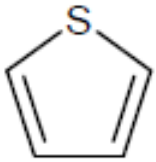
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-02-1
Chemical Name	Thiophene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

Thiophene is a colourless liquid at standard temperature and pressure with slight aromatic odour resembling that of benzene. Melting point and boiling point are -38.3 °C and 84.4 °C, respectively. The measured partition coefficient between octanol and water (log Kow) is 1.81. The measured vapour pressure is 1.06×10^4 Pa at 25 °C. The measured water solubility is 3015 mg/L at 25°C. Thiophene has no dissociable group.

Human Health

Nose-only inhalation exposure to [^{14}C] thiophene at 8000 ppm for 1 h showed that at least 16.3% of the inhaled thiophene was absorbed from the respiratory system in rats. At 72-h after exposure, concentrations of thiophene were in the following order: blood cells > liver > kidney, heart, and lung > brain, fat, and skeletal muscles. Within 72 h following exposure, 73.9% of the absorbed thiophene was excreted in expired air, 24.8% in urine, 0.6% in feces, and 0.8% in the cage wash. Excretion primarily occurred within the first 8 h. In rats, orally administered thiophene (240–300 mg/kg bw) was partly excreted unchanged in expired air (32%) and feces (<1%), and partly (40%) in urine as two mercapturic acids within 6 h. The result indicated that the absorption via oral exposure could be more than 70 % in rat. In rabbits, 38% of orally administrated thiophene (150–225 mg/kg bw) was excreted in urine as two mercapturic acids (same metabolites as in rats). No increase in the excretion of glucuronic acid or ethereal sulfate was observed. By intraperitoneal administration, the major metabolite of thiophene (30% of the administered dose) excreted in rat urine was dihydrothiophene sulfoxide mercapturate, which suggests that thiophene undergoes S-oxidation and glutathione conjugation.

The oral LD_{50} has been reported as more than 2000 mg/kg bw in female rats (OECD TG 423). At the lower test dose used in this study, 300 mg/kg bw, the rats showed drooping eyelids, salivation and soiled perineal region. Additional effects seen at 2000 mg/kg bw included decreased locomotor activity, smudges around the mouth and nose, unkempt fur, and a temporary reduction in body weight (evident at 4 days but not at 8 days). Macroscopic examination revealed no abnormal changes. The inhalation LC_{50} was reported to be 4525 ppm (15.6 mg/L) for a 6 h exposure in rats. The dermal LDL_0 was determined to be >3160 mg/kg after single doses of the undiluted test material applied to the closely clipped, intact skin of albino rabbits.

Thiophene caused low to moderate skin and eye irritation in rabbits. Occlusive dermal application for 24 h caused severe irritation in guinea pigs. Although no reliable information for skin sensitization is available,the limited data suggests no skin sensitization in guinea pigs.

In a repeated-dose oral toxicity study in rats (OECD TG 422 except for the limited haematological and clinical chemistry examination in only males), thiophene was administered via gavage to 13 animals/sex/dose at 0, 25, 100, or 400 mg/kg bw/day for 7 days/week. The male rats were dosed from 14 days before mating to the day before necropsy (including the mating period; 42 days in total) and the female rats from 14 days before mating to day 3 of lactation (including the mating period, gestation period, and delivery; 53 days in total). Incomplete eyelid opening, irregular respiration, decrease in locomotor activity, abdominal position and leaning position

were observed in males at 100 and 400 mg/kg bw/day and in females at 400 mg/kg bw/day. Three females showed ataxia and one of them showed tonic convulsions in the lactation period at 400 mg/kg bw/day. Decreases in food consumption and body weight gain were observed in the 400 mg/kg bw/day groups in both sexes. At necropsy, hypertrophy of hepatocytes was observed in the groups given 100 mg/kg bw/day or more in both sexes. In males of the 400 mg/kg bw/day group, infiltration of macrophages, necrosis of hepatocytes, and homogenous or vesicular cytoplasmic change of hepatocytes in the central zones were observed. In addition, pyknosis/necrosis of granular cells (male: 1/13; female: 8/13) and necrosis in the laminae albae (female: 7/13) in the cerebella were observed in the 400 mg/kg bw/day group. Pyknosis/necrosis of granular cells was also observed in one female at a dose of 100 mg/kg bw/day. Increase in relative liver weights were observed in males of the 100 mg/kg bw/day or more group and in females of the 400 mg/kg bw/day group. Decrease in glucose and ALP and increase in inorganic phosphorus was observed in males of the 100 mg/kg bw/day or more groups. Vacuolar degeneration of the tubular epithelium in the kidney was observed in females of the 100 mg/kg bw/day or more group.

