Sediment	< 0.001
Suspended sediment	< 0.001
Fish	< 0.001
Aerosol	< 0.001

The estimates show that, after equilibrium, practically all TFE released into the environment will be found in the air; the amounts in water, soil and sediment are negligible.

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric fate and impact

The physico-chemical properties of TFE, i.e. its high vapour pressure, indicate that it should remain essentially in the gas phase.

TFE can react with the hydroxyl radical (·OH) through addition on the double bond. Other atmospheric species can also react with TFE, in particular ozone (O_3) and the nitrate radical (NO_3·). The value of the rate constant for the reaction of TFE with ·OH has been measured (Orkin *et al*, 1997; Acerboni *et al*, 1999). For comparison purposes, Table 3 also lists the rate constants measured for some other haloethenes.

Table 3: ·OH rate constants of TFE, other haloethenes and halomethane

Compound	**Formula**	**k_{OH} (10^{-12} cm^3/molecule/s)**	**Reference**
TFE	C_2F_4	11.3 ± 3.3	Acerboni *et al*, 1999
		10.2	Orkin *et al*, 1997
Chlorotrifluoroethene	C_2F_3Cl	7.0	Kwok and Atkinson, 1995
1,1-Dichloro-2,2-difluoroethene	$C_2F_2Cl_2$	7.5	Kwok and Atkinson, 1995
Trichlorofluoroethene	C_2FCl_3	7.6	Kwok and Atkinson, 1995

For all of these compounds the corresponding rate constant calculated with the Atmospheric Oxidation Program (version 1.8) (SRC, 2000) would be 0.214×10^{-12} cm^3/molecule/s. This software has been developed on the basis of Atkinson's method (Meylan and Howard, 1993). There is discrepancy between calculated and measured rate constant, which is often the case with fluorinated compounds.

Using the rate constant measured by Acerboni *et al* (1999) and an average ·OH concentration of 10^6 molecule/cm^3 (Prinn *et al*, 1995), the corresponding atmospheric lifetime [a] is calculated to be approximately 1 day and the half-life [b], 0.69 day. Acerboni *et al* (2001), using the same rate constant in a 3-dimensional chemical transport model (representing more closely the average behaviour of TFE in the atmosphere), predicted a ·OH-related lifetime of 1.9 days for TFE.

TFE can equally react with O_3. Several authors have reported values of the rate constant and lifetime for this pathway (Table 4).

Table 4: Reaction of TFE with O_3

k_{O_3} (10^{-21} cm^3/molecule/s)	Lifetime [a]	Reference
4.80 ± 0.62	9 y	Acerboni *et al*, 1999
92	179 d	Adeniji *et al*, 1981
498	33 d	Heicklen, 1966 [b]
28.4	1.59 y	Toby and Toby, 1976 [b]

[a] Assuming an O_3 concentration of 7 x 10^{11} molecules/cm^3 26 ppbv

[b] As cited by Acerboni *et al*, 1999

Thus, the O_3-related lifetime of TFE may range from 33 days to 9 years depending on the different experimental conditions. This pathway appears to be of minor importance since at most 3% of TFE could be converted within a lifetime of 33 days on the basis of the ratio between the rates of the reaction with O_3 and the overall reaction (O_3 + ·OH), i.e. 1/34 (Heicklen, 1966 as cited by Acerboni *et al*, 1999).

Acerboni *et al* (1999) also studied the possible reaction of TFE with NO_3·. His model calculations suggest that, due to the lifetime of > 156 days associated with this reaction, only a small part of the TFE would be converted in this manner.

In all, the average atmospheric lifetime of TFE is considered to be < 2 days.

The main oxidation pathway of TFE in the atmosphere due to &OH addition can be described as follows :

$$CF_2 = CF_2 + \cdot OH \longrightarrow CF_2(OH) - C\cdot F_2 \quad \text{(Eq. 2)}$$

$$CF_2(OH) - C\cdot F_2 + O_2 \longrightarrow CF_2(OH) - C(OO\cdot)F_2 \quad \text{(Eq. 3)}$$

$$CF_2(OH) - C(OO\cdot)F_2 + NO \longrightarrow CF_2(OH) - C(O\cdot)F_2 + NO_2 \quad \text{(Eq. 4)}$$

$$CF_2(OH) - C(O^\circ)F_2 \longrightarrow \underline{C(=O)F_2} + C\cdot F_2(OH) \quad \text{(Eq. 5)}$$

$$C\cdot F_2(OH) + O_2 \longrightarrow \underline{C(=O)F_2} + HO_2\cdot \quad \text{(Eq. 6)}$$

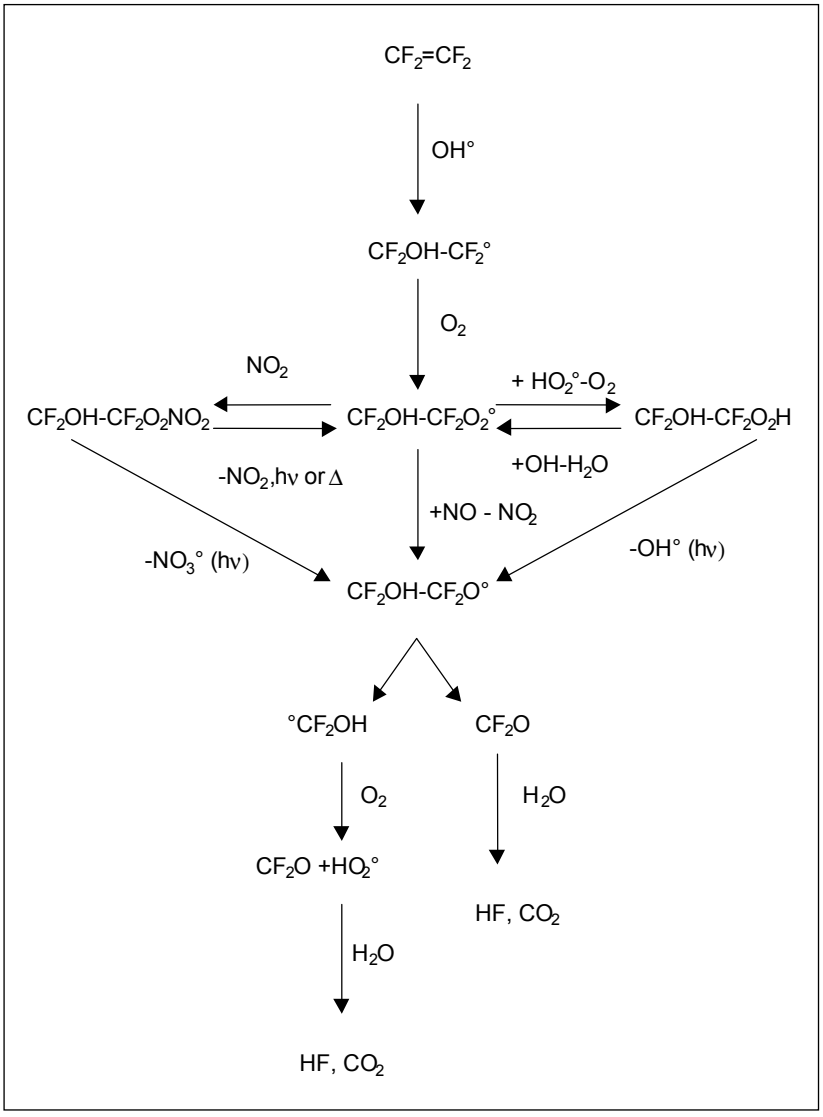
[a] Lifetime is defined as $\tau = 1/k(OH)$

[a] Half-life is defined as $\tau_{1/2} = \tau$ x In2

The above reactions can be expected from the degradation pathways already observed for several fluorocarbons and described in various atmospheric impact assessments of CFC alternatives (WMO/UNEP, 1995, 1998), and also from the expected mechanisms for degradation of perchloroethylene by reaction with ·OH (Franklin, 1994; ECETOC, 1999). Furthermore, the formation of carbonyl fluoride as the main degradation product is consistent with experimental work (Acerboni *et al*, 1999). The intermediate compound $C(=O)F_2$ hydrolyses in atmospheric water and forms carbon dioxide (CO_2) and hydrogen fluoride (HF) as the end products, the HF being removed by rain (wash out). The lifetime of this general process has been estimated to be of the order of 10 weeks in the case of $COCl_2$ (WMO/UNEP, 1998, Chapter 2) and can be expected to be similar for COF_2.

Figure 1 shows a general scheme of the different reaction routes that might be expected in atmospheric conditions.

Figure 1: Atmospheric pathways of TFE



Greenhouse effect

Because of its short lifetime, the direct impact of TFE on the greenhouse effect is expected to be negligible. This has been confirmed by a calculation of global warming potential (GWP) of 0.021 (CO_2 = 1) for an integration horizon of 100 years (Acerboni *et al*, 2001).

Tropospheric O_3 formation

TFE emitted to the atmosphere will contribute to the formation of tropospheric O_3. Model calculations would be required to quantify this effect that also depends on the quantity emitted to the atmosphere.

Stratospheric O_3 depletion

Since TFE does not contain chlorine or bromine atoms it has no effect on stratospheric O_3 content.

4.3.2 Aquatic fate

TFE is only slightly soluble in water at ambient temperature (Table 1). Owing to the lack of hydrolysable functional groups, it is not expected to hydrolyse.

On the basis of the estimated values for Henry's Law constant (Table 1), TFE is expected to volatilise from water into the atmosphere (Howard and Meylan,1997).

The half-life for volatilisation from a model river (1 m depth, 1 m/s current) and 3 m/s wind speed was calculated to be 2.9 hours (Lyman *et al*, 1990).

The low log Koc value of 2.03 (Table 1) suggests that TFE released into water is not expected to adsorb to sediment or suspended solids.

4.3.3 Terrestrial fate

If released to soil, owing to its low log K_{oc} value of 2.03 (Table 1), TFE is expected to have a high mobility in the soil.

Volatilisation from wet and dry soil surfaces is expected to be an important fate process, based upon the estimated Henry's Law constant and this compound's high vapour pressure (Table 1).

4.3.4 Biodegradation

No data are available.

Highly fluorinated compounds such as TFE are not expected to biodegrade rapidly (Boethling *et al*, 1994).

4.3.5 Bioaccumulation

The estimated log Kow of 1.21 suggests a low bioaccumulation potential for TFE. Using the regression equation log BCF = 0.76 x log Kow - 0.23 (Lyman *et al*,1990) a theoretical bioconcentration factor of 4.9 can be estimated.

