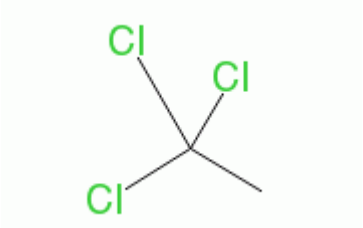
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	71-55-6
Chemical Name	1,1,1-Trichloroethane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

1,1,1-Trichloroethane is a clear/colourless liquid at room temperature with a melting point of -30.4°C, a boiling point of 74°C and a measured vapour pressure of 13,300 Pa at 20°C. The measured octanol-water partition coefficient (log K_{ow}) is 2.47, and the water solubility is 300 mg/L at 25°C.

Human Health

Experiments with animals and humans have demonstrated that the toxicokinetic behaviour of 1,1,1-trichloroethane has the same qualitative pattern in human, rats and mice, with some quantitative differences among the species. 1,1,1-Trichloroethane is rapidly absorbed by the lung, skin, and gastrointestinal tract, and distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues. The predominant pathway of elimination of 1,1,1-trichloroethane is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In both animals and humans, a small amount (< 10%) of 1,1,1-trichloroethane is metabolized to trichloroethanol and trichloroacetic acid; these metabolites are excreted in the urine, and other minor metabolites (carbon dioxide and acetylene) are excreted in expired air.

The 3-hr inhalation LC_{50} for rats was 18,000 ppm (98.3 mg/L) and the 7-hr LC_{50} was 14,250 ppm (77.8 mg/L). The principal toxic effects were depression of the central nervous system. Marked changes were seen at necropsy in the liver (hepatocellular damage, liver necrosis, enzyme activity changes, and accumulation of fat in the liver). Other acute inhalation studies show similar results. The dermal LD_{50} [OECD TG 402] was > 2000 mg/kg bw in rats. Examination of the animals revealed an increased incidence of swollen livers. In an OECD TG 401 study, the oral LD_{50} was > 2000 mg/kg bw in rats. Clinical signs were indicative of effects on the autonomic nervous system, the central nervous system, motor-coordination, motor activity and on muscle tone. Macroscopic examination revealed swollen livers and microscopic examination revealed an increase in the incidence of hydropic degeneration of the hepatocytes and cloudy swelling of the renal tubular epithelium. Available human data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Exposure of 1,1,1-trichloroethane resulted in cardiac sensitization to adrenaline. Increases in concentration and duration of exposure were accompanied by a decrease in the amount of adrenaline needed toinduce arrhythmia. 1,1,1-Trichloroethane is potentially toxic to the cardiovascular system by sensitizing the heart to adrenaline. Based on the effects noted in dogs and a limited number of humans, there is a potential for adverse cardiac effects following high exposures to 1,1,1-trichoroethane.

1,1,1-Trichloroethane is irritating to rabbit skin. 1,1,1-Trichloroethane is slightly irritating to the eyes of rabbits causing slight to moderate pain, slight conjunctival irritation but essentially no corneal damage. Any initial irritation disappeared within a few days. 1,1,1-Trichloroethane is irritating to human skin . The irritation increased from mild to chemical burns as exposure duration increases however, these effects are reversible. 1,1,1-Trichloroethane was mildly irritating to human eyes (most likely due to direct contact with the eye) when individuals were briefly exposed to high vapour concentrations. 1,1,1-Trichloroethane may have the potential for respiratory tract irritation.

No experimental data are available for skin sensitization in animals.