Based on hepatic toxicity in both sexes together with histopathological changes in the cerebella and kidneys in females and clinical changes in males at 100 mg/kg bw/day, the no observed adverse effect level (NOAEL) for toxicity of thiophene administered repeatedly under conditions of this study was determined to be 25 mg/kg/day for both sexes. Some case reports for the therapeutic use of thiophene indicated that the liver injury with jaundice and pruritus was caused after the repeated doses for 3 to 10 days.

In a summary report of a subacute inhalation toxicity study (5 male rats/concentration at 0 (air), 1600, or 3200 ppm (0, 5.52 or 11.04 mg/L, respectively) for 6 h/day, for 12 exposures over a 15-day period), the sites of toxic action were the liver, kidney, thymus, nasal passages, and central nervous system. The NOAEL could not be determined in this study.

In a bacterial reverse mutation assay (Ames test) with multiple strains of *Salmonella typhimurium* and *Escherichia coli* (OECD TG 471; Guidelines for Screening Mutagenicity Testing of Chemicals, Chemical Substances Control Law of Japan), thiophene was negative both with and without metabolic activation. In addition, an *in vitro* chromosomal aberration test using cultured Chinese hamster lung cells (OECD TG 473) was also negative both with and without metabolic activation. In a mouse lymphoma mutagenicity assay, positive findings were obtained with and without S9, but only at a concentration that decreased survival below 10%. No information is available on *in vivo* genotoxicity testing. Based on these results, thiophene is considered to be non genotoxic *in vitro*.

No data were available on the carcinogenicity of thiophene.

The reproductive toxicity of thiophene was investigated in a study that combined repeated-dose toxicity with reproductive or developmental toxicity screening in rats (OECD TG 422, see above). In that study, there were no adverse effects on copulation, ovulation, and fertility in any thiophene-treated group. Three females showed ataxia and one of them showed tonic convulsions in the lactation period at 400 mg/kg bw/day. Extinction of nursing and/or lactation was observed in 1, 2, and 3 animals at 25, 100, and 400 mg/kg bw/day doses, respectively. No adverse effects on pup viability on postnatal day 0 or the sex ratio were detected in any thiophene-treated group. In the 400 mg/kg bw/day group, pup weights at birth and on postnatal day 4, along with their viability, were decreased, but these changes were statistically insignificant and considered to be secondary effects of maternal toxicity. No morphological abnormalities associated with the administration of thiophene were found in any pup. Based on abnormal lactation and cessation of nursing, the LOAEL for reproductive toxicity in females is considered to be 25 mg/kg bw/day and the NOAEL for fertility and developmental toxicity is considered to be 400 mg/kg bw/day (the highest dose). The parental NOAEL was considered to be 25 mg/kg bw/day (see repeated dose toxicity).

Thiophene possesses properties indicating a hazard for human health (repeated-dose toxicity, eye and skin irritation, and reproductive toxicity (abnormal lactation and cessation of nursing)). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

Thiophene entering in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (version 1.92), a calculated half-life time of 1.12 days and a rate constant of 9.53×10^{-12} cm^3/molecule-sec are obtained for

the indirect photo-oxidation of thiophene by reaction with hydroxyl radical in air. Concentration of hydroxyl radicals was assumed to be 1.5×10^6 OH/cm^3 and the time frame of hydroxyl radicals was 12 hours/day.

Thiophene is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups. A study according to the equivalent protocol of OECD TG 111 showed no hydrolysis of thiophene in water at pH 4, 7 and 9 in 50 °C after five days.

A test similar to OECD TG 301C was conducted with thiophene with activated sludge for two weeks. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matters. The test results showed 0% degradation by BOD. Thiophene is not readily biodegradable according to a protocol similar to OECD TG 301C.