4.3.6 Evaluation

Any TFE released into the environment is expected to partition almost entirely to the atmosphere, where it will quickly react with atmospheric ·OH, with an average atmospheric lifetime of less than 2 days. Subsequent decomposition yields $C(=O)F_2$ that is further hydrolysed in the presence of atmospheric water to form HF and CO_2, the HF being washed out by rain.

TFE does not contribute directly to the greenhouse effect (global warming), but may enhance the formation of tropospheric O_3 depending on the emitted quantities. TFE has no effect on the stratospheric O_3 layer.

In the aquatic environment, no hydrolysis of TFE will occur. TFE is not prone to rapid biodegradation and bioaccumulation. TFE will not adsorb significantly to soils and sediments.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

No data are available.

5.2 Human exposure levels and hygiene standards

5.2.1 Non occupational exposure

There are no reports dealing with non-occupational exposure to TFE.

5.2.2 Occupational exposure

There are no case reports. A multi-centre epidemiological study of workers potentially exposed to TFE during manufacture and polymerisation has been commissioned (Bertazzi and Consonni, 2002).

Exposure in the workplace may occur through inhalation during the manufacturing of TFE and its subsequent polymerisation. Atofina (2001) reported the outcome of workplace measurements made at a factory in October 2000, where 8-h TWA levels were between 0.16 and 6.00 mg TFE/m^3 (0.04 - 1.47 ppm). Asahi Glass (2000) stated that 95% of 240 personal monitoring measurements taken over 2 years in workers exposed to TFE during its polymerisation to PTFE did not exceed 0.5 ppm (range < 0.1 - 1.5 ppm TWA) (2.0, < 0.4 - 6.1 mg/m^3).

Analysis was carried out on blood and urine samples of 129 workers at a plant producing TFE and PTFE. The workers were also exposed to several fluoroalkanes (concentration not measured). The concentration of urinary inorganic fluorides was elevated (Xu *et al*, 1992).

5.2.3 Hygiene standards

In the USA, the ACGIH has adopted a Threshold Limit Value (TLV, 8-h TWA) of 2 ppm TFE (8.2 mg/m^3), based on kidney and liver effects. TFE was a designated as "confirmed animal carcinogen with unknown relevance to humans (A3)" (ACGIH, 2000, 2002).

The German MAK Commission intends to evaluate TFE for its carcinogenic effects (DFG, 2002).

5.2.4 Public and environmental health standards

TFE is included in the positive list of monomers and other starting substances for plastic materials and articles intended to come into contact with foodstuffs. A specific migration limit of 0.05 mg/kg (foodstuffs) has been assigned (EC, 2002).

5.3 Other standards

The American Industrial Hygiene Association (AIHA, 1991) has established Emergency Response Planning Guideline (ERPG) values for TFE as the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without:

- Experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odour (ERPG-1: 200 ppm) (820 mg/m^3);
- experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action (ERPG-2: 1,000 ppm) (4,100 mg/m^3);
- experiencing or developing life-threatening health effects (ERPG-3: 10,000 ppm) (41,000 mg/m^3).

Du Pont (1987) set exposure limits (EELs) for emergency situations, such as a major spill or the accidental release of a chemical, and specified brief durations and concentrations from which escape is feasible without any escape-impairing or irreversible effects on health. The EEL for short exposures (up to 60 min) to TFE was 100,000 ppm·min (410,000 mg/m^3·min) with a ceiling of 20,000 ppm TFE (82,000 mg/m^3). It should be noted that EELs are only applicable to emergency situations that are expected to occur rarely in the lifetime of an individual.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

In the absence of experimental data, a modelling approach has been used to assess the effects of tetrafluoroethylene on aquatic and terrestrial organisms.

6.1 Aquatic organisms

The toxicity of TFE to fish, daphnia and algae was estimated using the US EPA program ECOSAR 51994 (Boethling *et al*, 1994) (Table 5).

Table 5: Predicted acute toxicity to aquatic organisms

Organisms	Duration (h)	Effect / Parameter	Concentration (mg/l)
		Lethality	
Fish	96	LC_{50}	646
		Immobility	
Daphnia	48	EC_{50}	646
		Growth inhibition	
Algae	96	EC_{50}	381

6.2 Terrestrial organisms

Using the ECOSAR model (Boethling *et al*, 1994) a 14-d LC_{50} of 1,077 mg TFE/l was predicted for earthworms.

6.3 Evaluation

The predicted toxic concentrations of TFE to either aquatic or terrestrial organisms are considerably greater than the solubility level of TFE in water in equilibrium with a gas phase containing 1 atmosphere of TFE (110 mg/l, Table 1), and many orders of magnitude greater than any likely environmental concentration. Therefore, it can be assumed that TFE will not be toxic in the environment.

TFE is expected to quickly disappear from the soil or water phase. Moreover, a (theoretical) build-up of concentrations over time is not expected (Section 4.3.6).

7. KINETICS AND METABOLISM

7.1 In vivo studies

Humans

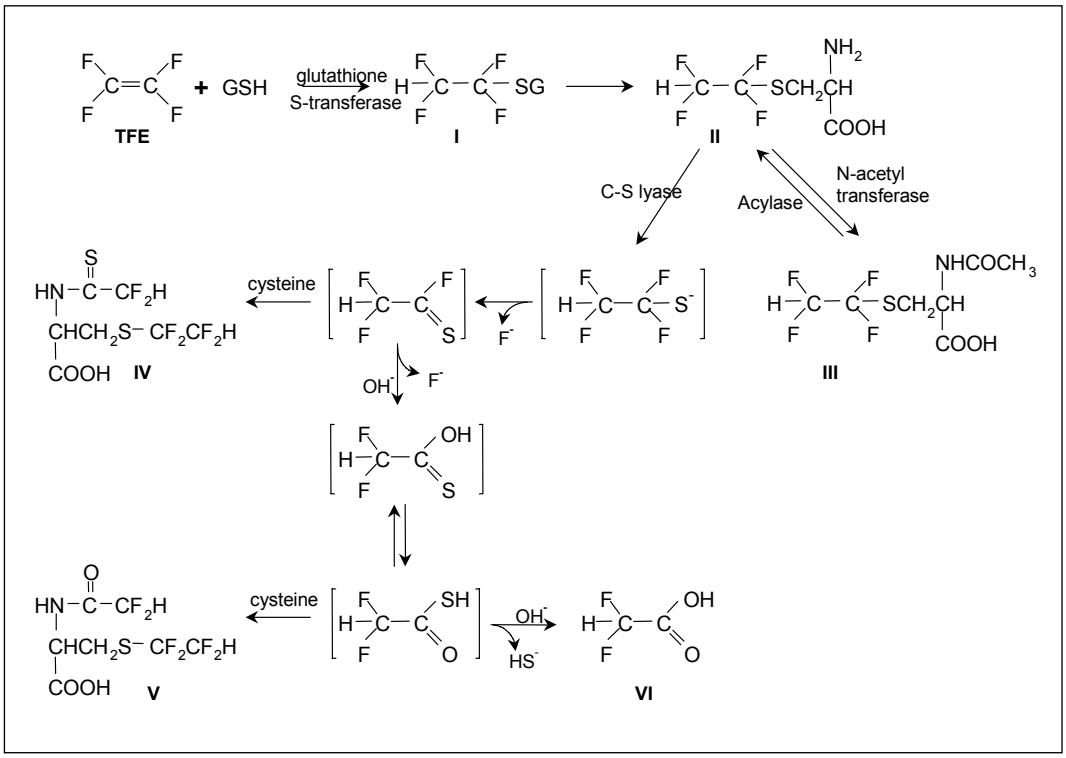
The metabolism of TFE has not been studied in humans *in vivo*. Using PBPK modelling uptake has been calculated to be poor; approximately 1% of TFE entering the airways passes into the systemic circulation (Green and Mainwaring, 1998). Evidence of exposure and metabolism has been demonstrated by the presence of fluoride ion in the urine of exposed workers (Xu *et al*, 1992). Exposure via the skin or other routes is not considered to be significant because of the volatility and slight solubility (in aqueous and organic solvents) of TFE.

Animals

The chemical properties of TFE preclude its synthesis in a radiolabelled form. Consequently, there are no quantitative *in vivo* data describing uptake, distribution and excretion. As in humans, uptake in the rat has been calculated to be approximately 1% of the inhaled dose (Green and Mainwaring, 1998).

Metabolism of TFE was first demonstrated by the presence of fluoride ion in the urine of TFE-exposed rats and hamsters (Dilley *et al*, 1974; Schneider, 1983). Subsequently, the urine of rats and mice exposed to 6,000 ppm (25,000 mg/m^3) TFE for 6 hours was analysed by F-19 NMR and a number of metabolites identified (Figure 2) (Odum and Green, 1984; Green, 2000). Based on the fluorine signals in the NMR spectra, difluoroacetic acid (VI) was identified as the major metabolite in the rat, accounting for > 90% of all fluorine-containing metabolites found in urine. Trace amounts of N-acetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine (III), N-difluorothionoacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine (IV) and N-difluoroacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine (V) were also present. In mouse urine, the mercapturate (III), N difluorothionoacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine (IV) and N-difluoroacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine (V) were present in similar amounts. The concentration of difluoroacetic acid was approximately half that of the combined total of the cysteine conjugates (Green, 2000). Fluoride ion excretion was approximately 1.7-fold greater in rats than in mice. Cysteinylglycine and cysteine conjugates of TFE have been identified in the bile of exposed rats (Odum and Green, 1984).

Figure 2: The metabolism of TFE in rats and mice



I, S-(1,1,2,2-tetrafluoroethyl)-L-glutathione
II, S-(1,1,2,2-tetrafluoroethyl)-L-cysteine
III, N-acetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine
IV, N-difluorothionoacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine
V, N-difluoroacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine
VI, Difluoroacetic acid
[ ], Postulated acylating intermediates

Rats dosed *in vivo* with the cysteine conjugate of TFE, S-(1,1,2,2-tetrafluoroethyl)-L-cysteine, yielded the same urinary metabolites as those seen in rats exposed to TFE itself, confirming a single metabolic pathway through glutathione conjugation (Commandeur *et al*, 1988; 1991; Green, 2000). As with TFE, the major metabolite was difluoroacetic acid. Following an intra-peritoneal dose of either deuterated N-acetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine or S-(1,1,2,2-tetrafluoroethyl)-L-cysteine, only 2-3% of the dose appeared in urine as mercapturates in the 24 hour period following dosing, suggesting extensive metabolism of these cysteine conjugates *in vivo* (Commandeur *et al*, 1991).

