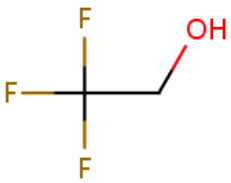
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

2,2,2-Trifluoroethanol (2016)

I. IDENTIFICATION[1]

Chemical Name: Ethanel, 2,2,2-Trifluoro
Synonyms: 2,2,2-Trifluoroethanol; 2,2,2-Trifluoroethyl; Alcohol; TFE
CAS Number: 75-89-8
DOT Number: UN 1993
Molecular Formula: $C_2H_3F_3O$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[2]

Physical State and Appearance: Colorless liquid
Odor Description: Ethanol-like odor
Odor Threshold: No data available
Molecular Weight: 100.04
Conversion Factors: 1 ppm (v/v) = 4.1 mg/m^3 (v/v); 1mg/m^3 – 0.244 ppm (v/v)
Boiling Point: 71°C-78°C (160°F-172°F)
Vapor Pressure: 52 mmHg at 25°C; method: SCC
Specific Gravity: 1,4 g/mL
Flash Point: 28°C (82°F), flammable liquid
Flammability Limits: Lower explosive limit: 5.5%; Upper explosive limit 42%
Solubility in Water: Complete
Incompatibilities: Incompatible with strong oxidizing agents
Stability: Material is stable.

III. USES

TFE is an alcohol used as an intermediate in the production of other fluorinated industrial chemicals and fluorinated pharmaceutical agents like Fluoroxene® Isoflurane®, and Desflurane®, which are inhalation anesthetics, and other drugs like Flurethyl® and Halazepan®. It is also used as a working fluid in Rank-ine-cycle engines for recovering energy from waste heat sources because of its physical and thermodynamic properties.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Lethality Data

On an acute oral basis, TFE is moderately toxic in rodents.

Species	Route	LD_{50} or LC_{50}
Rat	Oral	210 mg/kg[3]
Rat	Oral	236 mg/kg[4]
Rat	Inhalation (2-hr)	4850 ppm[9]
Rat	Inhalation (6-hr)	550 ppm[4]
Rat	Inhalation (6-hr)	470-640 ppm[8]
Rat	Intraperitoneal	210 mg/kg[10]
Mouse	Oral	366 mg/kg[5]
Mouse	Intraperitoneal	210 mg/kg[10]
Hamster	Intraperitoneal	350 mg/kg[5]

2. Eye Irritation

Undiluted TFE and aqueous solutions (≥ 50%) of TFE were severe eye irritants when instilled into the eyes of rabbits. Water irrigation shortly after dosing was not effective in reducing the degree of injury. Severity of lesions (corneal opacity, severe chemosis and mild conjunctival irritation) was not completely reversible even after 3 weeks.[6]

3. Skin Absorption

TFE does not appear to be a skin irritant in rabbits when applied to either intact or abraded skin (0.5 mL undiluted).[3,6] However, TFE can be absorbed through the skin as shown by a rabbit LD_{50} of 1670 mg/kg.[7] In one other limited study.[8] rabbits treated dermally with TFE showed mortality at 1382 mg/kg (2

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of 4) and 4360 mg/kg (3 of 4) but not at 436 mg/kg (0 of 4) or below.

4. Inhalation Toxicity

TFE is moderately toxic to rats by the inhalation route. Clinical signs of toxicity in rats inhaling TFE include protection, humped position, bloody nasal discharge, ataxia, depression, decreased activity, eye irritation and mild tremors, [8]

In the only acute rat inhalation study involving histopathology[9], 2-hr exposures to TFE at 400 to 5000 ppm produced damage to spermatocytes, spermatogonia and Sertoli cells. These testicular effects persisted for at least 86 hr post-exposure.

5. Other Toxicity

TFE is moderately toxic to a variety of species by the intraperitoneal (i.p.) route.

By the i.p. route, testicular damage has also been reported in several species. Dogs given 100 mg/kg for 2 days or 50 mg/kg for 4 days, and hamsters given 5, 25, or 100 mg/kg for 4 days, showed epithelial degeneration in testicular tissue, spermatogonia, spermatocytes, and spermatids were affected.[11] When rats were given i.p. doses of 50 mg/kg, testicular damage was also seen.[9]

B. Subacute/Subchronic Toxicity

In one inhalation toxicity study[12], rats were exposed to TFE vapor for 6 hr/day 5 day/week for 4 weeks at exposure levels of 10, 50, or 150 ppm (v/v). Exposure to the 2 higher doses resulted in decreased testicular weight and hypospermatogenesis. Regeneration and normal spermatogenesis were seen in many of the rats exposed to 150 ppm after a 57-day recovery period, Extensive histopathology evaluation of other organ systems showed no differences from the control. No adverse effects occurred at the 10 ppm exposure level.