The repeated-dose toxicity of the 1,1,1-trichloroethane has been investigated in several inhalation and a few oral studies. In a repeated-dose inhalation toxicity study the substance was administered to male mice (160/concentration) via whole body exposures at 0, 1.37, or 5.46 mg/L/day, continuously for 14 weeks. No deaths were observed in either sex. This study identified a NOAEL of 1.37 mg/L/day and LOAEL of 5.46 mg/L/day for liver effects in mice with continuous exposure. In a repeated-dose oral toxicity study in mice, 1,1,1-trichloroethane was administered via microencapsulation to 10 animals/sex/dose at 0, 850, 1750, 3500, 7370, and 15,000 mg/kg bw/day (males) and 0, 1340, 2820, 5600, 11,125, and 23,000 mg/kg bw/day (females), for 7 days/week for 13 weeks. No deaths were observed in either sex. The males exhibited decreased epididiymal sperm counts at the highest dose. The National Toxicology Program estimated the doses of 1750 mg/kg bw/day (males) and 2,820 mg/kg bw/day (females) to represent NOAELs. LOAELs were 3500 and 5600 mg/kg-bw/day in males and females, respectively based on reduced body weights. In a repeated dose oral toxicity study in rats, 1,1,1-trichloroethane was administered via microencapsulation to 10 animals/sex/dose at 0, 300, 600, 1200, 2400, and 4800 mg/kg bw/day (males) and 0, 300, 650, 1250, 2500, and 5,000 mg/kg-bw/day (females), for 7 days/week for 13 weeks. No death was observed in either sex. The final mean body weight and body weight gain of females at 1250 mg/kg bw/day were significantly less than those of the untreated controls. The final mean body weights and body weight gains of males at 2400 mg/kg bw/day (and higher) and the final mean body weight of females at 5000 mg/kg bw/day were significantly less than the vehicle controls. There was no decrease seen in final mean body weight or body weight gain for the 2500 mg/kg bw females compared to untreated or vehicle controls. The liver weights of female rats administered 5000 mg/kg bw/day were statistically significantly decreased. Male rats exposed to 1200 mg/kg bw/day or greater had a spectrum of non-neoplastic kidney lesions consistent with hyaline droplet nephropathy. At the highest dose, males also had lower sperm numbers in the epididymis. No treatment-related gross or microscopic lesions were observed in female rats. The NOAELs were estimated to be 2400 and 2500 mg/kg-bw/day in males and females, respectively. The LOAELs were 4800 and 5000 mg/kg-bw/day in males and females, respectively based on decreased liver weights in females and decreased epididymal sperm counts in males. Neurobehavioural effects have been observed in some epidemiological studies in humans.

In a subchronic neurotoxicity study, Fischer 344 rats were exposed to 200, 600, or 2000 ppm 1,1,1-trichlorethane via inhalation for 6 hour/day, 5 days/week, for 13 weeks. Rats were clinically examined regularly and were given a functional observational battery monthly (FOB, including forelimb and hindlimb grip performance testing). At the end of exposure, the rats were evaluated by FOB and by visual, auditory, somatosensory, and caudal nerve-evoked potentials. There were no post-exposure treatment-related findings in any parameters except for a slightly smaller forelimb grip performance in the 2000 ppm group. The toxic significance of this finding is unclear. There was also a lack of findings in any other clinical, evoked potential or morphologic parameter.

Available human and animal data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Lower-level exposure to 1,1,1-trichloroethane may result in more subtle neurological effects such as impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time.

In bacterial reverse mutation assays with multiple strains of *Salmonella typhimurium* /*E. coli*, 1,1,1-trichloroethane was negative both with and without metabolic activation in open systems but was positive when tested in closed systems. In an *in vitro* mouse lymphoma assay with L5178Y cells, 1,1,1-trichloroethane was negative with and without metabolic activation at one laboratory, and an equivocal (weakly positive) response was obtained at the second laboratory in the presence of metabolic activation only); 1,1,1-trichloroethane was not considered mutagenic in this test. In an *in vitro* chromosomal aberration test using CHO cells in the presence and absence of metabolic activation, 1,1,1-trichloroethane was positive without metabolic activation. In a sister chromatid exchange (SCE) assay with CHO cells, 1,1,1-trichloroethane was considered to be equivocal both with and without metabolic activation systems. In several *in vivo* micronucleus assays conducted in mice using oral, inhalation or intraperitoneal exposure, 1,1,1-trichloroethane was negative up to the maximum tolerated dose. In an oral multi-generation reproduction study modified to include screening for dominant lethal effects in mice, no effects on reproductive function or performance were observed. Overall, gene mutation studies conducted *in vitro* and micronucleus studies conducted *in vivo* showed no evidence of potential genotoxicity.

Exposure to 1,1,1-trichloroethane was not associated with treatment-related increases in tumour incidence in most studies in mice or rats exposed by inhalation or oral (gavage) routes of exposure, although high mortality and less than lifetime exposure in some studies limited the ability to make firm conclusions about

carcinogenicity. Most studies in humans did not find associations with cancers although some association has been found between 1,1,1-trichloroethane and multiple myelomas or cancers of the nervous system. The United Stated Environmental Protection Agency has concluded that the database is inconclusive as to the carcinogenicity of 1,1,1-trichloroethane in humans.