7.2 In vitro studies

Rat

A number of *in vitro* studies have investigated the metabolism of TFE and provided a partial explanation for the formation of the metabolites seen *in vivo*. TFE is metabolised by addition of glutathione across the double bond to give S-(1,1,2,2-tetrafluoroethyl) glutathione without liberation of fluoride (I, Figure 1) (Odum and Green, 1984). The reaction is catalysed by hepatic microsomal and cytosolic glutathione S-transferases and occurs at very similar rates (1.0 - 1.3 nmol/min/mg microsomal protein) in rat and mouse (Green, 2000). There is no evidence for oxidation of TFE by cytochrome P 450 enzymes (Odum and Green, 1984).

S-(1,1,2,2-tetrafluoroethyl)-L-cysteine has been shown to be a substrate for both hepatic and renal cysteine conjugate C-S lyases (Green and Odum, 1985; Green, 2000, 2001). The initial products of the reaction are believed to be a thiol, pyruvate and ammonia. Further reactions of the thiol liberate fluoride ion and lead to the formation of an acylating species, difluorothionoacyl fluoride, which reacts with S-(1,1,2,2-tetrafluoroethyl)-L-cysteine to give N-difluorothionoacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine or, following hydrolysis and rearrangement, to give N-difluoroacetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine and difluoroacetic acid (Figure 2) (Commandeur *et al*, 1988, 1989, 1996). In the rat liver and kidney fractions, metabolism of S-(1,1,2,2-tetrafluoroethyl)-L-cysteine by C-S lyases was approximately 4-fold higher in the kidney than that in the liver.

Comparison between rodents and humans

S-(1,1,2,2-tetrafluoroethyl)-L-cysteine, the metabolite of TFE found in rodents, has been shown to be a substrate for human renal cysteine conjugate C-S lyase (McCarthy *et al*, 1994; Hawksworth *et al*, 1996; Green, 2001). Green (2001) compared the metabolism of TFE and its conjugates in liver and kidney fractions from rat, mouse and human. The rates of conjugation of TFE with glutathione were measured in liver fractions and the metabolism of the S-(1,1,2,2-tetrafluoroethyl)-L-cysteine by C-S lyases and N-acetyltransferases was compared in kidney fractions. The de-acetylation of N-acetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine by renal acylases was also compared (Table 6). The highest rates of C-S lyase metabolism were found in mouse liver and rat kidney. Human C-S lyase activities were significantly lower than those in rodents.

Table 6: Metabolism of TFE and its cysteine conjugates in liver and kidney fractions from rats, mice and humans

Organ/ Species	GST [a] Vi (nmol/min/ mg protein)	C-S lyase [b] Km (mM)	Vmax (nmol/min/ mg protein)	N-acetyl transferase [b] Km (mM)	Vmax (nmol/min/ mg protein)	Acylase [c] Km (mM)	Vmax (nmol/min/ mg protein)
Liver							
Rat	94	2.0	5.9	2.0	3.9	0.3	37
Mouse	79	3.0	40	7.0	69	0.2	18
Human	87	5.4	1.7	4.9	3.5	0.3	48
Kidney							
Rat	ND	2.6	21.9	2.9	91	0.4	216
Mouse	ND	5.9	4.0	9.0	48	1.0	248
Human	ND	5.0	3.4	4.2	56	0.4	91

[a] Glutathione S-transferase (GST) activity was measured with TFE

[b] C-S lyase and N-acetyl transferase activities were measured with S-(1,1,2,2-tetrafluoroethyl)-L-cysteine

[c] Acylase activity was measured with N-acetyl-S-(1,1,2,2-tetrafluoroethyl)-L-cysteine

ND Not determined

7.3 Summary

TFE is metabolised in rodents by conjugation with glutathione in a reaction catalysed by glutathione S-transferases. The glutathione conjugate is metabolised to the equivalent cysteine conjugate, which is further metabolised via the mercapturic acid pathway and by renal and hepatic C-S lyases. Metabolism by C-S lyases leads to a number of acylating intermediates that react with the amino group of cysteine or are hydrolysed to difluoroacetic acid (Figure 2). *In vitro* studies indicate that the same pathways exist in humans. However, in humans, the C-S lyase activity is much lower that that seen in rodents.

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

No specific oral and dermal toxicity data are available (TFE is a gas at room temperature).

8.1 Acute toxicity

8.1.1 Inhalation

Details and outcomes of the available acute inhalation toxicity studies with TFE are summarised in Table 7.

Table 7: Acute inhalation toxicity

Species / Strain, number, sex	Concentration (ppm) [a]	Time(h)	LC_{50} (ppm)[a]	Remark (mg/m^3) [a]		Reference	CoR
Mouse							
Not stated	Not specified	4	(35,000)	143,000	Not reported	Sakharova and Tolgskaya, 1977	3a
Rat							
Not stated	Not specified	2	(25,000)	102,000 [b]	"Absolute lethal concentration"	Zhermedei, 1958 as cited by Danishevskii and Kochanov, 1961	4
Sprague-Dawley 4 M/group	0, 10,000, 20,000, 40,000 or 80,000 [d] (0, 41,000, 82,000, 164,000 or 327,000 mg/m^3)	4	40,000[c]	(164,000)	At ≥ 10,000 ppm: laboured breathing, kidney damage At ≥ 20,000 ppm: sedation At ≥ 40,000 ppm : lethal (2/4 died at 40,000 ppm and 4/4 at 80,000 ppm[e]), damage of lung, liver and kidney	Du Pont, 1959	3a
F, M (strain and number not stated)	Not specified	4	(31,600)	129,100	Sedation, kidney damage (tubular necrosis) for both sexes	Sakharova and Tolgskaya, 1977	3a
		4	(32,200)	131,400			
Sprague-Dawley, 10 M/group	3,699 (15,100 mg/m^3)	4	> 3,699	(> 15,100)	No lethality, kidney damage at histology	Sarver and Trochimowicz, 1977	2e
Wistar, 4 M/ group	0, 1,000, 2,000, 3,000, 4,000 or 6,000[d] (0, 4,100, 8,200, 12,000, 16,000 or 25,000 mg/m^3)	6	> 6,000	(> 25,000)	No lethality, nephrotoxicity based on blood/urine analysis at ≥ 3,000 ppm Histology only at 6,000 ppm: renal tubular necrosis in 4/4 rats	Odum and Green, 1984	2e

Table 7: Acute inhalation toxicity (cont'd)

Species / Strain, number	Concentration (ppm) [a]	Time (h)	LC_{50} (ppm)[a]	LC_{50} (mg/m^3) [a]	Remark	Reference	CoR
Hamster							
Golden Syrian, 10 M/group	0, 10,200, 20,700, 25,000, 30,000, 40,100 or 78,100 (0, 41,700, 84,600, 102,000, 123,000, 164,000 or 319,000 mg/m^3)	4	28,500	(116,500)	Lethargy at 40,100 and 78,100 ppm Lethality : 1/10 at 25,000 ppm; 7/10 at 30,000 ppm; 10/10 at 40,100 and 78,100 ppm	Nash *et al*, 1980	2e
Guinea pig							
Not stated	Not specified	4	(28,300)	115,600	Not reported	Sakharova and Tolgskaya, 1977	3a

[a] Converted values are given in parentheses

[b] LC_{100}

[c] Approximate LC_{50}

[d] Nominal concentrations

[e] 4/4 rats died at 800,000 ppm (3,270 g/m^3) with 20% O_2 for 2.75 h

M Male

F Female

The LC_{50} values are relatively consistent and show no particular sex- or species-related sensitivity. Sakharova and Tolgskaya (1977) reported 4-h LC_{50} values around 30,000 ppm for the mouse, rat and guinea pig. Du Pont determined a 4-h LC_{50} of approximately 40,000 ppm in the rat (Du Pont, 1959) and 28,500 ppm in the hamster (Nash *et al*, 1980). General toxicity such as sedation was seen at concentrations ≥ 20,000 ppm in these studies.

Kidney damage occurred in rats exposed to levels as low as 3,700 ppm for 4 hours. Histological examination showed degeneration of the epithelium of kidney tubules upon cessation of exposure (at 3,700 ppm) and renal tubular fibrosis after a 14-d recovery period. This was considered as irreversible damage (Sarver and Trochimowicz, 1977).

In male rats, necrosis of the proximal tubules in the kidney was observed without any liver damage after exposure to 6,000 ppm for 6 hours. Based on nephrotoxicity as judged by urine analysis (changes in alkaline phosphatase and g-glutamyl-transpeptidase levels) at concentrations ≥ 3,000 ppm, the no-observed-adverse effect level (NOAEL) on kidney was 2,000 ppm (Odum and Green, 1984).

8.1.2 Other acute toxicity studies

One dog exposed to approximately 500 ppm of TFE (2,040 mg/m^3) for 4 hours did not show any clinical sign of toxicity. When exposed to 1,000 ppm or higher, a decrease in blood pressure was observed without any other untoward effect (Foulger and Flemming, 1946; CoR 4e).

In a study to assess the possible cardiac sensitisation potential of TFE, none of 4 dogs and neither of 2 cats tested were sensitised to the arythmogenic effects of an intravenous injection of adrenaline when exposed by inhalation to 250,000 to 500,000 ppm TFE (1,020 - 2,040 g/m^3) for 5 to 15 minutes (Burgison *et al*, 1955; CoR 2c).

TFE was found to be without anaesthetic potential in rats exposed to high concentrations ranging from 500,000 to 700,000 ppm (2,040 - 2,860 g/m^3) for 5 to 10 minutes (Foulger and Flemming, 1941; CoR 4e; concentrations as cited by Kennedy, 1990; CoR 4b; Lee, 1996; CoR 4b). However, Dimitrieva (1973; CoR 4c as cited by Kennedy, 1990) reported that rats could be placed under stage II anaesthesia (exposure conditions not reported) and that electrocorticograms showed decreased frequency and amplitude of rapid brain waves following exposure to TFE.

Cardiac sensitisation and anaesthesia are typical effects seen with other fluorinated compounds.

8.1.3 Summary

Acute inhalation LC_{50} values are relatively consistent and show no particular sex- or species-related sensitivity. The 6-h LC_{50} can be estimated as greater than or equal to 6,000 ppm (25,000 mg/m^3) and the 4-h LC_{50} about 30,000 ppm (123,000 mg/m^3) in rats. The primary toxic effect is kidney damage (proximal tubule necrosis) observed in the rat at concentrations around 3,700 ppm (15,100 mg/m^3) for 4 hours in absence of any clinical sign of toxicity.