In another inhalation study[13], 4 beagle dogs/exposure level were exposed to 0, 100 mg/m^3 (-24 ppm v/v), or 400 mg/m^3 (-98 ppm v/v) TFE for 6 hr/day 5 days a week for 8 weeks. At the high exposure level, body weight loss was significant and a stress lymphopenia was also seen. Testicular atrophy was observed in TFE-exposed dogs as evidenced by a decrease in testicle cross-sectional area of 15% at 100 mg/m^3 and 35% at 400 mg/m^3 over the duration of the 8 weeks of exposure. At exposure termination, sperm counts had decreased 30% at 100 mg/m^3, and dogs at the 400 mg/m^3 were azospermic. Two dogs/group sacrificed after 8 weeks of exposure showed dose-related testicular lesions. Severe testicular degeneration, characterized by loss of spermatocytes, many spermatogosia and spermatid giant cells were observed in dogs exposed at the high level. At the lower exposure level, decreased numbers of spermatozoa were seen, and a low frequency of giant cells was noted, Testicular dysfunction was still measurable 4 weeks post-exposure.

C. Chronic Toxicity/Carcinogenicity

No definitive studies are available.

D. Reproductive/Developmental Toxicity

No developmental toxicity studies have been conducted on TFE.

Relative to effects on male reproductive performance, groups of male rats were exposed 6 hr/day for 4 weeks to 10, 50, or 150 ppm (v/v) of trifluoroethanol. Serial mating was used to assess fertility. Testes weight was reduced in a dose-related manner at exposure levels of 50 ppm or more. Functional impairment of reproductive capability and pathological testicular changes were found in all rats exposed to 50 ppm or more as measured by decreases in conception rate, number of corpora lutea, implantation sites and number of live fetuses, as well as increases in pre-implantation losses and post-implantation losses. The latter effects were attributed mainly to hypospermatogenesis. No other signs of toxicity were observed. In rats exposed to 50 ppm, normal spermatogenesis was seen after a 57-day recovery period. In the group of rats exposed to 10 ppm, no differences from the control group were observed.[12] Similar effects on male reproductive performance were seen in male rats administered TFE by i.p. injection.[9]

There were no studies found to assess the effects of TFE on female reproductive performance.

E. Genotoxicity/Mutagenicity

1. In vitro

TFE was not mutagenic as a liquid suspension to four *Salmonella typhimurium* strains or to *Escherichia coli*, with or without a metabolic activation system prepared from mouse, hamster and human tissues.[14] Other Ames Test results[6,15] have also been negative.

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2. In vivo

No dose-dependent change was observed in the frequency of sister chromatid exchanges in bone marrow cells from Chinese hamsters one day after completion of an i.p. dosing regimen of TFE at 5, 25, or 100 mg/kg/day for 4 days.(11)

F. Metabolism/Pharmacokinetics

TFE metabolism involves glucuronidation and urinary excretion as well as oxidation to trifluoroacetaldehyde (TFALD) and then to trifluoroacetic acid (TFAA). In the male Wistar rat, for example, 84% of administered TFE was oxidized, 50% excreted as TFALD and 34% as TFAA, and 5% was glucuroni dated and excreted in urine.(16)

The half- life of TFE in rat blood after intravenous injection was 7.3 hr.(17)

Eighty percent of C^{14} -labeled TFE injected into human subjects was recovered as TFALD in the urine.(18)

TFALD is believed to be the metabolite responsible for the testicular toxicity of TFE. TFALD, like TFE, has been shown to damage the tastes in oral rat studies.(19)

V. HUMAN USE AND EXPERIENCE

There are no epidemiology studies on workers exposed to TFE. Toxic effects of TFE were not seen in production workers at Halocarbon Products Corporation, the largest TFE producer.(20) However, in a pilot plant involved m polymer production, a "cluster" of 5 men were reported to have slightly-to-significantly smaller testes (no measurement criteria were reported). Over a 16-year period, they were potentially exposed to some unknown concentrations of TFE. Although workplace assessments did not conclusively show significant TFE exposures, the preceding finding in man is consistent with the toxicology of TFE.(21)

VI. RATIONALE

In a 4-week subacute inhalation toxicity study in rats, exposure levels of 50 ppm and above resulted in decreased testicular weight and hypospermatogenesis while 10 ppm produced no adverse effects. Based on the preceding 10 ppm NOEL in rats, and information suggesting that TFE exposure can induce similar testicular effects in humans, a WEEL of 0.3 ppm as an 8-hr time-weighted average (TWA) is recommended.

VII. RECOMMENDED WEEL

8-hour Time-Weighted Average: 0.3 ppm

This WEEL value was originally established in 1999. No significant new literature was identified since 1999 that supports a change to the recommended WEEL value.

VIII. REFERENCES

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