TETRAFLUOROETHYLENE

Data were last reviewed in IARC (1979) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 116-14-3
Chem. Abstr. Name: Tetrafluoroethene
IUPAC Systematic Name: Tetrafluoroethylene
Synonyms: Perfluoroethene; perfluoroethylene; 1,1,2,2-tetrafluoroethylene

1.1.2 *Structural and molecular formulae and relative molecular mass*

C_2F_4 Relative molecular mass: 100.02

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless gas (Lewis, 1993)
(*b*) *Boiling-point*: –75.9°C (Lide, 1997)
(*c*) *Melting-point*: –142.5°C (Lide, 1997)
(*d*) *Solubility*: Insoluble in water (Lide, 1997)
(*e*) *Reactivity*: May polymerize in the absence of an inhibitor, especially when heated or in the presence of oxygen (United States National Library of Medicine, 1998)
(*f*) *Explosive limits*: Upper, 60%; lower, 11% by volume in air (United States National Library of Medicine, 1998)
(*g*) *Conversion factor*: $mg/m^3 = 4.1 \times ppm$

1.2 Production and use

Worldwide production of tetrafluoroethylene in 1977 was estimated to have been 15–20 thousand tonnes. No information on current production quantities was available to the Working Group. Information available in 1995 indicated that it was produced in Germany and the United States (Chemical Information Services, 1995).

Tetrafluoroethylene has been used primarily as a monomer for polytetrafluoroethylene and other fluorinated resins, and as a chemical intermediate for hexafluoropropylene synthesis (United States National Library of Medicine, 1998).

1.3 Occurrence

No data were available to the Working Group.

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not proposed any occupational exposure limit for tetrafluoroethylene in workplace air. Russia has a short-term exposure limit of 30 mg/m^3 for exposure in workplace air (International Labour Office, 1991).

No international guideline for tetrafluoroethylene in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 58 male and 58 female B6C3F$_1$ mice, seven weeks of age, were administered tetrafluoroethylene (purity, > 98%) by whole-body inhalation at concentrations of 0, 312, 625 or 1250 ppm [0, 1280, 2560 or 5125 mg/m^3] for 6 h per day on five days per week for 95–96 weeks. Ten male and 10 female mice from each exposure group were evaluated at 15 months. Survival in all of the dose groups of mice was significantly reduced, so that, at 90 weeks, the survivors in the control, low-, mid- and high-dose groups, respectively, were: males—41/48, 17/48, 9/48, 7/48; females—38/48, 20/48, 18/48, 10/48. All mice, except one in each of the middle and high-dose groups of females, were necropsied and tissues were examined histologically. At the 15-month evaluation, haemangiosarcomas in the liver were found in three males of the high-dose group and one female of the low-dose group. At termination, the incidences of haemangiosarcomas in the liver in the control, low-, mid- and high-dose groups, respectively, were: males—0/48, 21/48, 27/48, 37/48 ($p \leq 0.01$ for all dose groups, Fisher's exact test); and females—0/48, 27/48, 27/47, 34/47 ($p \leq 0.01$ for all dose groups). The incidences of hepatocellular adenomas were: males—17/48, 17/48, 12/48, 20/48; and females—15/48, 17/48, 20/47 ($p \leq 0.05$), 15/47. The incidences of hepatocellular carcinomas were, for males, 11/48, 20/48, 33/48, 26/48 ($p \leq 0.01$ for all dose

groups) and, for females, 4/48, 28/48, 22/47, 20/47 ($p \leq 0.01$ for all dose groups). The incidences of histiocytic sarcomas (all organs combined) also were increased as follows: males—0/48, 12/48, 7/48, 7/48 ($p < 0.001$ for all dose groups, life table test); and females—1/48, 21/48, 19/47, 18/47 ($p < 0.001$ for all dose groups, life table test) (United States National Toxicology Program, 1997).