TFE does not induce cardiac sensitisation up to 500,000 ppm (2,040 g/m^3) for 15 minutes in dogs or cats. It does not present any significant anaesthetic potential at concentrations up to 700,000 ppm (2,860 g/m^3) for 10 minutes in rats.

8.2 Skin, respiratory tract and eye irritation, sensitisation

No data are available on skin and eye irritation or sensitisation. No signs of respiratory tract irritation were seen in the inhalation studies in animals following single or repeated doses (Section 8.1.1 and 8.3.1).

8.3 Repeated dose toxicity

8.3.1 Inhalation

Several subacute and subchronic inhalation toxicity studies with TFE in rats, mice and hamsters are available; details and results are presented in Table 8. Most of these studies were conducted in compliance with GLP guidelines.

A number of inhalation studies in animals have been performed with decomposition (pyrolysis) products of TFE-based polymers. These studies are not reported here because the tested products are mixtures of a number of chemical vapours and particulates, and any observable effects cannot be attributed solely to the inhalation of TFE monomer.

Table 8: Repeated dose toxicity

Species / Strain, number, sex	Exposure regime and duration	Concentration [a] (ppm)	(mg/m^3)	Result and remarks	Reference	CoR
Mouse						
B6C3F$_1$, 5 F/group	6h/d for 1, 5 or 9 days over a 12-d period to assess cell proliferation	0, 30, 300, 600 or 1,200	(0, 120, 1,200, 25,000 or 4,900)	No mortality, no significant effects on body weight, no adverse clinical signs. No effects on haematology, clinical chemistry or urinary parameters. No increase in urinary fluoride.	Keller *et al,* 2000	1a
B6C3F$_1$, 10 F/group	6h/d for 9 days over a 12-d period for pathological assessment	0, 30, 300, 600, 1,200	(0, 120, 1,200, 2,500 or 4,900)	Increased liver weight in 300 ppm group only. No effect on kidney or spleen weights although increased cell proliferation in kidney in groups exposed to 600 and 1,200 ppm for 5 days, but not 1 or 9 days. Minimal pathological changes in renal tubular epithelial cells (individual cell necrosis, very slight karyomegaly and cytoplasmic basophilia) in animals exposed to 1,200 ppm for 9 days. No cell proliferation or pathological changes in liver.	Keller *et al,* 2000 2000	1a
B6C3F$_1$, 5/sex/group	6h/d, 5d/wk; 12 exposures for 16 days	0, 312, 625, 1,250, 2,500, 5,000	(0, 1,275, 2,555, 5,110, 10,200 or 20,400)	No mortality, no significant effects on final mean body weight and body weight gain, haematology, no clinical signs of toxicity related to exposure. Increased relative liver weight in F at 5,000 ppm. Increased incidences of renal tubular karyomegaly (essentially in inner renal cortex) in both sexes at 1,250, 2,500, 5,000 ppm, severity increased with concentration. NOAEL = 625 ppm.	NTP, 1997	1a
B6C3F$_1$, 10/sex/group	6h/d, 5d/wk for 13 weeks	0, 312, 625, 1,250, 2,500 5,000	(0, 1,275, 2,555, 5,110, 10,200 or 20,400)	No mortality, no significant effects on final mean body weight and body weight gain, no clinical signs of toxicity related to exposure. Anaemia at 2,500 and 5,000 ppm in M and at 5,000 ppm in F. Increased incidences of renal tubule karyomegaly (primarily in the inner renal cortex) in both sexes ≥ 1,250 ppm. NOAEL = 625 ppm.	NTP, 1997	1a
Rat						
F344, 5 F/group	6 h/d for 1, 5 or 9 days over 12-d period to assess cell proliferation	0, 30, 300, 600, 1,200	(0, 120, 1,200, 2,500 or 4,900)	No mortality, no significant effects on body weight, no adverse clinical signs. Increased cell proliferation in kidney, but not liver, in group exposed to 1,200 ppm for 5, but not 1 or 12 days.	Keller *et al,* 2000	1a

Table 8: Repeated dose toxicity (cont'd)

Species / Strain, number, sex	Exposure regime and duration	Concentration [a] (ppm)	(mg/m^3)	Result and remarks	Reference	CoR
Rat						
F344, 10 F/group	6 h/d for 9 days over a 12-d period for pathological assessment	0, 30, 300, 600, 1,200	(0, 120, 1,200, 2,500 or 4,900)	No mortality, no significant effects on body weight, no adverse clinical signs No effects on clinical chemistry or urinary parameters. Urinary fluoride increased in groups exposed to 300 ppm and above. Small decreases in indicators of circulating erythrocyte mass in group exposed to 1200 ppm. Increased relative liver weight in group exposed to 600 ppm only. No effect on spleen weight. Increased relative kidney weight in groups exposed to 600 and 1,200 ppm. Increased cell proliferation in kidney, but not liver, in group exposed to 1,200 ppm for 5, but not 1 or 12 days. Evidence of minimal microscopic lesions in tubular epithelial cells (individual cell necrosis, giving large rounded cells with marked cytoplasmic vacuolation and pyknotic nuclei) in groups exposed to 600 and 1,200 ppm for 12 days. NOAEL = 300 ppm	Keller *et al*, 2000	1a
Not stated	4 h/d, 5d/wk for 2 weeks, 14-d recovery	4,000	(16,000)	No visible clinical signs of toxicity. At end of exposure and recovery period: histological kidney damage and, to a lesser extent, changes in the lungs, colon, haematopoietic system, and endocrine glands.	Du Pont, 1961[c]	4c
Sprague-Dawley Charles River	4 h/d, 5d/wk for 2 weeks, 14-d recover	0, 1,099 or 3,510	(0, 4,490 or 14,300)	Intermittent reduced rate of bodyweight gain in high dose group, no changes in urine parameters examined. Extensive histological kidney damage at top dose, almost unchanged at the end of 2-wk recovery period; moderate kidney damage at low dose, not totally reversible at the end of recovery period.	Sarver and Trochimowicz, 1977	2e
CD, 10 M/dose [b]				LOAEL = 1,099 ppm.		
Sprague-Dawley Crl:CD M/dose [b]	6 h/d, 5d/wk for 2 weeks, 14-d recovery	0, 101, 500, 991 or 2,489	(0, 413, 2,040, 4,050, 10,180)	Parameters assessed: clinical signs, body weight, haematology, blood/urine chemistry, and histopathology. No mortality, no clinical signs of toxicity. Increased relative kidney and liver weight at the two highest doses, totally reversible at the end of recovery period. Mild swelling of tubular epithelium of juxtaglomerular cortex and sparse cellular degeneration at top dose only, totally reversible after 14-d recovery period. NOAEL = 500 ppm.	Nash *et al*, 1981	1a

Table 8: Repeated dose toxicity (cont'd)

Species / Strain, number, sex	Exposure regime and duration	Concentration [a] (ppm)	(mg/m^3)	Result and remarks	Reference	CoR
F344/N, 5 sex/dose	6 h/d, 5d/wk for 16 days	0, 312, 625, 1,250, 2,500 or 5,000	(0, 1,275, 2,555, 5,110, 10,200 or 20,400)	No mortality; decreased body weight and body weight gain in both sexes at the top dose; increased relative kidney and liver weight in all exposed M groups and increased relative kidney weight at the two highest doses in F; Increased incidences of renal tubule degeneration in both sexes at ≥ 625 ppm (located at corticomedullary junction). Severity of this lesion increased with exposure concentration and was slightly greater in males. No histological anomaly in liver. LOAEL = 312 ppm.	NTP, 1997	1a
F344/N, 10/sex/dose	6 h/d, 5d/wk for 13 weeks	0, 312, 625, 1,250, 2,500 or 5,00	(0, 1,275, 2,555, 5,110, 10,200 or 20,400)	No mortality; decreased body weight and/or body weight gain in both sexes at the top dose. Minimal, treatment-dependent normocytic, normochromatic and non-responsive anaemia in all M and at the top dose in F. An exposure concentration dependant proteinuria in M at all dose levels and F exposed to 2,500 and 5,000 ppm. Increased liver weights of all M and in F at 2,500 and 5,000 ppm. Increased kidney weight at ≥ 1,250 ppm in M and ≥ 625 ppm in F. Increased incidences of renal tubule degeneration (similar to those of 16-d study) in M at ≥ 625 ppm and in F at ≥ 2,500 ppm. No differences between control and exposed groups in sperm morphology parameters or in the length of oestrous cycle. LOAEL = 312 ppm.	NTP, 1997	1a
CD, 15/sex/dose	6 h/d, 5d/wk for 13 weeks	0, 203, 605 or 1,989	(0, 830, 2,473 or 8,130)	Parameters assessed: clinical signs, body weight, haematology, blood/urine chemistry, and histopathology. No mortality; decreased body weight in top dose groups; increased relative kidney weight in both sexes at top dose. Kidney damage in both sexes at ≥ 605 ppm, both functional (increased urine volume and decreased urinary creatinine) and histological (toxic tubular nephrosis, primarily in proximal convoluted tubules). Rats (both sexes) exposed to 1,989 ppm showed a decreased rate of weight gain, and more marked kidney changes. NOAEL = 203 ppm.	Schneider *et al*, 1982	1a

Table 8: Repeated dose toxicity (cont'd)

Species / Strain,	Exposure regime and duration number, sex	Concentration [a] (ppm)	(mg/m^3)	Result and remarks	Reference	CoR
Hamster						
Lak:LVG (Syr), 10 M/group[b]	6 h/d, 5d/wk for 2 weeks, 14-d recovery	0, 101, 500, 991 or 2,489	(0, 410, 2,040, 4,050, 10,180)	Parameters assessed: clinical signs, body weight, haematology, blood/urine chemistry, and histopathology. No mortality and no clinical signs of toxicity attributable to exposure; no significant changes in organ weights. Degeneration of germinal epithelial cells of testis observed only at end of the 14-d recovery period at high dose of 2,500 ppm, but not in animals sacrificed after the tenth exposure; treatment related effect cannot be excluded. A clear NOAEL could not be determined (see text).	Nash *et al*, 1981	1a
Lak:LVG (Syr), 15 M/group	6 h/d, 5d/wk for 13 weeks	0, 203, 605 or 1,989	(0, 830, 2,473 or 8,130)	Parameters assessed: clinical signs, body weight, haematology, blood/urine chemistry, and histopathology. No exposure related mortality; no clinical signs clearly related to exposure. M in 605 and 1,989 ppm groups exhibited a variable incidence of testicular immaturity, against which a TFE-induced focal hypocellularity of the germinal epithelium of seminiferous tubule was observed in the 1,989 ppm group. Considerable variability in testes weights and tissue (immaturity) among the 4 groups renders data interpretation difficult, especially at the mid dose. Testicular atrophy at the top dose. NOAEL = 203 ppm.	Schneider *et al*, 1982	1a

[a] Converted values are given in parentheses

[b] 5/dose for examination at end of exposure and 5/dose for recovery

[c] As cited by Sarver and Trochimowicz, 1977

Mouse

In the 12-d inhalation studies of Keller *et al* (2000), there were no effects attributable to TFE other than some kidney cell proliferation and signs of a minimal pathological effect in the renal tubular epithelial cells.