The aerobic biodegradation of thiophene was studied in microcosm experiments using groundwater microorganisms as inoculum. The inoculum used was an aerobic, free-living enrichment culture that originated from the ground water at a creosote-contaminated site. Thiophene was not used as a sole source of carbon. However, it was completely biodegraded aerobically with benzene and toluene as primary substrates in 18 days, and to 80% with ethylbenzene. Some 5-20% biodegradation of thiophene was observed in 18 days when *p*-xylene, *o*-xylene, *m*-xylene, naphthalene, and 1-methylnaphthalene were the primary substrates. These results show that thiophene can be degraded concomitantly under aerobic conditions by adapted microorganisms by co-metabolism.

In a study performed according to a protocol similar to OECD TG 305 with carp exposed to thiophene, bio-concentration factors of less than 9.0 were obtained for the concentration of 15 µg/L for six weeks exposure period. In this test, the lipid content value of the test fish was 4.8 %. Taking into account the octanol-water partition coefficient, a bio-concentration factor can be calculated as 7.265 according to a log Kow of 1.81 by BCFBAF, version 3.00. Thiophene is not expected to bioaccumulate.

Fugacity modeling (level III) for thiophene was conducted using EPISUITE, version 4.0. Input parameters were water solubility of 3015 mg/L, boiling point of 84.4 °C, melting point of -38.3 °C, log Kow of 1.81, vapour pressure of 9.68×103 Pa, Henry's law constant of 2.97×10^2 Pa.m3/mole. When equal and continuous release to air, water and soil is assumed, thiophene is mainly distributed in water and soil compartments. If released to the water compartment only, thiophene mostly stays in the water compartment. A Henry's law constant of 2.97×10^2 Pa.m3/mole (2.93×10-3 atm.m3/mole) at 25 °C suggested that volatilization of thiophene from water is moderate. A soil adsorption coefficient of log Koc = 1.903 indicated thiophene has low adsorption to soil and sediment.

The following acute and prolonged toxicity test results have been determined for aquatic species;

Fish [*Oryzias latipes*, OECD TG 203]: 96 h LC_{50} = 31 mg/L (measured)
Fish [*Oryzias latipes*, OECD TG 204]: 14 d LC_{50} > 30 mg/L (measured)
14 d NOEC = 12 mg/L (behaviour, nominal)
Daphnid [*Daphnia magna*, OECD TG 202]: 48 h EC_{50} = 21 mg/L (measured)
Algae [*Pseudokirchneriella subcapitata*, OECD TG 201]:
72 h ErC_{50} = 113 mg/L (measured, growth rate)
72 h EbC50 = 106 mg/L (measured, area under growth curve)

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

Daphnid [*Daphnia magna*, OECD TG 211]: 21 d LOEC = 8.1 mg/L (measured)
21 d NOEC = 2.8 mg/L (measured)
Algae [*Pseudokirchneriella subcapitata* OECD TG 201]:
72 h NOErC and 72 h NOEbC 12 mg/L (measured)

Thiophene possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for fish and invertebrates). This chemical is considered not readily biodegradable and is not expected to have bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the Cooperative Chemicals Assessment Programme.

Exposure

Production volume and/or import volume of thiophene in Japan (sponsor country) was probably less than 100 tonnes in 2009. Information of the current production volume in other areas is not available.

Thiophene is synthesized from heating sodium succinate with phosphorus trisulfide. Thiophene is made available in commercial quantities by a process utilizing the dehydrogenation of butane with sulfur as the dehydrogenating agent, followed by cyclization with sulfur to form the thiophene ring.

Thiophene is used as a solvent similar to benzene and as raw materials for resins. Thiophene is also used as raw materials for dyes or pharmaceuticals. Thiophene is used as an intermediate for medicines/pesticides/dyes and a chemical reagent in Japan. Thiophene is found in coal tar, in coal gas, and in technical benzene. According to monitoring data in Japan in 1985, thiophene was present in sediments at 0.0002 - 0.0015 μg/g dry weight. However it was not detected in surface water at the detection limit of 0.005 μg/L. Information on the processing site in a Japanese company is available. In this company, exhaust gas from ventilations and reactors is cleaned by using tail gas scrubber. Then, this exhaust gas is discharged into the atmosphere. The waste water from washing scrubber is disposed by an industrial waste disposer. There is little potential for environmental exposure in the sponsor country.

Occupational exposure through inhalation of vapour and via the dermal route is anticipated.

Thiophene becomes another material at the stage of processing. Therefore, thiophene is not expected to be included in consumer products. It is expected that there is no consumer exposure potential.