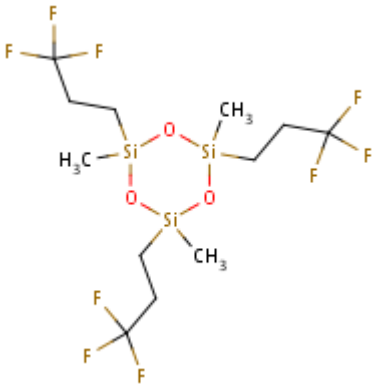
SIDS INITIAL ASSESSMENT PROFILE

CAS No(s).	2374-14-3
Chemical Name(s)	2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)cyclotrisiloxane (Fluorosilicone trimer)
Structural Formula(s)	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

Fluorosilicone trimer is a cyclotrisiloxane comprised of a six-membered siloxane ring having alternating silicon and oxygen atoms (three each). Each silicon atom is bonded to two pendant groups: one methyl group (A=CH_3) and one 3,3,3-trifluoropropyl group (B=$CH_2CH_2CF_3$). The fluorosilicone trimer can exist as two distinct configurational isomers, referred to as the cis- and trans- forms. In the cis- form, all identical pendant groups lie on the same side of the siloxane ring (i.e. AAA and BBB), whereas in the trans- form, one of the pendant groups is different on each side (AAB and BBA). Fluorosilicone trimer is a liquid containing suspended solids[1] with a measured melting point range of -1.9°C (cis- isomer) to 35°C (trans- isomer), a measured boiling point range of 239°C (cis- isomer) to 242°C (trans- isomer), and a vapour pressure of 0.88 hPa at 25 °C (extrapolated from measured data). The calculated octanol-water partition coefficient (log K_{ow}) is 9.84 at 25 °C and the calculated water solubility is 4.7E-07 mg/L at 25 °C (both values RL=4[2]).

Human Health

Although no toxicokinetic studies are available for Fluorosilicone trimer, the treatment-related adverse health effects observed with oral and dermal exposure imply some level of bioavailability with exposure by these routes.

The acute oral LD50 values of Fluorosilicone trimer are 4659 (50% in maize oil; according to OECD TG 401), 10,000 (undiluted), 3750 (50% in corn oil), and 252 (5% in corn oil) mg/kg bw in rats (no guideline specified); sluggishness, piloerection and coma, reduced body weight gain and/or body weight loss, and bloody nasal discharge were observed. Adverse effects were noted at necropsy in the stomach, intestines, liver and kidneys. The acute dermal LD50 was 25,400 mg/kg bw in rabbits; decreased activity, lacrimation, nasal discharge, transient erythema and reduced body weight gain were observed (similar to OECD TG 402). Adverse effects were noted at necropsy in the kidneys, liver, gastrointestinal tract, thymus and lungs. No acute inhalation studies are available.

[1] The solid is one of the two stereoisomers that comprise the sponsored substance, which can have a melting transition above room temperature. The lower and upper melting transitions depend on the isomer composition of the mixture.

[2] Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow and water solubility modules, found in the current version of EPI Suite (v4.11), give reasonable estimates for silanes and siloxanes.

The substance is not considered irritating to the skin or eye of rabbits (OECD TG 404 and 405), and is not considered a skin sensitizer in guinea pigs (OECD TG 406).

In a 21 day dermal repeated dose study, male and female rabbits (no guideline specified) were administered the test substance (99.7% purity) under occlusive cover for 6 hours per day, five days per week at doses of 0, 40, 200 and 400 mg/kg/day. Five rabbits in the 400 mg/kg bw dose group died. A single female died at 200 mg/kg bw, but this death was not considered treatment related (pneumonia). A reduced rate of weight gain, lower food consumption, and decreased serum alkaline phosphatase activity was observed at 200 and 400 mg/kg bw. Significant increases in serum glutamic-pyruvic transaminase and glutamic oxalacetic transaminase activities were observed in male animals at 200 and 400 mg/kg bw. In females, serum glutamic oxalacetic transaminase activity was increased in the 200 mg/kg bw group. Relative liver weights were decreased in all female treated groups; in males, the relative liver weights were decreased only in 200 mg/kg bw group. Gross and microscopic pathologic examination revealed no treatment-related effects. The NOAEL was considered to be 40 mg/kg bw/day for male and female rabbits when applied dermally, based on the correlation of decreased liver weights and changes in serum enzymes, suggesting effects on the liver at 200 and 400 mg/kg bw.