In a 16-d inhalation study (NTP, 1977), there was an increase of relative liver weight in the females. Renal tubular karyomegaly was seen at > 1,250 ppm TFE in both sexes, and increased in severity with increasing TFE exposure concentrations.

In the NTP (1997) 13-wk study in mice, the authors reported a concentration-dependent normocytic, normochromatic and non-responsive anaemia that is consistent with secondary hypoproliferative anaemia at the two highest dose levels ≥ 2,500 ppm TFE. (In the opinion of the Task Force, although the changes were statistically significant, they were minimal, ranging from less than 5 to 10% across the exposure range, and their toxicological significance remains unclear.) Differences in epididymal spermatozoal parameters and oestrous cycle characterisation were not considered to be exposure related. Karyomegaly was similar to that observed in the 16-d study. The NOAEL is 625 ppm.

Rat

In the 12-d studies of Keller *et al* (2000), there were no effects other than some evidence of increased liver and kidney weights and kidney cell proliferation. There were signs of minimal pathological lesions in the renal tubular epithelial cells at the two highest concentrations. At 300 ppm TFE, the only observed effect was an increase in urine fluoride excretion. This was not associated with any change in kidney weight or detectable histological lesion and, therefore, was not considered as an adverse effect. The NOAEL is 300 ppm.

In a 2-wk study, pathologic examination revealed kidney damage in particular (Du Pont, 1961 as cited by Sarver and Trochimowicz, 1977). A similar study showed degenerative changes in the kidney at 1,099 ppm TFE and, more pronounced, at 3,510 ppm. After recovery lesions were almost completely resolved in rats exposed to 1,099 ppm (LOAEL), but persisted to some extent in rats exposed to 3,510 ppm (Sarver and Trochimowicz, 1977).

In a later 2-wk study, increased relative kidney and liver weights were reported at the two highest concentrations and renal lesions, consisting of minimal proximal tubule damage, were observed at the end of the treatment but not at the end of recovery period (Nash *et al*, 1981). The NOAEL is 500 ppm.

In a 16-d study (NTP, 1997), there was found to be a significant effect on kidney and liver weight at all exposure levels. Increased incidences of renal tubule degeneration occurred in males and in females exposed to 625 ppm or greater. The lowest-observed-effect-level (LOAEL) is 312 ppm.

In a 13-wk study (NTP, 1997), the authors reported a concentration-dependent anaemia, consistent with secondary hypoproliferative anaemia, in males. However, while reductions from control values were statistically significant in all treated male groups, they were minimal, ranging from less than 5 to 10% across the exposure range. The changes in females were limited to the highest concentration (5,000 ppm). An exposure concentration-dependent proteinuria also occurred in all treated rats at all dose groups, consistent with renal tubule degeneration observed histopathologically. The LOAEL is 312 ppm.

In the 13-wk study of Schneider *et al* (1982), no changes were seen in the low dose group (203 ppm). At 605 ppm both sexes showed functional and histological kidney damage. The NOAEL is 203 ppm.

Hamster

In the 2-wk study of Nash *et al* (1981), histopathological examination showed no kidney anomaly. However, there was evidence of testicular atrophy at the top dose of 2,489 ppm after the 14-d recovery period, but not in animals sacrificed after the tenth exposure. Testicular atrophy was also seen in young control hamsters, making interpretation of the data difficult. A clear NOAEL could not be determined.

In the 13-wk study of Schneider *et al* (1982), atrophic testicular changes were noted at 605 and 1.989 ppm, both in hamsters with mature and immature testes. Because of the nature of the lesions and the confounding effect presented by delayed testicular maturation, the available data do not permit an interpretation of the presence or absence of a TFE-related effect on the testes at 605 ppm. No effects were seen at the low dose of 203 ppm (NOAEL).

Dog

Two dogs were exposed (4 h/d, 5d/wk) to approximately 1,000 ppm TFE for 6 weeks (25 exposures). No particular signs of toxicity were observed except for a decrease in blood pressure in one dog during the exposure periods. No effect on body weight gain was noted. No macroscopic or histological examinations were performed (Foulger and Flemming, 1946; CoR 4e).

8.3.2 Summary

The toxicity of TFE following repeated exposure by inhalation has been studied in the mouse, rat and hamster for durations up to 13 weeks. In the mouse, the most significant finding was renal tubular karyomegaly, the NOAEL being 625 ppm (2,555 mg/m^3) in a 13-wk study. The rat showed greater sensitivity to the kidney toxicity, with effects including proteinuria being seen at concentrations of ≥ 312 ppm (1,275 mg/m^3) in a 13 week study (LOAEL). The effects were also more severe, with renal tubular degeneration, accompanied by increases in kidney weight at higher concentrations. Increases in liver weight were also seen in rats exposed to 5,000 ppm (20,400 mg/m^3) TFE for 13 weeks. A NOAEL of 203 ppm (830 mg/m^3) for kidney effects was observed in the rat study.

In addition, both species showed a secondary hypoproliferative anaemia when exposed to TFE. The changes in the various indices were minimal, but statistically significant at higher exposure concentration levels in rats. For the rat, the haematological changes were more pronounced in males than in females.

In contrast, no evidence of kidney toxicity or anaemia was seen in hamsters exposed to TFE at concentrations up to 1,989 ppm (8,130 mg/m^3) in a 13 week study. However, atrophic effects in the testes accompanied by a focal hypocellularity of the germinal epithelium of the seminiferous tubule were observed in males exposed to TFE at concentrations of 600 ppm (2,500 mg/m^3) (Section 8.6.1). The NOAEL for these effects was 203 ppm (830 mg/m^3). Testicular atrophy was not seen in rats or mice.

(Indications of possible toxicity of metabolites are discussed in Chapter 9.)

8.4 Genetic toxicology

Results and details of the available mutagenicity tests with TFE are summarised in Table 9.

8.4.1 Gene mutation in vitro

Bacteria

TFE did not induce gene mutations in the Ames test (Longstaff and Ashby, 1976; Rickard *et al*, 1986a). The latter test was conducted in the presence and absence of the so-called S9 metabolic activation system [a]. A cysteine conjugate of TFE, S-1,1,2,2-tetrafluoroethyl-L-cysteine, was also without mutagenic activity in the Ames test without and with (Aroclor induced rat kidney S9) metabolic activation. The conjugate was tested in strains TA 1537, TA 1535, TA 100, TA 98, and TA 97 at concentrations reaching 500 μg/plate (Green and Odum 1985). Kidney S-9 was used for metabolic activation because of the marked nephrotoxicity noted in rats exposed to TFE.

[a] S9 (supernatant of centrifuged 9,000 x g liver homogenate), containing the microsome and cytosol fractions, usually derived from rates previously treated with microsomal enzyme inducing compounds such as phenobarbital or Aroclor.

Table 9: Mutagenicity tests

Endpoint / Organism	Strain / Target cells	Exposure regime, duration	Nominal concentration	(g/m^3) [a]	Result [b]	Remark	Reference	CoR
Gene mutation								
Salmonella typhimurium (Ames test)	Not stated	Not stated	Not stated		-ve	No indication of metabolic activation	Longstaff and Ashby, 1976	3a
Salmonella typhimurium (Ames test)	TA 1535, TA 97, TA 98 and TA 100	48 h	0, 0.5, 3, 4 or 5%	(0, 20, 120, 160 or 200)	-ve	With and without metabolic activation	Longstaff and Ashby, 1976; Rickard *et al*, 1986a	1c
In vitro CHO/HPRT	Chinese hamster ovary (CHO) cells	5 h with activation, 18 - 19h without activation	0, 20, 40, 60, 80 or 100%	(0, 800, 1,600 2,500 or 3,300)	-ve	With and without metabolic activation	Rickard *et al*, 1986b	1c
In vitro CHO/HPRT	CHO cells	5 h	0, 20, 40, 60, 80 or 100%	(0, 800, 1,600, 2,500 or 3,300)	-ve	With metabolic activation	Stahl, 1988	1c
Chromosome aberration								
In vitro structural chromosome aberrations	CHO cells	2 h with activation, 5h without activation	0, 25, 50, 75 100%	(0, 1,000, 2,000, 3,070 or 4,000)	-ve -ve	With and without metabolic activation	Vlachos, 1987	1c
In vivo mouse micronucleus	Bone marrow cells of C57BL/6JfC-1/Alpk mice, M and F	Animals exposed to TFE by inhalation for 6h; bone marrow samples taken at 24, 48, and 72h post exposure	M: 0, 5,000, 12,000 or 19,000 ppm; F: 0, 7,000, 17,000 or 28,000 ppm	(M: 0, 20, 49 or 78; F: 0, 29, 69 or 114)	-ve	No statistically significant increases in micronucleated polychromatic erythrocytes (MPE) in F. In M, numerically small increases in MPE at 72 h sampling time of the 5,000 and 12,000 ppm groups but not in the 19,000 ppm dose group or in any of the dose levels at 24 and 48 hour sampling times. These increases were determined of no biological significance.	Sheldon *et al*, 1988	1c

Table 9: Mutagenicity tests (cont'd)

Endpoint / Organism	Strain / Target cells	Exposure regime, duration	Nominal concentration	(g/m^3) [a]	Result [b]	Remark	Reference	CoR
In vivo mouse micronucleus	Peripheral blood cells of B6C3F$_1$ mice, M and F	Animals exposed to TFE by inhalation for 6 h/day, 5 d/wk for	0, 312, 625, 1,250, 2,500 or 5,000 ppm	(0, 1.275, 2.555, 5.11, 10.2 or 20)	-ve	No biologically significant increases in the frequency of micronucleated erythrocytes at the end of 13-wk inhalation period.	NTP (1997)	1c
Unscheduled DNA Synthesis (UDS)								
In vivo mouse liver UDS	Hepatocytes of CD-1 M mice	Animals exposed to TFE for a single 6-h period	0, 20,000 or 40,000 ppm	(0, 80 or 160)	-ve	No UDS induction	Fox, 1998	1c
Other studies								
Expression of H-ras codon *in vivo*	Hepatocellular tumours from B6C3F$_1$ mice	Animals exposed to TFE by inhalation 6 h/d, 5 d/wk for 95 to 96 weeks	0, 312, 625 or 1,250 ppm	(0, 1.275, 2.555, 5.11 or 10.2)	-ve	Hepatocellular tumours are induced via a ras-independent pathway	NTP, 1997	2e

[a] Converted values

[b] -ve, negative

Mammalian Cells

TFE did not induce gene mutations at the HPRT locus in cultured Chinese hamster ovary (CHO) cells with or without metabolic activation (Rickard *et al*, 1986b). The negative results with metabolic activation were subsequently confirmed at the request of the US-EPA (Stahl, 1988).

