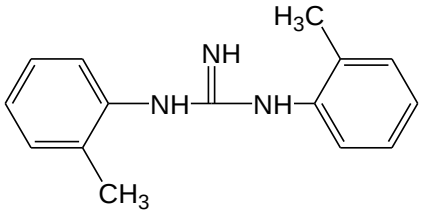
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	97-39-2
Chemical Name	1,3-di-*o*-tolylguanidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No information on toxicokinetics or metabolism is available.

1,3-Di-*o*-tolylguanidine is known to be a selective ligand for the sigma site in the mammalian central nervous system. Behavioral changes, such as hypothermia, reduced pain behaviour, circling behaviour, and decreased locomotor activity in mice and/or rats were observed after intraperitoneal, subcutaneous, intravenous and/or intranigral injection.

The oral LD_{50} (rat) was 85.3 mg/kg bw and 56.0 mg/kg bw for males and females, respectively. No information is available regarding acute toxicity via the dermal or inhalation routes.

Based on studies available in the secondary literature, the substance was not a skin irritant, but was irritating to eyes in animals.

No information is available concerning sensitisation in animals. No effect was reported in human sensitization studies that are less valid.

In a 28-day repeated dose toxicity study [Japanese TG equivalent to OECD TG 407], rats were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 7.5, 15, 30 or 60 mg/kg bw/day. At 60 mg/kg bw/day, one male and one female in the test group and six females in the recovery group died during the administration period. Clinical observation revealed mydriasis, salivation, tremors, decrease in locomotor activity, bradypnea, hypothermia, soiling of the lower abdomen, adoption of a prone or lateral position and gasping in males and females at 60 mg/kg. Mydriasis and salivation were also observed in males and females at 30 mg/kg. Body weights and food consumption were decreased in males and females at 60 mg/kg, but there was no significant difference by the end of the recovery period. Urinalysis showed a tendency for increase in urine volume in males at 30 and 60 mg/kg and increased urine volume in females at 15 mg/kg and higher, with resulting low values for osmotic pressure and specific gravity. Hematological examination revealed a shortened APTT in males at 30 and 60 mg/kg. Blood chemical examination revealed a low value for total protein, and high values for GPT and potassium in males and females at 60 mg/kg. A low value for albumin, high values for ALP and blood urea nitrogen were observed in males at 60 mg/kg. Low values for GOT and sodium, high values for total cholesterol, triglycerides and phospholipids were observed in females at 60 mg/kg. High values for total cholesterol and phospholipids were also observed in females at 30 mg/kg. Relative liver weights were higher in females at 30 and 60 mg/kg. Necropsy revealed light red spots on the mucosa of the glandular stomach, which were histopathologically confirmed to be erosion in one dead female at 60 mg/kg. Histopathological examination revealed hypertrophy of the centrilobular

hepatocytes in one surviving female at 60 mg/kg. The above-mentioned changes recovered after cessation of treatment. As for hypertrophy of the centrilobular hepatocytes, restoration was not confirmed because examination of recovery was not performed for females at 60 mg/kg. Based on mydriasis and salivation and changes in total cholesterol and phospholipids levels in plasma at 30 mg/kg bw/day, the NOAEL from this study is 15 mg/kg bw/day for males and females.

In a reproduction/developmental toxicity screening test [OECD TG 421], rats were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 8, 20, or 50 mg/kg bw/day. Males were dosed for a total of 49 days, from 14 days before mating, and females were dosed from 14 days before mating throughout the mating and pregnancy period to day 3 of lactation (40-49 days). Two males and three females at 50 mg/kg died. Salivation, mydriasis, hypoactivity, bradypnea, adoption of a prone position and/or tremors were observed in males and females at 20 and 50 mg/kg. Decreased body weight gain and food consumption in males and females at 50 mg/kg group and decreased food consumption in females at 20 mg/kg were observed. No effects related to administration of the test substance were noted at necropsy, or on organ weight or histopathological examination in any treatment group. Based on the behavioral changes, the NOAEL for repeated dose toxicity is considered to be 8 mg/kg bw/day in males and females.

In a prenatal developmental toxicity study [OECD 414], rats (24 females/group) were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 10, 20 or 40 mg/kg bw/day on days 6-19 of pregnancy. The rats were terminated and examined on day 20 of pregnancy. A total of four females died at 40 mg/kg. The incidences of females showing mydriasis at 20 and 40 mg/kg and showing decreased locomotor activity at 40 mg/kg were increased. Alopecia, bradypnea, prone position and tremor were also observed at 40 mg/kg. The maternal body weight gain at 20 and 40 mg/kg and food consumption at 40 mg/kg were reduced. The NOAEL for maternally repeated dose toxicity is considered to be 10 mg/kg bw/day.

Based on the behavioural changes at 20 mg/kg and higher, the overall NOAEL for repeated dose toxicity is considered to be 8-10 mg/kg bw/day in male and female rats.

1,3-Di-*o*-tolylguanidine was not mutagenic in bacteria [OECD TG 471] and did not induce chromosomal aberrations in mammalian cells in vitro [OECD TG 473] without S9 mix. However, structural chromosomal aberrations were induced in the presence of S9 mix in CHL cells at 600µg/ml. The substance was non-clastogenic in an in vivo mouse micronucleus assay [OECD TG 474] These data indicate that this substance is not genotoxic in vivo.

No information on carcinogenicity is available.

