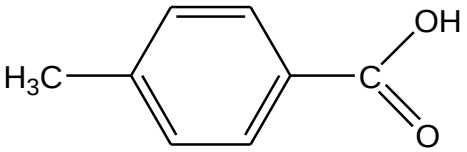
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-94-5
Chemical Name	*p*-Toluic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No data are available on the toxicokinetics, metabolism and distribution of *p*-toluic acid.

The oral LD_{50} values were 2340 mg/kg bw for male and 2484 mg/kg bw for female ICR mice, and 3113 mg/kg bw for male and 2115 mg/kg bw for female Wistar rats. *p*-Toluic acid administered orally caused reversible disturbances (anesthetic action) of the central nervous system, including sedation, decrease in spontaneous locomotion, limb weakness, etc. in both species. Furthermore, *p*-toluic acid caused hemorrhage in the mucosa of the stomach and small intestine under oral administration in both species, suggesting that *p*-toluic acid has a local irritating effect.

No experimental data are available for skin and eye irritation in animals, but it has to be considered as skin and eye irritant according to its acidic properties.

There are no experimental animal data for sensitisation. In humans *p*-toluic acid is skin sensitizing. A cross-sensitivity between all three isomers, *p*-toluic acid, *m*-toluic acid and *o*-toluic acid, was found.

In a repeated dose oral toxicity study in Crj: CD(SD)rats [OECD TG 407], *p*-toluic acid was administered by gavage to male and female rats (5 or 10 animals/sex/group) for 28 days at 0, 100, 300 and 1000 mg/kg bw/day. No deaths were observed in any group. Although a transient salivation and urinary changes in male and female rats and increased food intake in female rats due to the increased water consumption were observed at 1000 mg/kg bw/day, these changes were considered to result from the local irritating effect of *p*-toluic acid and not due to its systemic toxicity. In females, a trend of decreased platelet count and blood protein together with an increase in AST were detected at the dose of 1000 mg/kg bw/day. Based on these findings, the NOAELs for repeated oral dose toxicity in male and female rats were considered to be 1000 and 300 mg/kg bw/day, respectively. In a reproductive and developmental toxicity screening test in Crj: CD(SD) rats [OECD TG 421], *p*-toluic acid was administered by gavage at 0, 100, 300 and 1000 mg/kg bw/day. A decreased body weight gain was found in females at 300 mg/kg bw/day and higher, but not in males at all doses. Histopathological examinations revealed an increased number of cauda epididymal lumen with a decreased number of spermatozoa and slightly increased cell debris in the epididymis at 1000 mg/kg bw/day. Based on these findings, the NOAELs for repeated dose toxicity is considered to be 100 mg/kg bw/day in maternal females and 300 mg/kg bw/day in males. The overall NOAEL for repeated dose toxicity is considered to be 100 mg/kg bw/day in females and 300 mg/kg bw/day in males.

No data are available for the repeated dose inhalation and dermal toxicity of *p*-toluic acid.

A bacterial reverse mutation assay [OECD TG 471] on *p*-toluic acid was negative both with and without metabolic activation. An *in vitro* chromosome aberration test using CHL/IU cells [OECD TG 473] was positive under continuous treatment without a decrease in the pH in the absence of metabolic activation. *p*-Toluic acid is considered to be clastogenic *in vitro*. However, the micronucleus assay [OECD TG 474] using CD-1 male mice was negative up to the limit dose of 2000 mg/kg. Although there are no ADME studies, it can be predicted, based on physical chemical considerations and toxicokinetic prediction, that the substance is likely to reach the

target tissue, the bone marrow. Based on these results, *p*-toluic acid is not anticipated to be genotoxic *in vivo*.

No data are available for the carcinogenicity of *p*-toluic acid.

In a reproductive and developmental toxicity screening test in Crj: CD(SD) rats [OECD TG 421], *p*-toluic acid was administered by gavage at 0, 100, 300 or 1000 mg/kg bw/day. A decreased body weight gain was found in females at 300 mg/kg bw/day and higher, but not in males at any dose. Histopathological examinations revealed an increased number of cauda epididymal lumen with a decreased number of spermatozoa and slightly increased cell debris in the epididymis at 1000 mg/kg bw/day and no abnormalities in the testis and ovary. No adverse effects were noted on the estrous cyclicity, precoital interval, copulation index, gestation index, gestation length, or numbers of corpora lute. There were decreases in the fertility index at 1000 mg/kg bw/day and implantation index at more than 300 mg/kg bw/day. Decreased numbers of pups born at 300 mg/kg bw/day and higher, and of live pups on postnatal days 0 and 4 at 1000 mg/kg bw/day were observed. No changes were found in the sex ratio or body weight of pups. No structural abnormalities of pups were detected in any groups. P-toluic acid causes adverse effects on fertility at doses of 300 mg/kg bw/day and above. These changes are not considered to have occurred as a consequence of maternal toxicity. Based on these findings, the NOAELs were 100 mg/kg bw/day for general toxicity in females, and 100 mg/kg bw/day for reproductive toxicity.