8.4.2 Chromosome aberration

Mammalian cells in vitro

TFE did not induce structural chromosome aberrations (clastogenicity) in CHO cells with and without activation (Vlachos, 1987).

Mammalian cells in vivo

Small but statistically significant increases in micronucleated polychromatic erythrocytes (MPE) were seen in the bone marrow of male mice 72 h following single exposure to 5,000 and 12,000 ppm TFE but not in the corresponding 19,000 ppm exposed animals. Following further evaluation and consideration of the historical database, these small increases in MPE were determined not to be biologically significant (Sheldon *et al*, 1988).

In a 13-wk inhalation study, groups of mice were exposed to TFE at atmospheric concentrations of up to 5,000 ppm. At the end of the exposure period, peripheral blood cells of male and female animals were isolated and the frequency of micronucleated erythrocytes assessed. There were no biologically significant increases in micronucleated cells of either sex above control levels (NTP, 1997).

8.4.3 Unscheduled DNA synthesis (UDS) *in vivo*

Following exposure of mice to single TFE concentrations up to 40,000 ppm, hepatocytes were isolated and examined for DNA excision repair. TFE did not induce UDS in mouse liver cells (Fox, 1998).

8.4.4 Other studies

The frequency of H-ras mutations was investigated in hepatocellular tumours taken from $B6C3F_1$ mice in the NTP carcinogenicity study (Hong *et al*, 1998). A low frequency of these mutations (15%) was observed compared to that in controls (59%) and in spontaneous liver neoplasms of this mouse strain (56%). This frequency is similar to that from liver tumours induced by the structurally-related chemical, tetrachloroethylene (24%). Although a few tumours in the tetrachloroethylene study were found to have a K-ras mutation, none were found in the liver tumours induced by TFE. These data indicate that TFE and tetrachloroethylene induce liver tumours via a ras-independent pathway.

8.4.5 Summary and evaluation

TFE has been assessed for its genotoxic potential in a number of studies. It does not induce gene mutations in bacteria and mammalian cells *in vitro* and is not clastogenic in CHO cells *in vitro* or in two micronucleus tests in mice. Hepatocytes isolated from mice exposed to TFE showed no evidence of unscheduled DNA synthesis (UDS). Therefore, TFE is not genotoxic both *in vitro* and *in vivo*. A cysteine conjugate of TFE, S-1,1,2,2-tetrafluoroethyl-L-cysteine, a nephrotoxic metabolite activated by renal C-S lyases, is also without mutagenic activity *in vitro*.

8.5 Chronic toxicity and carcinogenicity

8.5.1 In mice

Groups of 58 male and female $B6C3F_1$ mice were exposed (6 h/d, 5 d/wk) by inhalation to 0, 312, 625 or 1,250 ppm TFE (0, 1,275, 2,555, 5,110 mg/m^3) for 95 weeks. Ten male and 10 female mice from each exposure group were evaluated at 15 months with gross necropsy and histopathological examination (NTP, 1997).

Survival, body and organ weights, and clinical findings

The survival rates of all exposed groups of males and females were significantly less than those of the controls. Because of the reduced survival, the study was terminated during week 96. Mean body weights of exposed groups of males and females were generally similar to those of controls, except at the end of the study, when they were somewhat less than those of the controls. At the 15-month interim evaluation, there were no differences between exposed and control groups of mice in the absolute or relative kidney, liver or lung weights. There were no clinical findings related to TFE exposure.

Pathology findings

The most significant findings in both sexes in this study were a dose-related increase in the incidence of haemangiosarcomas of the liver, of hepatocellular tumours and of histiocytic sarcomas in the haematopoietic system.

Liver: non-neoplastic findings

At the 15-month interim sacrifice, an increased incidence of angiectasis was observed in all exposed groups of both male and female mice. At the end of the study, the angiectasis was accompanied by multifocal coagulative necrosis of the liver in all exposed groups of males. Also, at the end of the study, the incidences of haematopoietic cell proliferation in the liver of all exposed groups of females were greater than in the controls.

Table 10: Incidence of animals with tumours of the liver and haematopoietic system in B6C3F$_1$ mice exposed to TFE for 95 weeks (NTP, 1997)

Organ / Tumour	M				F			
Concentration (ppm)	0	312	625	1,250	0	312	625	1,250
(mg/m^3)	0	1,275	2,555	5,110	0	1,275	2,555	5,110
Liver								
Haemangioma (single and multiple)	0/48	10/48 [a]	5/48 [b]	2/48	0/48	5/48 [b]	2/47	1/47
Haemangiosarcoma (single and multiple)	0/48	21/48 [a]	27/48 [a]	37/48 [a]	0/48	27/48 [a]	27/47 [a]	34/47 [a]
Haemangioma and haemangiosarcoma (single and multiple)	0/48	26/48 [a]	30/48 [a]	38/48 [a]	0/48	31/48 [a]	28/47 [a]	35/47 [a]
Hepatocellular adenoma (single and multiple)	17/48	17/48	12/48	20/48	15/48	17/48	20/47	15/47
Hepatocellular carcinoma (single and multiple)	11/48	20/48 [b]	33/48 [a]	26/48 [a]	4/48	28/48 [a]	22/47 [a]	20/47 [a]
Hepatocellular adenoma and carcinoma (single and multiple)	26/48	34/48	39/48 [a]	35/48 [b]	17/48	33/48 [a]	29/47 [a]	28/47 [a]
Haematopoietic system (all organs)								
Histiocytic sarcoma	0/48	12/48 [a]	7/48 [a]	7/48 [a]	1/48	21/48 [a]	19/47 [a]	18/48 [a]

[a] Significant, $p \leq 0.01$

[b] Significant, $p \leq 0.05$

Liver: neoplastic findings

At the 15-month interim evaluation, an increased incidence of haemangiosarcoma in the liver occurred in males exposed to 1,250 ppm TFE (3/100) and in females exposed to 312 ppm TFE (1/10). At the end of the study, the incidence of haemangiosarcoma in all exposed groups of males and females was significantly greater than that in the controls. The incidence of haemangioma in the liver in males and females exposed to 312 ppm TFE and in males exposed to 625 ppm TFE was also significantly greater than that in the controls. These findings exceeded the range in historical chamber controls.

At 15 months, hepatocellular neoplasms occurred in all exposed groups of males and females. Additionally, incidences of eosinophilic foci in females exposed to 625 or 1,250 ppm TFE were significantly greater than those in the controls at the 15-month interim evaluation. At the end of the study, the incidences of eosinophilic foci in males exposed to 625 or 1,250 ppm TFE and in females exposed to 312 or 625 ppm TFE were significantly greater than those in the controls. There were treatment-related increases in a variety of hepatocellular neoplasms in both male and female mice, including adenomas, multiple adenomas, carcinomas, and multiple carcinomas.

Haematopoietic system: histiocytic sarcoma

At the 15-month interim evaluation, one histiocytic sarcoma was observed in the liver of a female exposed to 1,250 ppm TFE. At the end of the study, the incidences of histiocytic sarcoma (all organs) in all exposed groups of males and females were significantly greater than those in the controls. The incidences of histiocytic sarcoma in all exposed groups of male and female mice exceeded historical control ranges for all organs. The greatest incidences of histiocytic sarcomas were observed in the liver and lung, but these neoplasms were also observed in the spleen, lymph nodes, bone marrow, and kidney.

Findings in the kidney

Significantly increased incidences of renal tubule dilatation (males) and karyomegaly (males and females), located predominantly in the inner cortex, were observed in mice exposed to 625 or 1,250 ppm TFE for 15 months. At study termination, there were increased incidences of dilatation and karyomegaly in all exposed groups of males and of karyomegaly in females exposed to 1,250 ppm TFE. The effects were dose-related and statistically significant at the higher exposure concentrations.

At the end of the study, incidences of haematopoietic cell proliferation in the spleen of all exposed groups of males and females were significantly greater than those in the controls. Additionally, the severity of this lesion increased with exposure concentration.

8.5.2 In rats

Groups of 60 male and female F344 rats were exposed (6 h/d, 5 d/wk) by inhalation to a range of concentrations of TFE for 103 weeks, with an observation period of 11 days following the final exposure. The males were exposed to either 0, 156, 312 or 625 ppm TFE (0, 638, 1,275 or 2,555 mg/m^3) and the females were exposed to either 0, 312, 625 or 1,250 ppm TFE(0, 1,275, 2,555, 5,110 mg/m^3). Ten male and 10 female rats from each exposure group were evaluated at 15 months with gross necropsy and histopathological examination (NTP, 1997).

Survival, body and organ weights, and clinical findings

The survival rates of males exposed to 625 ppm TFE, and of all exposed groups of females, were significantly less than those of the controls. Mean body weights of males exposed to 625 ppm TFE were lower than those of the controls from week 81 until the end of the study, and the mean body weight of females exposed to 1,250 ppm TFE was slightly lower than that of the controls at the end of the study.

At the 15 month evaluation, the absolute and relative weights of the right kidney of males exposed to 625 ppm TFE and of females exposed to 1,250 ppm TFE were significantly greater than those of the controls, and the absolute weight of the right kidney of females exposed to 625 ppm TFE was significantly greater than that of the controls. Also, the absolute and relative liver weights of females exposed to 1,250 ppm TFE and the absolute liver weight of females exposed to 625 ppm TFE were significantly greater than those of the controls.

The only clinical finding associated with exposure to TFE was opacity of eyes that was increased in incidence in female rats exposed at 1,250 ppm TFE. This change was observed microscopically as cataracts.