In a 90-day gavage study, male and female rats (EPA OPPTS 870.3100, similar to OECD TG 408) were administered the test substance (98.3 %; in sesame oil) by gavage at doses of 0.8, 4, 20 and 50 mg/kg bw/day for 90 days. There were an additional ten rats/sex included as recovery groups in the control and high dose groups; due to excessive mortality in the high dose group, the recovery period was not conducted. After severe toxicity was noted during the first week of dosing, the dose level was reduced from 50 to 35 mg/kg bw/day and the high dose group was relabelled as 50/35 mg/kg bw/day. Eighteen of twenty animals (eight male/ten female) died in the 50/35 mg/kg bw/day group, two 20 mg/kg bw/day group females died, and two control group males died. Clinical findings were consistent with indications of skeletal muscle toxicity, were observed predominantly in the 50/35 mg/kg bw/day group females. Clinical signs for the 20 mg/kg bw/day group females and 50/35 mg/kg bw/day group males and females also included prostration, lethargy, piloerection, biting of cage bottom, head bobbing and hyperactivity. Increased salivation and wet and/or dried red or yellow material on various body surfaces were noted in the 20 and 50/35 mg/kg bw/day groups. Test article-related decreases in mean body weights were noted in the 20 mg/kg bw/day group males and the 50/35 mg/kg bw/day group males and females. Slight decreases in food consumption were also noted in the 50/35 mg/kg bw/day group males and females. Test article-related increases in urea nitrogen, phosphorus and potassium and decreased cholesterol were noted at the 20 and 50/35 mg/kg bw/day dose levels. Increased mean liver weights correlated with periportal hepatocellular vacuolar changes and were noted in the 20 and 50/35 mg/kg bw/day groups. Decreased mean seminal vesicle and prostate weights group (20 and 50/35 mg/kg bw/day), were not considered adverse due to the lack of correlating histological findings in these tissues or in the testes and epididymides. Periportal vacuolar change was noted for males and females in all treated groups, but there was no indication of impaired liver function based on serum chemistry results and these changes were not considered adverse. In the skeletal muscle (rectus femoris), minimal to moderate degeneration was noted in the 20 and 50/35 mg/kg bw/day groups; this finding is consistent with the clinical findings of skeletal muscle toxicity. In the heart, treatment-related cardiomyopathy (subacute or chronic) was noted in the 4, 20 and 50/35 mg/kg bw/day group males and females; the findings were significant at 20 and 50/35 mg/kg bw/day. The NOAEL was 0.8 mg/kg bw based on effects on the heart, skeletal muscle and liver at 20 mg/kg bw/day and above.

In a 28-day gavage range-finding study groups of five male and female rats were administered the test substance (>98%, in sesame oil) by gavage for 28 days at doses of 0.2, 1.0, 5.0, 31.25, 62.5, 125 and 250 mg/kg bw/day. Two additional high concentration gavage dose groups, 125 and 250 mg/kg bw/day, were evaluated using five males per dose level and one to two females (respectively) per dose level. All animals dosed with either 125 or 250 mg/kg bw/day and three males dosed with 62.5 mg/kg bw/day died.One male died at 31.25 mg/kg bw/day (gavage error). Clinical signs of toxicity preceding death included the inability to use hind legs, tremors, loss of righting reflex, lethargy, decreased body temperature, tremors, fecal soiling or bleeding from the penis. Clinical signs in animals that survived to necropsy included an inability to use hind legs, tremors and lethargy. There was a reduction in mean male body weights at 31.25 mg/kg bw/day. After adjusting for the body weight, there were also significant decreases in mean ventral prostate and seminal vesicle weights at 31.25 mg/kg bw/day and a significant increase in liver weight at 62.5 mg/kg bw. Generally, increases in female liver weights were also observed up to 62.5 mg/kg bw/day. Severe diffuse inflammation and hyperplasia of the urinary bladder mucosa and renal pelvis and slight hyperplasia of the urinary bladder epithelium were noted in two animals in the 31.25

mg/kg bw/day group. The NOAEL for male and female rats was 5 mg/kg bw/day, based on urinary bladder hyperplasia seen at 31.25 mg/kg bw/day and above.

Fluorosilicone trimer was negative for gene mutations (*S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvr A) in vitro (similar to OECD TG 471), mammalian cell transformation (no guideline specified) in vitro, and chromosome aberration in vivo (OECD TG 474). The substance is not considered to be genotoxic.

No data are available for the carcinogenicity of Fluorosilicone trimer.