3.1.2 *Rat*

Groups of 60 male Fischer 344 rats, seven weeks of age, were administered tetrafluoroethylene (purity, > 98%) by whole-body inhalation at concentrations of 0, 156, 312 or 625 ppm [0, 640, 1280 or 2560 mg/m^3] and groups of 60 female Fischer 344 rats were administered concentrations of 0, 312, 625 or 1250 ppm [0, 1280, 2560 or 5125 mg/m^3] for 6 h per day on five days per week for 104 weeks. Ten male and 10 female rats from each exposure group were evaluated at 15 months. Survival in the high-dose male rats was significantly reduced, so that, at two years, the survivors in the control, low-, mid- and high-dose groups, respectively, were: males—17/50, 12/50, 17/50 and 1/50; females—28/50, 16/50, 15/50 and 18/50. Mean body weights in high-dose males were reduced from week 81 until the end of the study, while there was a marginal reduction in body weight in females of the high-dose group at the end of the study. All rats were necropsied and tissues examined histologically. The incidences of renal tubule neoplasms in the control, low-, mid- and high-dose groups, respectively, were: males—adenomas, 2/50, 4/50, 9/50 ($p \leq 0.05$, Fisher's exact test), 13/50 ($p \leq 0.01$); carcinomas, 1/50, 1/50, 2/50, 0/50; and, females—adenomas, 0/50, 3/50, 3/50, 8/50 ($p \leq 0.01$); carcinomas, 0/50, 0/50, 0/50, 3/50. Liver neoplasms were also increased in both males and females. The incidences were: males—hepatocellular carcinomas only, 1/50, 1/50, 10/50 ($p \leq 0.01$), 3/50; hepatocellular adenomas and carcinomas combined, 4/50, 7/50, 15/50, 8/50; and females—hepatocellular carcinomas only, 0/50, 4/50 ($p \leq 0.05$), 9/50 ($p \leq 0.01$), 2/50; hepatocellular adenomas and carcinomas combined, 0/50, 7/50, 12/50, 8/50 (United States National Toxicology Program, 1997).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

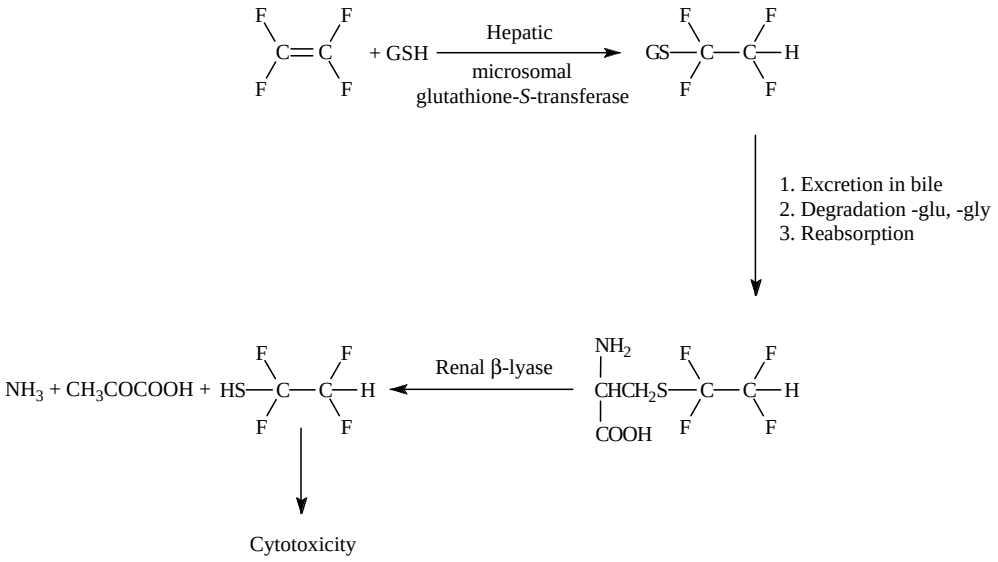
No data were available to the Working Group.

4.1.2 *Experimental systems*

Male rats exposed to 14 000 mg/m^3 tetrafluoroethylene in air for 30 min excreted small amounts of fluoride ion in the urine over a 14-day period, indicating that metabolism can occur (IARC, 1979).