Haematology, clinical chemistry, and urinalysis

At the 15-month interim evaluation, there were no differences in haematology, clinical chemistry, or urinalysis parameters considered to be related to TFE exposure.

Pathology findings

The main findings of the study were an increased incidence of renal tubular adenomas and hepatocellular tumours in both sexes.

Table 11: Incidence of animals with tumours in the kidney and liver in F344 rats exposed to TFE for 24 months (NTP, 1997)

Organ / Tumour	M				F			
Concentration (ppm)	0	156	312	625	0	312	625	1,250
(mg/m^3)	0	638	1,275	2,555	0	1,275	2,555	5,110
Kidney (renal tubular cells)								
Adenoma, single sections	0/50	0/50	6/50 [b]	3/50	0/50	3/50	1/50	3/50
single and step sections	2/50	4/50	9/50 [b]	13/50 [a]	0/50	3/50	3/50	8/50 [a]
Carcinoma, single sections	1/50	0/50	2/50	0/50	0/50	0/50	0/50	2/50
single and step sections	1/50	1/50	2/50	0/50	0/50	0/50	0/50	3/50
Adenoma and carcinoma								
single sections	1/50	0/50	6/50	3/50	0/50	3/50	1/50	5/50 [a]
single and step sections	3/50	5/50	9/50	13/50 [b]	0/50	3/50	3/50	10/50 [a]
Liver								
Haemangiosarcoma	0/50	0/50	0/50	0/50	0/50	0/50	5/50[b]	1/50
Hepatocellular adenoma	3/50	6/50	8/50	5/50	0/50	4/50	5/50 [b]	6/50 [b]
Hepatocellular carcinoma	1/50	1/50	10/50 [a]	3/50	0/50	4/50	9/50 [a]	2/50
Hepatocellular adenoma and carcinoma	4/50	7/50	15/50 [a]	8/50	0/50	7/50 [a]	12/50 [a]	8/50 [a]
Mononuclear cell leukaemia	34/50	43/50 [b]	38/50	31/50	16/50	31/50 [a]	23/50	36/50 [a]

[a] Significant, $p \leq 0.01$

[b] Significant, $p \leq 0.05$

Findings in the kidney

At the 15-month interim sacrifice, increased incidences of renal tubule hyperplasia were observed in males exposed to 312 ppm TFE and in males and females exposed to 625 ppm TFE. At the end of the study, the incidences of renal tubule hyperplasia in males exposed to 625 ppm TFE and females exposed to 1,250 ppm TFE were significantly greater than those in the controls. At 15 months and at the end of the study, the incidences of renal tubule degeneration in all exposed groups of males, and in females exposed to 625 ppm and 1,250 ppm TFE, were greater than those in the controls. Renal tubular degeneration was similar to that observed in the 13-wk study (Section 8.3.1) and was located predominantly at the corticomedullary junction. The severity of nephropathy generally increased with increasing exposure concentration in male rats exposed for 15 months and 2 years.

A statistically siginificant increase in the incidence of renal tubule adenoma and of renal tubule adenoma or carcinoma (combined) was observed in males exposed to 312 and 625 ppm TFE and in females exposed to 1,250 ppm TFE was observed. The effect was confirmed using step sections of the kidney (Table 11).

Findings in the liver

At the end of the 2-year study, increased incidences of hepatic angiectasis were observed in all exposed groups of female rats.

At the 15 month interim evaluation and after exposure for 2 years, the incidences of clear cell and mixed cell foci in all exposed groups of males were greater than those in the controls, as were the incidences of mixed cell foci at 15 months in females exposed to 625 or 1,250 ppm TFE, and at 2 years in females exposed to 1,250 ppm TFE.

At the end of the study, the incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in males exposed to 312 ppm TFE, the incidences of hepatocellular adenoma and adenoma or carcinoma (combined) in females in all exposed groups, and the incidences of hepatocellular carcinoma in females exposed to 312 or 625 ppm TFE, were significantly greater than those in the controls. Also at 2 years, the incidence of haemangiosarcoma in females exposed to 625 ppm TFE was significantly greater than that in the controls (Table 11).

Mononuclear cell leukaemia

Increased incidences of mononuclear cell leukaemia were observed in some of the exposed groups, particularly in females where the increased incidences were statistically significantly different from controls, although the effect was not dose-related in either sex (Table 11). The incidence in the control males (68%) was outside the historical control range for the conducting laboratory (38 - 66%), as were the incidences observed in males exposed to 156 (86%) and 312 ppm (76%). In females, the incidences in rats exposed to 312 (62%) and 1,250 (72%), but not 625 (46%) ppm TFE, were also outside the range of historical controls.

8.5.3 Evaluation

TFE causes toxic effects in various organs and is carcinogenic in both the rat and the mouse after lifetime exposure.

The survival rates of all groups of mice exposed to TFE were reduced compared to controls, although there were no significant reductions in the mean body weights of survivors at the end of the study. In the liver, multifocal coagulative necrosis was observed in all groups of exposed males, whilst haematopoietic cell proliferation was observed in all groups of exposed females. Angiectasis was also observed in all groups of exposed males and females. In addition, increase incidences of renal tubular dilatation and karyomegaly, principally in the inner cortex, were also observed. No NOAEL can be established in the mouse on the basis of the information currently available.

Exposure of mice to TFE caused increased incidences of haemangiosarcoma of the liver and histiocytic sarcoma (all organs) in all groups of exposed males and females at the end of the study. Increased incidences of haemangiosarcoma were also apparent in groups of both males and females exposed to the highest concentrations of TFE for 15 months. Increased incidences of hepatocellular tumours were also observed in all treated groups of males and females.

In the rat, there was increased mortality following exposure to 625 ppm TFE (2,555 mg/m^3) and in all groups of females (up to 1,250 ppm; 5, -110 mg/m^3) when exposed for their lifetime. The primary target organs for toxicity in the rat were the liver and the kidney. Increased absolute and relative kidney weights and excesses of renal tubular adenoma, or adenoma and carcinoma combined, were reported. In addition, increases in absolute and relative liver weight were observed in both sexes, along with increased incidences of clear cell and mixed cell foci and hepatic angiectasis in all exposed groups. TFE caused an increase in the incidence of hepatocellular adenoma and/or carcinoma combined in both males and females, along with an increased incidence of haemangiosarcoma in the liver in females exposed to a high concentration of TFE.

No NOAEL for the liver effects could be determined in the male or female rat or for renal effects in male rats following life-time exposure to TFE, although 156 ppm (638 mg/m^3) was a NOAEL for effects in the kidney in both sexes and for the carcinogenic effects in all organs in both sexes.

8.6 Reproductive and developmental toxicity

No specific toxicity studies are available for reproductive and developmental toxicity.

Rat and mouse

In the 13-wk repeated-dose toxicity studies in F344 rats and B6C3F$_1$ mice exposed to TFE for 13 weeks (for details see Section 8.3), there were no treatment-related differences in epididymal spermatozoa or vaginal cytology parameters between control and exposed groups of rats or mice (NTP, 1997)

Hamster

Groups of 10 male Lak:LVG (Syrian) hamsters were exposed (6 h/d, 5 d/wk) for 14 days to TFE at concentrations of 0, 101, 500, 991 or 2,489 ppm TFE (0, 413, 2,040, 4,050, 10,180 mg/m^3) (Nash *et al*, 1981). Half of the animals from each group were killed immediately after the tenth exposure; the others were maintained for a 14-d recovery period. No clinical signs of toxicity were seen. There were no significant changes in organ weights. There was evidence of testicular atrophy in hamsters exposed to 2,489 ppm TFE (10,180 mg/m^3) after the 14-d recovery period, but not in those sacrificed after the tenth exposure.

Groups of 15 male and 15 female Lak:LVG (Syrian) hamster were exposed (6 h/d, 5 d/wk) to 0, 203, 605 or 1,989 ppm TFE (0, 830, 2,473 or 8,130) for 13 weeks (Schneider *et al*, 1982). No TFE-related effects were observed in the females. Male hamsters exposed to either 605 or 1,989 ppm TFE exhibited a variable incidence of testicular immaturity. In addition, a TFE-induced focal hypocellularity of the germinal epithelium of seminiferous tubules was observed in those exposed to 1,989 ppm TFE. The atrophic testicular changes were noted in hamsters that had either mature or immature testes. Because of the nature of the lesion and the confounding effect presented by delayed testicular maturation, it could not be determined with certainty whether or not a TFE-related effect had occurred in hamsters exposed to 605 ppm TFE. As no such effects were seen in hamsters exposed to 203 ppm TFE, this dose was a clear NOAEL for the effect on the testes.

8.6.1 Evaluation

No specific reproductive toxicity studies are available on TFE.

No TFE-related effects on sexual organs were seen in rats and mice following repeated exposure for 13 weeks (Section 8.3).

In hamsters, there was some evidence of testicular atrophy (focal hypocellularity of the germinal epithelium of the seminiferous tubules) following repeated exposure to TFE for 14 days or 13 weeks. In the 13-wk study there was a confounding testicular immaturity in the hamsters, which made it difficult to determine whether the effect was exposure related. The NOAEL was determined to be 203 ppm TFE (830 mg/m^3). Furthermore, it is not clear whether the degree of toxicity seen, if any, would result in any impairment of reproductive performance.

9. MECHANISTIC STUDIES

S-(1,1,2,2-tetrafluoroethyl)-L-cysteine is one of the best known substrates for the hepatic C-S lyase kynureninase, and the renal enzyme, glutamine transaminase K. Numerous studies have used S-(1,1,2,2-tetrafluoroethyl)-L-cysteine as a standard substrate for these enzymes, as a marker for renal transport systems, and as a model nephrotoxicant. These studies have been conducted *in vivo* in rodents (Green and Odum, 1985; Commandeur *et al*, 1988, 1991; Lock and Ishmael, 1998; Green, 2000) and in rodent and human tissues and cells *in vitro* (Commandeur *et al*, 1989; McCarthy *et al*, 1994; Boogaard *et al*, 1989; Hawksworth *et al*, 1996; Green, 2001).