The reproductive toxicity of the 1,1,1-trichloroethane has been well investigated in several studies. In a two generation study in mice, 1,1,1-trichloroethane was administered via drinking water to 30 female and 10 male animals/dose at 0, 100, 300, or 1000 mg/kg bw/day, for 5 weeks prior to mating and throughout gestation and lactation of the F1a litters. At 2 weeks post-weaning of the F1a litters, the F0 adults were re-mated to produce F1b litters. At 2 weeks post-weaning of the F1b litters, the F0 adults were re-mated for teratology screening of F1c pups. The F1b litters were culled to 30 females and 10 males at weaning and placed on test solutions until age 14 weeks when they were mated to produce the F2a litters. At 2 weeks post-weaning of the F2a pups, the F1b adults were re-mated for teratology screening of F2b pups. Adult mortality among the treated and control F0 and F1b generations was sporadic. Among the naïve controls, there was 20% mortality in both sexes in the F0 generation. For the vehicle control, there was 10% and 3.3% mortality among the males and females, respectively, in the F0 generation. Mortality in the F0 generations was 0%, 10%, and 20% among males and 10%, 6.7%, and 13.3% among females exposed at 0.58, 1.75, and 5.83 mg/L, respectively. With the exception of 7.4% rate mortality in the females dosed at 0.58 mg/L, no mortality was observed in F1b generation. The reason for the sporadic incidences of increased mortality could not be discerned at necropsy. No adverse reproductive effects were observed up to the highest dose tested. There were no effects on reproductive function and there was no increase in the incidence of skeletal or visceral malformations in either generation, indicating the NOAEL for reproductive toxicity was 1000 mg/kg bw/day, the highest dose tested. Epididymal sperm counts were decreased at 4,800 mg/kg-bw/day in rats in 13-week dietary studies.

The developmental toxicity of 1,1,1-trichloroethane has also been investigated in several studies. In a standard one generation study in rats, 1,1,1-trichloroethane was administered via inhalation to 30 animals/sex/ concentration at 0, 1000, 3000 or 6000 ppm (corresponding to 0, 5.4, 16.4 or 32.8 mg/L), for 6 hours/day on GD 6-15. No deaths were observed. Maternal effects were seen at 32.8 mg/L (hypoactivity, reductions in food consumption, body weight gain, body weight, and gravid uterine weight) and at the two lower doses (reduced body weight gain and reduced food consumption); the NOAEL for maternal toxicity was < 5.4 mg/L. Fetal body weight was significantly reduced only for female fetuses in the 32.8 mg/L group; decreases for male fetuses and all fetuses combined were not statistically significant. No increases in fetal malformations were observed. Effects suggesting slight developmental delay (poorly or unossified cervical centrum) were observed at the high dose. A NOAEL of 16.4 mg/L for mild fetotoxicity demonstrated by developmental delay and decreased body weights of female fetuses were identified in this study. In other inhalation studies, neurobehavioural effects were observed; across studies, effects occurred at 10.9 mg/L or higher. The developmental toxicity of 1,1,1,-trichloroethane has been well investigated in oral studies in rats and mice; no toxicologically significant effects have been observed. In humans, epidemiological studies failed to find statistically-significant associations between 1,1,1-trichloroethane and adverse reproductive outcomes.

1,1,1-Trichloroethane may present a hazard for human health (mild skin, eye and respiratory irritation, cardiac sensitization, central nervous system effects, and liver effects (at higher concentrations)). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Chemicals Programme.

Environment

The measured hydrolysis half-life for this compound is 0.5 to 1 year at 25°C. In the atmosphere, before it reaches the stratosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 3.1 – 3.7 years, assuming a diurnally averaged OH radical concentration of $1.5x10^{6}$/ cm^{-3} or $5x10^{5}/cm^{-3}$, respectively). In the Sponsor country, 1,1,1-trichoroethane has been recognized as an ozone depleting substance. 1,1,1-Trichoroethane has an ozone depletion potential (ODP) of 0.11 (compared to an ODP of 1.0 for CFC-11; trichlorofluoromethane). An OECD 301 C Ready Biodegradability: Modified MITI Test resulted in 0% biodegradation after 14 days. 1,1,1-Trichloroethane is considered not readily biodegradable under aerobic conditions.