In an OECD Guideline 415 (One-Generation Reproduction Toxicity Study), groups of twenty-five rats/sex were administered the test substance (98.3%) in sesame oil by gavage at doses of 0, 0.8, 4, 20, and 50 mg/kg bw/day. The test substance was administered daily for a minimum of 70 days prior to mating. Treatment of the F(0) males continued throughout mating and continuing until one day prior to euthanasia. Treatment of the F(0) females continued throughout mating, gestation, and through lactation day 20. The high dose group was labeled as 50/35 mg/kg bw/day due to a reduction in dose level from 50 to 35 mg/kg bw/day after severe toxicity was noted during the first week of dosing. Clinical signs noted in dams were predominantly in the 50/35 mg/kg bw/day group included impaired use of the hindlimbs, reduced hindlimb resistance, a hunched appearance, and rocking, lurching, or swaying while walking. The most frequently observed clinical findings, noted in the 20 and 50/35 mg/kg bw/day groups and considered to be exposure-related, included red and yellow material on various body surfaces and exophthalmus. Mean absolute prostate gland and pituitary gland weights were reduced in the 20 and 50/35 mg/kg bw/day group males, and mean absolute seminal vesicle, epididymal and testicular weights were reduced in the 50/35 mg/kg bw/day group. The decrease in prostate and pituitary gland weights appear to be at least partly related to decreased body weight. The effect on organ weight was without microscopic correlates and male reproductive performance was unaffected by treatment. As such, the modest decrease in prostate and pituitary gland weight is not considered to represent an adverse effect. There were four and five unscheduled deaths within the period from G20 to PND 3 for the 20 and 50/35 mg/kg bw/day dose group females. Of these, one of the deaths in the 50/35 mg/kg bw/day dose group females was considered possibly related to dystocia. Several unscheduled deaths occurred in both groups both prior to (2 at 20 mg/kg bw/day; 4 at 50/35 mg/kg bw/day) and after (5 in the 20 mg/kg bw/day and 4 in the 50/35 mg/kg bw/daydose groups) the G20 – PND 3 period. Significant mortality was also present in the 20 and 50/35 mg/kg bw/day dose group males, 5 and 10 respectively. Treatment related mortality is considered to represent maternal systemic toxicity unrelated to parturition. Mean body weight gains and food consumption were reduced in the 50/35 mg/kg bw/day group (males and females) early in the pre-breeding period. Mean body weight gain in the 50/35 mg/kg bw/day group females was reduced late in gestation, and mean body weights and food consumption were reduced in these females throughout lactation. Mean body weights in the 20 mg/kg bw/day group males were reduced from week 5 through the remainder of the study, while food consumption in the females in this group was reduced throughout lactation. In the 50/35 mg/kg bw/day group F0 females, the mean number of implantation sites was reduced, and the mean calculated difference between the number of pups born and the number of implantation sites was increased. For dams that delivered and were evaluated at scheduled necropsy on lactation day 21, in the 50/35 mg/kg bw/day group, a statistically significant ($p<0.01$) reduction was observed in the mean number of implantation sites, and a statistically significant ($p<0.01$) increase was observed in the mean calculated difference between the number of pups born and the number of implantation sites counted at necropsy. Total litter losses between lactational days 0 and 4 occurred in three females in the 50/35 mg/kg bw/day group. Mean postnatal survival was reduced at 50/35 and 20 mg/kg bw/day from birth to PND 4 and from PND 4 to PND 21, but was statistically significant in only the 50/35 mg/kg bw/day group. Mean male and female pup body weights in the 20 and 50/35 mg/kg bw/day groups were generally reduced during the entire postnatal period. There was a dose-related decrease in mean postnatal survival from birth-PND4 and PND 4-21 in the 20 mg/kg bw/day and 50/35 mg/kg bw/day groups (statistically significant only in the 50/35 mg/kg/day group). There were no gross findings for the pups. Based on an increase in the mean number of days between pairing and coitus and an increase in mean gestation length, the NOAEL for reproductive toxicity was 20 mg/kg bw/day. Based on mortality and clinical signs of skeletal muscle pathology, the NOAEL for parental toxicity in rats was 4 mg/kg bw/day. Based on dose-related effects at 20 and 50/35 mg/kg bw/day during the postnatal period, the NOAEL for developmental toxicity of rats was 4 mg/kg bw/day.
In a rat uterotropic assay, using the ovariectomized rat model (no guideline specified), Fluorosilicone trimer did not produce estrogenic activity at doses up to 500 mg/kg bw.

2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)cyclotrisiloxane (Fluorosilicone trimer) possesses properties indicating a hazard for human health (repeated dose toxicity, reproductive toxicity). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow and water solubility modules, found in the current version of EPI Suite (v4.11), give reasonable estimates for silanes and siloxanes. For example, KOWWIN (v1.68 in EPI v4.11) has 32 chemicals containing Si in its combined training and validation sets. The water solubility programs WSKOWWIN and WATERNT have 0 and 19 combined training/validation chemicals with Si, respectively.