9.1 Mechanisms of nephrotoxicity

Both TFE and S-(1,1,2,2-tetrafluoroethyl)-L-cysteine are nephrotoxic in rodents *in vivo* where they caused necrosis in the pars recta of the proximal tubule following single or repeated doses (Odum and Green, 1984; Commandeur *et al*, 1988; NTP, 1997; Lock and Ishmael, 1998). *In vitro*, S-(1,1,2,2-tetrafluoroethyl)-L-cysteine has been shown to be toxic to isolated rat proximal tubular cells (Boogaard *et al*, 1989). The primary target within the proximal tubular cells appears to be the mitochondria where the reactive intermediates formed from S-(1,1,2,2-tetrafluoroethyl)-L-cysteine by C-S lyase are known to modify covalently a number of proteins including the a-ketoglutarate dehydrogenase complex, a key regulatory component of oxidative metabolism. A number of stable difluorothionoacetyl adducts, particularly at protein lysine residues, have been characterised, both immunohistochemically and by F 19 NMR, and have been associated with toxicity and cell death (Hayden *et al*, 1991; Chen *et al*, 1992; Hargus and Anders, 1991; Harris *et al*, 1992; Bruschi *et al*, 1993, 1998; Fisher *et al*, 1993).

S-(1,1,2,2-tetrafluoroethyl)-L-cysteine has been shown to cause renal injury but not bone marrow toxicity in calves (Lock *et al*, 1996). This is in contrast to S-(1,2-dichlorovinyl)-L-cysteine, a C-S lyase substrate, which caused both renal toxicity and aplastic anaemia in cattle (McKinney *et al*, 1957).

9.2 Mechanisms of carcinogenicity

Exposure of rats and mice to TFE by inhalation, 6 h/d, 5 d/wk for 103 or 95 weeks, respectively, resulted in increased incidences of kidney tumours in rats and increases in liver tumours in both mice and rats (Section 8.5). Mononuclear cell leukaemia was also increased in female rats and the incidence of histiocytic sarcoma was increased in mice of both sexes.

A number of studies have sought explanations for the development of the kidney tumours seen in rats and liver tumours seen in both species (Green, 2000; Keller *et al*, 2000). With respect to TFE induced liver cancer, particularly haemangiosarcoma, the mouse was far more sensitive than the rat and, consequently, mechanistic studies to-date have concentrated on the mouse. The mechanism(s) associated with increased incidences of histiocytic sarcomas in mice have not been investigated to date.

The metabolic activation of TFE has been compared in liver and kidney fractions from rats, mice and humans in order to help to assess the risks to humans exposed to TFE (Green, 2001).

9.2.1 Rat kidney tumours

Both TFE and S-(1,1,2,2-tetrafluoroethyl)-L-cysteine have been shown to be cytotoxic to the rat kidney and to increase renal cell division (Odum and Green, 1994; NTP, 1997; Keller *et al*, 2000). Since neither of these two chemicals are mutagenic (Longstaff and Ashby, 1976; Green and Odum, 1985; Rickard *et al*, 1986a), it is reasonable to assume that the kidney tumours develop as a result of chronic toxicity and reparative cell division. The activation of TFE to cytotoxic metabolites has been described previously (Section 7.1). The mouse is markedly less sensitive to TFE induced nephrotoxicity, which is consistent with the lack of kidney tumours in this species (Green, 2000). Furthermore, the mouse is known to be less susceptible than the rat to the development of renal cancer as a result of chronic damage (Dietrich and Swenberg, 1991).

9.2.2 Mouse liver tumours

An explanation for the development of the endothelial tumours in mouse liver or the hepatocellular tumours in rats and mice is not currently available. Neither TFE nor S-(1,1,2,2-tetrafluoroethyl)-L-cysteine were hepatotoxic in any cell type in the livers of mice and rats following exposure or dosing for up to 12 days (Lock and Ishmael, 1998; Green, 2000; Keller *et al*, 2000). Transient increases in cell division were seen at 5 days in hepatocytes, but not in endothelial cells, in both rats and mice dosed with S-(1,1,2,2-tetrafluoroethyl)-L-cysteine. The increases were not sustained, and in mouse liver, cell replication was significantly decreased after 12 days of dosing (Keller *et al*, 2000).

However, there is evidence in mouse liver for extensive metabolism of S-(1,1,2,2-tetrafluoroethyl)-L-cysteine by C-S lyases to the same reactive intermediates believed to be responsible for the kidney toxicity and cancer seen in the rat. Although the profile of urinary TFE metabolites appears similar in rats and mice *in vivo*, it was found that while C-S lyase metabolism occurred mainly in the rat kidney, in the mouse, the same processes occurred mainly in the liver (Green, 2000). These observations provide a plausible explanation for the different tumour sites in the two species although, at the present time, evidence for a biological response similar to that seen in the rat kidney is lacking in the mouse liver.

An investigation of *ras* mutation frequencies in liver neoplasms from mice exposed to TFE for 95 weeks concluded that TFE induced hepatocellular neoplasms develop by pathways independent of ras mutations (Hong *et al*, 1998).

9.3 Extrapolation to humans

The kidney toxicity seen in rats exposed to TFE has been shown to be caused by metabolites formed from the C-S lyase pathway. Similarly, the incidences of liver and kidney tumours seen in laboratory animals also correlate well with the extent of metabolism of TFE via this pathway. Species comparisons *in vitro* have shown that rates of glutathione conjugation of TFE in the liver are comparable in rats, mice and humans. The highest C-S lyase activities are found in mouse liver and rat kidney, the target organs in the NTP cancer bioassay. Human C-S lyase activities were significantly lower, the rate in human liver being 23-fold lower than that in mouse liver and that in human kidney, 6-fold lower than that in rat kidney. Further comparison of the relative activities of renal β-lyase, N-acetyl transferases, and acylases in rat and human kidney, suggests that the human kidney is at significantly less risk from the potentially adverse effects of TFE than the rat kidney (Green, 2001; Table 6 Section 7.2).

Comparison of the same metabolic rates in mouse and human liver also suggests that the risks to human liver will be significantly lower than those to mouse liver following exposure to TFE. However, the relevance to humans cannot be fully defined at this time in the absence of a mode of action for the development of the mouse liver tumours. In addition to the liver and kidney tumours seen in the rodent bioassay, a significant increase in histiocytic sarcomas was seen in the mouse. At the present time neither a metabolic basis, nor a mode of action, is available to explain this increase in tumours and consequently their relevance to humans is unknown.

The mononuclear cell leukaemias occur in high incidences in control F344 rats and are not considered to indicate a hazard to human health.

9.4 Evaluation

The data available suggest that the hepatic and renal carcinogenicity of TFE in rodents is associated with its metabolism via the glutathione and C-S lyase pathways. In rats and mice the highest C-S lyase activities are found in the target organs, the rat kidney and mouse liver. Comparisons of the metabolism of TFE and its cysteine conjugates in rodent and human tissues *in vitro* has identified quantitative differences between rodents and humans which suggest that the risks to humans of developing these tumours following exposure to TFE are significantly less than those in either rats or mice. Although an excellent correlation exists between the metabolism of TFE and cancer in rodents, lack of knowledge about the mechanisms involved in the development of the mouse liver tumours and the mouse histiocytic sarcomas precludes a full evaluation of the hazard to humans from exposure to TFE.

10. EFFECTS ON HUMANS

There are no case reports. A multi-centre epidemiological study of workers potentially exposed to TFE during TFE manufacture and polymerisation has been commissioned (Bertazzi and Consonni, 2002).

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APPENDIX A: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

Code of Reliability (CoR)	Category of reliability
1	Reliable without restriction
1a	GLP guideline study (OECD, EC, EPA, FDA, etc.)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, etc.)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	Reliable with restrictions
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	Not reliable
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	Not assignable
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated (e.g. Russian)
4e	Documentation insufficient for assessment

APPENDIX B: CONVERSION FACTORS FOR VAPOUR CONCENTRATIONS IN AIR

Conversion factors for vapour concentrations in air can be calculated from the molar volume of an ideal gas at 0°C: 22.4136 litre.

$$1\ mg/m^3 = 22.41/Mw \times 1{,}013.25/P \times (273+T)/273\ ppm \quad \text{(Eq. B.1)}$$

$$1\ ppm = Mw/22.41 \times P/1{,}013.25 \times (273+T)\ mg/m^3 \quad \text{(Eq. B.2)}$$

where Mw = molecular weight, T = temperature (°C) and P = pressure (hPa)

For European standard conditions, 20°C and 1,013.25 hPa (= 1 atm = 760 mm Hg), the formulas become

$$1\ mg/m^3 = 24.0556/Mw\ ppm \quad \text{(Eq. B.3)}$$

$$1\ ppm = Mw/24.0556\ mg/m^3 \quad \text{(Eq. B.4)}$$

In the USA and other countries 25°C is used, and the formulas are:

$$1\ mg/m^3 = 24.4661/Mw\ ppm \quad \text{(Eq. B.5)}$$

$$1\ ppm = Mw/24.4661\ mg/m^3 \quad \text{(Eq. B.6)}$$

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No. 8	HAZCHEM; A Mathematical Model for Use in Risk Assessment of Substances
No. 9	Styrene Criteria Document
No. 10	Hydrogen Peroxide OEL Criteria Document (CAS No. 7722-84-1)
No. 11	Ecotoxicology of some Inorganic Borates
No. 12	1,3-Butadiene OEL Criteria Document (Second Edition) (CAS No. 106-99-0)
No. 13	Occupational Exposure Limits for Hydrocarbon Solvents
No. 14	n-Butyl Methacrylate and Isobutyl Methacrylate OEL Criteria Document
No. 15	Examination of a Proposed Skin Notation Strategy
No. 16	GREAT-ER User Manual
No. 17	Risk Assessment Report for Existing Substances Methyl tertiary-Butyl Ether

Documents

No.	Title
No. 32	Environmental Oestrogens: Male Reproduction and Reproductive Development
No. 33	Environmental Oestrogens: A Compendium of Test Methods
No. 34	The Challenge Posed by Endocrine-disrupting Chemicals
No. 35	Exposure Assessment in the Context of the EU Technical Guidance Documents on Risk Assessment of Substances
No. 36	Comments on OECD Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals
No. 37	EC Classification of Eye Irritancy
No. 38	Wildlife and Endocrine Disrupters: Requirements for Hazard Identification
No. 39	Screening and Testing Methods for Ecotoxicological Effects of Potential Endocrine Disrupters: Response to the EDSTAC Recommendations and a Proposed Alternative Approach
No. 40	Comments on Recommendation from Scientific Committee on Occupational Exposure Limits for 1,3-Butadiene
No. 41	Persistent Organic Pollutants (POPs) Response to UNEP/INC/CEG-I Annex 1
No. 42	Genomics, Transcript Profiling, Proteomics and Metabonomics (GTPM). An Introduction
No. 43	Contact Sensitisation: Classification According to Potency, A Commentary