Level III fugacity model with equal and continuous distributions to air, water and soil compartments suggests that 1,1,1- trichloroethane will distribute mainly to the air (46%) and water (45%) compartments with minor distribution to the soil compartment (9%) and negligible amount in the sediments compartment. However, the emission to air only resulted in 99.8 % to air. A Henry

law's constant of 1.62 x 10^{-2} atm-m^3/mole (16.4 hPa-m^3/mole) at 25°C suggests that volatilization of 1,1,1- trichloroethane from the water phase is expected to be high.

1,1,1-Trichloroethane is not expected to bioaccumulate in the aquatic environment based on a measured bioconcentration factor of 9 in *Lepomis macrochirus*; the half-life of 1,1,1-trichloroethane in the tissues (bioelimination) was less than 24 hours after reaching an equilibrium.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Pimephales promelas*]:	96 h LC_{50} = 52.8 mg/L (measured)
Invertebrate [*Daphnia magna*]:	48 h LC_{50} = 60 mg/L (measured)
Algae[*Chlamydomonas reinhardtii*]	72 h EC_{50} = 0.536 mg/L (measured; biomass)

The following subchronic toxicity test results have been determined for aquatic species:

Cyprinus carpio	14-d, LOEC = 30 mg/L (measured)
	14-d, NOEC = 7.7 mg/L (measured)
Daphnia magna	17-d, LOEC = 2.4 mg/L (measured)
	17-d, NOEC = 1.3 mg/L (measured)

1,1,1-Trichloroethane possesses properties that may present a hazard to the environment (acute toxicity to aquatic organisms < 1 mg/L [algae]). Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Chemicals Programme.

Exposure

1,1,1-Trichloroethane sales and use are governed under conditions outlined in the Montreal Protocol.

1,1,1-Trichloroethane is commercially produced with an annual production volume of 78,439 tonnes in the United States (2007). 1,1,1-trichoroethane is produced in closed systems. 1,1,1-Trichloroethane is used in the U.S. as feedstock for the production of hydroflurocarbons and hydrochloroflurocarbons. Greater than 98% of production used for feedstock use. In addition, developing countries also use 1,1,1-trichloroethane as a solvent in cleaning and adhesive applications; the provisions of the Montreal protocol establish that these uses must be phased out by 2015.

During the production of 1,1,1-trichloroethane, there is no intentional venting of the substance to the atmosphere. Releases of 1,1,1-trichloroethane to the atmosphere have dropped significantly in recent years in the U.S. and were reported to be 26 tonnes (57,299 pounds) based on the 2007 Toxics Release Inventory. Approximately one-half of the amount of 1,1,1-trichloethane released to the atmosphere was from the sole manufacturer with the other releases occurring from processors or others generating 1,1,1-trichoroethane in various chemical processes. Releases to other media reported in 2007 included 10.9 tonnes (24,111 pounds) released to soil and 0.03 tonnes (69 pounds) released to water. Any fugitive emissions are handled in compliance with US federal regulations (US EPA 40 CFR Part 63, Subpart H which defines a fugitive emissions leak detection and repair program). Any waste generated during the production of 1,1,1-trichloroethane is also handled appropriately according to US federal hazardous waste regulations (US EPA 40 CFR Part 265). Limited emissive uses of 1,1,1-trichoroethane are permitted in some countries only, as allowed by the Montreal Protocol. Engineering controls used in the production of 1,1,1-trichloroethane are subject to US EPA HON (Hazardous Organic National Emission Standards for Hazardous Air Pollutants) MACT (Maximum Achievable Control Technology) standards (40 CFR, Part 63) including venting of process streams and storage tanks to on-site incineration, activated carbon beds or refrigerated condensers, implementation of a Leak Detection and Repair program, and use of a closed purge sampling system. Workers are not exposed to non-accidental releases at the facility level; all exposures are maintained below American Conference of Governmental and Industrial Hygienists Threshold Limit Value. Potential routes of accidental exposures for workers are inhalation and dermal. Consumer exposure is not expected as there is no consumer use for 1,1,1-trichloroethane.