Environment

p-Toluic acid is white to yellow-brown crystal with a melting point of 179.3 °C, a boiling point of 273.9 °C and a vapour pressure of 8.11×10^{-3} Pa at 25 °C. The measured partition coefficient (Log K_{ow}) is 2.44 (neutral form), and water solubility is 349 mg/L at 20 °C. The dissociation constant (pKa) is 4.22 at 20 °C.

A hydrolysis test according to OECD TG 111 showed no hydrolysis at pH4, pH7 and pH9 at 50 °C for 5 days. As pKa is 4.22, *p*-toluic acid mainly exists in its dissociated form in water at environmentally relevant pH values. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 4.21 days. *p*-Toluic acid is readily biodegradable under aerobic conditions with BOD biodegradability of 95 % after 28 days(OECD TG 301C). Bioaccumulation potential is estimated to be low based on the Log K_{ow} of 2.44, which is supported by a calculated BCF value with BCFWIN of 3.16. A Henry law's constant of 1.2×10^{-2} Pa.m^3/mole at 25 °C suggests that volatilization of *p*-toluic acid from the water phase is not expected to be high.

Level III fugacity model with equal and continuous distributions to air, water and soil compartments suggests that *p*-toluic acid will distribute mainly to the soil (69.8 %) and water (28.5 %) compartments with minor distribution to the air compartment (1.6 %) and negligible amount in the sediment compartment. This model calculation is conducted based on the assumption that the substance is present in its neutral form in the aqueous compartments. As *p*-toluic acid exists in its dissociated form in aqueous solution at environmentally relevant pH, the amount of *p*-Toluic acid partitioning to the water compartment may be underestimated in these calculations.

Eco-toxicity data of this chemical are available in aquatic species from three trophic levels. GLP tests using a freshwater fish (OECD TG 203, *Oryzias latipes*), daphnids (OECD TG 202, *Daphnia magna*) and green alga (OECD TG 201, *Pseudokirchneriella subcapitata*) have been conducted.

The following acute toxicity values have been determined for aquatic species:

Oryzias latipes; 96 h LC_{50} = 64 mg/L(measured concentration)

Daphnia magna; 48 h LC_{50} = 42 mg/L (measured concentration)

Pseudokirchneriella subcapitata; 72 h ErC_{50} = 74 mg/L (growth rate method, measured concentration)

Pseudokirchneriella subcapitata; 72 h EbC_{50} = 63 mg/L (area under growth curve method, measured concentration)

The chronic toxicities on daphnids (OECD TG 211, *Daphnia magna*) and on algae (OECD TG 201, *Pseudokirchneriella subcapitata*) are available. The following chronic toxicity values have been

determined for aquatic invertebrates and algae:

Daphnia magna; 21 d NOEC = 3.2 mg/L (measured concentration)

Pseudokirchneriella subcapitata; 72 h NOErC = 46mg/L (growth rate method, measured concentration)

Pseudokirchneriella subcapitata; 72 h NOEbC = 46 mg/L (area under growth curve method, measured concentration)

Exposure

p-Toluic acid is commercially produced with an annual production volume of 100 – 1000 tonnes in Japan. Worldwide production volume outside Japan is not available. *p*-Toluic acid is mainly produced by the oxidation of *p*-xylene. *p*-Toluic acid is used as an intermediate for photosensitive pigments, fluorescent dyes and colorants.

In the sponsor country, *p*-toluic acid is produced and processed in a closed system. Even if a small amount of *p*-toluic acid is released into the waste-water stream at production/processing sites, the waste water stream is treated in the waste-water treatment plant. Furthermore, as *p*-toluic acid is readily biodegradable, emission of *p*-toluic acid from the production and processing sites into the environment is anticipated to be very low in the sponsor country. No monitoring data from production and processing sites are available in the sponsor country. Workers are using personal protective equipments to minimize intake. *p*-Toluic acid is used only as an industrial intermediate in the production of photo pigments, dyes and colorants in the sponsor country. Therefore, consumer exposure is considered to be negligible. No other information on consumer exposure is available.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (sensitization and repeated dose and reproductive toxicity). Based on exposure data presented by the Sponsor country (closed system site limited intermediate with no transport globally), relating to production in one country (which accounts for an unknown fraction of the global production) and relating to the use pattern in the sponsor country, exposure to human is expected to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity to aquatic organisms between 1 and 100 mg/L). However the chemical is readily biodegradable and has limited potential for bioaccumulation.