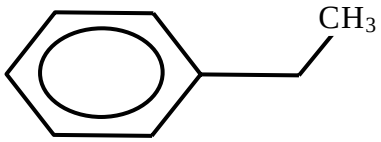
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-41-4
Chemical Name	Ethylbenzene
Structural Formula	

RECOMMENDATIONS

The chemical is a low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Ethylbenzene is readily absorbed following inhalation, oral, and dermal exposures, distributed throughout the body, and excreted primarily through urine. There are two different metabolic pathways for ethylbenzene with the primary pathway being the α-oxidation of ethylbenzene to 1-phenylethanol, mostly as the R-enantiomer. The pattern of urinary metabolite excretion varies with different mammalian species. In humans, ethylbenzene is excreted in the urine as mandelic acid and phenylgloxylic acids; whereas rats and rabbits excrete hippuric acid and phenaceturic acid as the main metabolites. Ethylbenzene can induce liver enzymes and hence its own metabolism as well as the metabolism of other substances. Ethylbenzene has a low order of acute toxicity by the oral, dermal or inhalation routes of exposure. Studies in rabbits indicate that ethylbenzene is irritating to the skin and eyes. There are numerous repeat dose studies available in a variety of species, these include: rats, mice, rabbits, guinea pig and rhesus monkeys. In a 13 week inhalation repeat-dose study in male and female rats, mild body weight or organ weight (kidney, liver, lung) effects occurred at doses $\geq$250 ppm without any accompanying histopathological or clinical chemistry changes, as a result these findings were not considered toxicologically significant. In chronic toxicity/carcinogenicity studies, both rats and mice were exposed via inhalation to 0, 75, 250 or 750 ppm for 104 weeks. In rats, the kidney was the target organ of toxicity, with renal tubular hyperplasia noted in both males and females at the 750 ppm level only. In mice, the liver and lung were the principal target organs of toxicity. In male mice at 750 ppm, lung toxicity was described as alveolar epithelial metaplasia, and liver toxicity was described as hepatocellular syncitial alteration, hypertrophy and mild necrosis; this was accompanied by increased follicular cell hyperplasia in the thyroid. As a result the NOAEL in male mice was determined to be 250 ppm. In female mice, the 750 ppm dose group had an increased incidence of eosinophilic foci in the liver (44% vs 10% in the controls) and an increased incidence in follicular cell hyperplasia in the thyroid gland. In addition, female mice exposed to 250 ppm and 750 ppm had an increase in hyperplasia of the pituitary gland. As a result, the NOAEL for female mice was 75 ppm. Hearing loss has been reported in rats (but not guinea pigs) exposed to relatively high exposures *(400 ppm and greater)* of ethylbenzene. Ethylbenzene was negative in bacterial gene mutation tests and in a yeast assay on mitotic recombination. In mouse lymphoma assays, positive responses were only observed at doses with excess cytotoxicity. No clear conclusion can be drawn from the chromosomal aberration tests *in vitro*. A single *in vitro* micronucleus test without S-9 mix was positive. An *in vitro* SCE test was clearly negative with and without S-9 mix. With *in vivo* tests, negative findings were obtained in micronucleus tests and in a mouse liver UDS test. In studies conducted by the U.S. National Toxicology Program, inhalation of ethylbenzene at 750 ppm resulted in increased lung tumors in male mice, liver tumors in female mice, and increased kidney tumors in male and female rats. No increase in tumors

was reported at 75 or 250 ppm. Ethylbenzene is considered to be an animal carcinogen, however, the relevance of these findings to humans is currently unknown. Although no reproductive toxicity studies have been conducted on ethylbenzene, repeated-dose studies indicate that the reproductive organs are not a target for ethylbenzene toxicity. Furthermore, in the 13-week NTP studies with rats and mice, no effects were observed for sperm, testicular morphology, spermatid counts, sperm motility, caudal or epididymal weights, or length of estrous cycle. Developmental toxicity studies have been conducted in the rabbit and rat with developmental effects (14% increase in incidence in pups with supernumerary ribs) observed in the rat only at 1,000 ppm ethylbenzene. Maternal effects in the dams at this dose consisted of increases in liver (approximately 22%), kidney (approximately 10%), and spleen (approximately 10%) weights in the absence of histopathology changes.

Environment

Ethylbenzene has the following physical chemical properties: molecular weight, 106.2; Log Kow, 3.15; water solubility, 169 mg/l at 25^0C ; vapor Pressure, 1270 Pa (1.27 kPa); melting point, -95C; Henry's Law Constant, 798.1 Pa.m3/mol. Ethylbenzene partitions to air from water and soil, and is degraded in air. Ethylbenzene is volatile and when released will quickly vaporize. Photodegradation is the primary route of removal in the environment. Photodegradation is estimated with a half-life of 1 day. Ethylbenzene is considered inherently biodegradable and removal from water occurs primarily by evaporation but in the summer biodegradation plays a key role in the removal process. Level I and Level III fugacity modeling indicate that partitioning is primarily to the air compartment, 98 and 96%, respectively. Ethylbenzene is inherently biodegradable in water and in soil under aerobic conditions, and not rapidly biodegradable in anaerobic conditions. Ethylbenzene is expected to be moderately adsorbed to soil. In acute aquatic toxicity testing LC_{50} values range approximately between 1 and 10 mg/l. In acute aquatic fish tests (fresh water species), the 96-hr LC_{50} for *Pimphales promelas* and *Oncorhynchus mykiss* are 12.1 and 4.2 mg/L, respectively. Data are available in the saltwater species *Menidia menidia* and give results within the same range as for the fresh water species with a 96-hr LC_{50} = 5.1 mg/L. In fresh water invertebrate species *Daphnia magna* and *Ceriodaphia dubia*, 48-hr LC_{50} values were 1.81 and 3.2 mg/L, respectively. Additional data is available in the saltwater species *Crangon franciscorium* (96-hr LC_{50} = 0.49 mg/L) and *Mysidopsis bahia* (96-hr LC_{50} = 2.6 mg/L). In 96-hr algal toxicity testing, results indicate that ethylbenzene inhibits algae growth in *Selanastrum capricornatum* at 3.6 mg/L and in *Skeletonema costatum* at 7.7 mg/L. Based on measured data, ethylbenzene is not expected to bioaccumulate (BCF 1.1 – 15).

Exposure

Ethylbenzene is an industrial chemical that is primarily produced and further reacted to make styrene in a closed continuous process; thus, occupational exposures are expected to be very low. In addition, ethylbenzene occurs in crude oil and as a component of mixed xylenes, which is used in gasoline or as a solvent. Emissions and exposures from solvent use are not well characterized. Ethylbenzene has been detected in urban and rural air and water samples at ppt to low ppb concentrations. Exposure to the general population is possible through extremely low ambient air concentrations, primarily due to gasoline and automobile emissions.

NATURE OF FURTHER WORK RECOMMENDED

Regional and national exposure and risk assessments are ongoing. This chemical is a substance of the 1st EU Priority List. An in-depth risk assessment will be performed within the framework of the EU Risk Assessment Programme under Regulation 793/93. This chemical is also to undergo review in the US Voluntary Children's Chemical Evaluation Programme and additional testing of reproductive toxicity (two generation study), adult neurotoxicity, and immunotoxicity is planned.