A modified OECD TG 111 (Hydrolysis as a Function of pH) study was conducted for Fluorosilicone trimer; to improve solubility, a much higher concentration of co-solvent was used (20 %v/v acetonitrile) than specified by the guideline (1 %v/v). Because of the effect that the co-solvent could have on the siloxane hydrolysis kinetics, the study was actually conducted as a comparative assessment using hexamethylcyclotrisiloxane (D3; CAS 541-05-9, available for review at http://www.oecd.org/env/hazard/data) as a reference substance. D3 was selected for its structural similarity to the Fluorosilicone trimer, and the fact that a OECD TG 111 hydrolysis study was conducted with D3. D3 half-lives were 2.5 to 60 times longer (depending on pH) in the presence of greater co-solvent concentration. This implies that the hydrolysis rates of the Fluorosilicone trimer are expected to be greater (i.e., shorter half-life) in fully aqueous solution. The $t_{1/2}$ (half-time) of Fluorosilicone trimer in 20% acetonitrile/80% aqueous buffer was >7.5 days, 6 days and 11 minutes at pH 5, 7 and 9 and at 25°C. The final hydrolysis product was identified as methylbis(3,3,3-trifluoropropyl)silanediol, although the kinetics of product formation were not determined.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 2.4 days. In an OECD TG 301 B (Ready Biodegradability: CO2 Evolution Test), Fluorosilicone trimer degraded -3.33% in 28 days; it was not "readily biodegradable".

Level III fugacity modelling, using loading rates of 1000 kg/h each for air, soil and water, shows the following percent distribution when it is released simultaneously to all three compartments: Air = 11.7%, Water = 22.1%, Soil = 23.7%, and Sediment = 42.5%. A Henry's law constant of 1.72E+07 Pa-m3/mole at 25 ºC; the fluorosilicone trimer is a large molecule having low diffusivity in water, so that it is slow to cross the air-water interface. The log KAW value of 3.84 at 25 ^{o}C. Test data for bioaccumulation is not available. For very hydrophobic substances uptake through the diet is likely to exceed uptake through water. Therefore, test data and modelling approaches based on aqueous exposure may not be adequate to characterize the bioaccumulation potential for the substance. The biotransformation rate in fish is estimated to be very slow (BCFBAF, v3.01) and therefore, the substance is predicted to accumulate if taken up by fish. However, the combination of very low water solubility and the ability to hydrolyze may significantly limit the presence of the dissolved substance in the aquatic environment. In conclusion, fluorosilicone trimer is estimated to have the potential to bioaccumulate in the aquatic environment but a quantitative measure cannot be provided based on currently available information.

Acute aquatic toxicity studies were not conducted due to the very low water solubility of the substance. However, a chronic Daphnia test performed at the limit of functional water solubility showed no acute effects. The following acute toxicity results were estimated for aquatic species:

Species	Estimated values (ECOSAR Program (v1.11) (mg/L)	Comments
Fish	96 hour LC_{50} = 3.52E-005	Neutral Organics SAR
Daphnid	48 hour LC_{50} = 4.13E-005	Neutral Organics SAR
Green Algae	96-hour EC50 = 0.000612	Neutral Organics SAR; Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation are reported.

The chronic (21 d) flow through toxicity limit test (OECD TG 211) was performed with *Daphnia magna*. The nominal concentration was 20 µg/L (which is far above water solubility of 0.00047 µg/L). A solvent (acetone) was used, and a solvent control was included in the study. The measured concentrations at days 0, 7, 14, and 21 were 0.51, 6.1, 0.79, and 3.1 µg/L with a geometric mean of 1.7 µg/L. The NOEC (mortality, adult length) >= 1.7ug/L; the NOEC (reproduction, offspring/female) <1.7 ug/L and the LOEC for mortality and body length > 1.7 mg/L.

2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)cyclotrisiloxane (Fluorosilicone trimer) possesses properties indicating a hazard for the environment at the limit of functional water solubility (chronic toxicity aquatic invertebrates <1 mg/L). Fluorosilicone trimer is not readily biodegradable. The fluorosilicone trimer has the potential to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

In the United States, production volume in 2005 was ca. 227-1134 tonnes; in Japan production volume in 2005 was < 227 tonnes, and in Europe production volume in 2014 was 102 – 1016 tonnes. Ranges are provided to protect confidential business information. Fluorosilicone trimer is used in formulations up to 100% as a chemical intermediate in polymer production.

Fluorosilicone trimer is handled in closed systems, and transported from the production site as the parent chemical, and then intended to be consumed during use. Less than 0.1 % of the total annual production volume is sold. Transfer is in closed pipe, drums, or tanks rather than in open systems to minimize loss of this material (through hydrolysis). There are no intentional releases to the environment from manufacturing processes. Engineering controls include general and local ventilation, water scrubber devices and related equipment, and closed sampling systems. In additional, employees are required to use personal protective equipment including impermeable chemical resistant gloves, goggles, fire resistant clothing, safety shoes, hard hats, and respirators. Potential routes of exposure include inhalation and dermal exposure. There are no consumer uses of the substance.