The metabolism of tetrafluoroethylene has been studied in rat liver fractions; both microsomal and cytosolic glutathione *S*-transferases catalyse the formation of *S*-(1,1,2,2-tetrafluoroethyl)glutathione. The rate with microsomes was four times greater than with cytosol. Fluoride ion release was equivalent to approximately 20% of the glutathione used. The quantities of glutathione used and of fluoride ion released in incubations were identical whether cytochrome P450 was active or had been inactivated with carbon monoxide. Thus, cytochrome P450 oxidation, a pathway common to many haloalkenes, does not appear to be involved in the metabolism of tetrafluoroethylene. Evidence for the glutathione conjugation pathway *in vivo* comes from the identification of the cysteinyl-glycine and cysteine conjugates of tetrafluoroethylene in rat bile, following oral administration of L-[^{35}S]cysteine and then inhalation exposure to 6000 ppm [24 600 mg/m^3] tetrafluoroethylene for 6 h. *S*-(1,1,2,2-Tetrafluoroethyl)-L-cysteine is metabolized *in vitro* in rat renal cortex slices to give pyruvate and ammonia, a reaction that is catalysed by β-lyase and which also generates a reactive thiol (Figure 1) that is probably important in renal cytotoxicity (Odum & Green, 1984; Green & Odum, 1985).

Figure 1. Proposed mechanism for the metabolic activation of tetrafluoroethylene



From Odum and Green (1984)

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

No gross lesions were noted in any of the organs of male rats exposed to 14 000 mg/m^3 tetrafluoroethylene in air for 30 min (IARC, 1979).

In male Alderley Park rats exposed to a tetrafluoroethylene atmosphere of 6000 ppm [24 600 mg/m^3] for 6 h, there was marked renal necrosis involving the pars recta of the proximal tubules (Odum & Green, 1984). In addition, a review of largely unpublished data on the toxicity of tetrafluoroethylene (Kennedy, 1990) indicates that, in rats exposed to 2500 ppm [10 250 mg/m^3] for 6 h per day on five days per week for two weeks, or to 2000 ppm [8200 mg/m^3] for 6 h per day on five days per week for 18 weeks, there was decreased body weight gain and renal proximal tubule damage, which was more severe after the longer-duration exposure. Renal toxicity was also observed in Fischer 344/N rats in the 16-day and 13-week studies preliminary to the carcinogenicity test described above (Section 3.1.2) at 625 ppm [2560 mg/m^3] and higher concentrations; the damage was located predominantly at the corticomedullary junction. In the 13-week study, liver weights were increased in both male and female rats exposed to 5000 ppm [20 500 mg/m^3]. In the two-year carcinogenicity study, increases in renal degeneration were observed in male rats at 156 ppm [640 mg/m^3] and in female rats at 625 ppm and increases in renal hyperplasia were observed in both male and female rats at 625 ppm (United States National Toxicology Program, 1997).

According to the review by Kennedy (1990), Syrian hamsters exposed to 2500 ppm [10 250 mg/m^3] for 6 h per day on five days per week for two weeks or to 2000 ppm [8200 mg/m^3] for 6 h per day on five days per week for 18 weeks showed no sign of renal toxicity, but there was testicular atrophy. No sign of toxicity was observed in dogs exposed to 1000 ppm [4100 mg/m^3] for 6 h per day on five days per week for six weeks (reviewed by Kennedy, 1990).

In the 16-day toxicity study with B6C3F$_1$ mice preliminary to the carcinogenicity study described above (Section 3.1.1), there were increases in liver weight of female mice exposed to 2500 ppm [10 250 mg/m^3] or more and in kidney weight of females exposed to 5000 ppm [20 500 mg/m^3]. Renal tubule karyomegaly was observed, mainly in the inner cortex, of males and females exposed to 1250 ppm [5125 mg/m^3] or more. Karyomegaly was observed in the same region in the subsequent 13-week study at the same concentrations. In the two-year carcinogenicity test, renal tubule karyomegaly was increased at 625 ppm in male mice and at 1250 ppm in female mice. In the same study, liver angiectasis was increased at or above 312 ppm in both male and female mice, while there was increased liver and spleen haematopoietic cell proliferation in female mice at these dose levels (United States National Toxicology Program, 1997).

Identical clinical evidence of nephrotoxicity comes from inhalation of tetrafluoroethylene at atmospheric concentrations greater than 2000 ppm [8200 m/gm^3] and from oral administration of tetrafluoroethylcysteine to male rats, suggesting that the latter is an important metabolite in the cytotoxic response. The cytotoxicity of the cysteine conjugate has also been demonstrated *in vitro* in rat kidney slices by reduced uptake of both

organic anion, *para*-aminohippuric acid and the cation, tetraethylammonium bromide (Odum & Green, 1984; Green & Odum, 1985).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

No increases were observed in the frequency of micronucleated erythrocytes from the peripheral blood of mice exposed by inhalation for 13 weeks. This appears to be the only study with tetrafluoroethylene itself. However, *S*-(1,1,2,2-tetrafluoroethyl)-L-cysteine was not mutagenic to *Salmonella typhimurium* in either the presence or absence of an exogenous metabolic system based upon rat kidney S9.

Modifications to oncogenes and tumour-suppressor genes

The mutational spectrum of H-*ras* codon 61 was examined in hepatocellular neoplasms of male and female B6C3F_1 mice exposed to tetrafluoroethylene in the carcinogenicity study described in Section 3. A low frequency (9/59, 15%) of H-*ras* mutations was detected among the tumours from the treated groups, compared with a high frequency in the concurrent controls (10/17, 59%) and in historical controls (183/333, 56%). The proportion of H-*ras* mutations in the tumours from the treated groups was 1:1:1 for codon 61 AAA, CGA and CTA mutations, respectively, compared with 3:6:1 for the concurrent control tumours and 5:2:1 in the historical control tumours. There were no important differences in the mutation frequencies and spectra between hepatocellular adenomas and carcinomas. No K-*ras* mutations were found. The decreased frequency of H-*ras* mutations in hepatic tumours of the exposed group in this study was similar to that found in B6C3F_1 mice exposed to tetrachloroethylene (24%) (Anna *et al*., 1994). The data suggest that the tumours arise by a *ras*-independent pathway (United States National Toxicology Program, 1997).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Tetrafluoroethylene is used in the manufacture of polytetrafluoroethylene and other polymers. No information on potential human exposure is available.

5.2 Human carcinogenicity data

No data were available to the Working Group.

Table 1a. Genetic and related effects of tetrafluoroethylene

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVM, Micronucleus test, $B6C3F_1$ mouse peripheral erythrocytes *in vivo*	–		5000 ppm, 6 h/d, 5 d/wk, 13 wk	US National Toxicology Program (1997)

Table 1b. Genetic and related effects of *S*-(1,1,2,2-tetrafluoroethyl)-L-cysteine

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250	Green & Odum (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250	Green & Odum (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	250	Green & Odum (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250	Green & Odum (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250	Green & Odum (1985)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	250	Green & Odum (1985)

[a] –, negative
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day

5.3 Animal carcinogenicity data

Tetrafluoroethylene was tested for carcinogenicity in one study in mice and one study in rats by inhalation. In both sexes of mice, it increased the incidence of hepatocellular carcinomas, histiocytic sarcomas and haemangiosarcomas in the liver. In rats of both sexes, it increased the incidence of hepatocellular carcinomas and kidney tubule cell adenomas.

5.4 Other relevant data

Tetrafluoroethylene is metabolized by hepatic glutathione *S*-transferase and the resulting cysteine conjugate is further metabolized by renal β-lyase. This pathway results in the formation of a reactive thiol that causes kidney toxicity in rats.

Tetrafluoroethylene did not induce micronuclei in mouse erythrocytes and the metabolite tetrafluoroethylcysteine was not mutagenic in *Salmonella typhimurium*.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of tetrafluoroethylene were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tetrafluoroethylene.

Overall evaluation

Tetrafluoroethylene is *possibly carcinogenic to humans (Group 2B)*.

6. References

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