In a reproduction/developmental toxicity screening test [OECD TG 421], no effects related to administration of 1,3-di-*o*-tolylguanidine were observed on the estrous cycle, number of corpora lutea or implantations, implantation index, copulation index, male or female fertility indices, number of days required for copulation, length of gestation or gestation index. With respect to developmental toxicity, decrease in the litter size and live newborns, birth index, body weights of the male and female live newborns and viability index on day 4, and increase in the incidence of pups with external malformations were observed at 50 mg/kg. There were no effects related to administration of the test substance on the stillbirth index or sex ratio of the live newborn. These data indicate that this substance adversely affects development, but not reproduction, at parentally toxic doses. Based on the lack of reproductive effects and decreased viability and weight of pups, the NOAELs for reproductive performance of the parents and for development of the offspring are considered to be 50 and 20 mg/kg bw/day, respectively.

In a prenatal developmental toxicity study [OECD 414], rats (24 females/group) were administered 1,3-di-*o*-tolylguanidine by gavage at 0 (vehicle), 10, 20 or 40 mg/kg bw/day on days 6-19 of pregnancy. The rats were terminated and examined on day 20 of pregnancy. A decreased weight of the gravid uterus, increased incidence of postimplantation loss, decreased number of live fetuses, and lowered weights of fetuses and placentae were found at 40 mg/kg. The incidences of fetuses with external malformations at 40 mg/kg and with skeletal malformations at 20 and 40 mg/kg were increased. Higher incidences of fetuses with brachydactyly and short tail and defects of caudal vertebrae, phalanges and metacarpals were observed at 40 mg/kg. Delayed ossification was also noted at 40 mg/kg. These data indicate that

this substance is developmentally toxic at maternally toxic doses. The NOAEL for developmental toxicity is considered to be 10 mg/kg bw/day in rats.

Environment

1,3-Di-*o*-tolylguanidine is a white crystal with melting point of 174.4 – 176.0 °C. Boiling point is not observed as this chemical is decomposed at 194 °C. Vapour pressure is 6.89×10^{-5} Pa at 25 °C. Partition coefficient (Log K_{ow}) is measured as 2.90 with neutral form, and water solubility is 70.0 mg/L at 20 °C.

Hydrolysis test according to OECD Test-guideline 111 shows no hydrolysis at pH4, pH7 and pH9 at 50 °C for 5 days. As the dissociation constant (pKa) is 10.67, 1,3-di-*o*-tolylguanidine mainly exists with its protonated form at environmentally relevant pH values. In the atmosphere, indirect photo-oxidation by reaction with hydroxy radicals is predicted to occur with a half-life of 1.2 hours. 1,3-Di-*o*-tolylguanidine is not readily biodegradable under aerobic conditions (Biodegradability by BOD = 1 % after 28 days). Bioaccumulation potential seems to be low based on the Log K_{ow} of 2.90, which is supported by a calculated BCF value with BCFWIN of 34.

Fugacity Model Mackay level III calculation indicates that 1,3-di-*o*-tolylguanidine will be distributed mainly to soil (95.8 %) and water (4.2 %) compartments if released to air. If released to water, this chemical will distribute mainly to water compartment (98.2 %). If released to soil, this chemical will be almost distributed to soil compartment (98.3 %). If released simultaneously to air, soil and water, 1,3-di-*o*-tolylguanidine will be distributed mainly to soil (86.5 %) and water (13.3 %) compartments with minor distribution to sediment (0.243 %) and negligible amount in air (0.0 %) These results should be treated with caution as the calculation are based on log K_{ow} of 2.90 with its neutral form although 1,3-di-*o*-tolylguanidine exists with its protonated form in the aqueous compartment. Henry's Law constant is 8.67×10^{-12} atm.m^3/mole.

Eco-toxicity data of this chemical were available in aquatic species from three trophic levels. The 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*) were conducted.
The following acute toxicity values have been determined for aquatic species:
Oryzias latipes; 96 h LC_{50} = 19 mg/L
Daphnia magna; 48 h LC_{50} = 7.2 mg/L
Pseudokirchneriella subcapitata; 72 h ErC_{50} = 8.9 mg/L (growth rate method)
Pseudokirchneriella subcapitata; 72 h EbC_{50} = 5.6 mg/L (area under growth curve method)

The chronic toxicities on daphnids (OECD TG 211, *Daphnia magna*) and on algae (OECD TG 201, *Pseudokirchneriella subcapitata*) were available according to the GLP tests. The following chronic toxicity values have been determined for aquatic invertebrates and algae:
Daphnia magna ; 21 d NOEC = 2.8 mg/L
Pseudokirchneriella subcapitata; 72 h NOErC = 2.3 mg/L (growth rate method)
Pseudokirchneriella subcapitata; 72 h NOEbC = 3.8 mg/L (area under growth curve method)

Exposure

1,3-Di-*o*-tolylguanidine is commercially produced with an annual production volume of 100 – 500 tonnes in Japan. Worldwide production volume outside Japan is not available. 1,3-Di-*o*-tolylguanidineis produced with raw materials of *o*-toluidine and cyanogen chloride. 1,3-Di-*o*-tolylguanidine is used for vulcanization accelerator mainly for tyres.

In the sponsor country, 1,3-di-*o*-tolylguanidine is produced and processed in a closed system. At production and processing sites, small amounts of 1,3-di-*o*-tolylguanidine might be released into waste-water stream. However, the waste water stream is treated in the waste-water treatment plant with bio-chemical treatment, adsorption and filtration. Therefore, emission of 1,3-di-*o*-tolylguanidine from the production and processing sites into the environment is anticipated to be low in the sponsor country. However, there is no emission monitoring data

available. 1,3-Di-*o*-tolylguanidine is degraded in the vulcanization process, and it does not remain in the final rubber products. Therefore, consumer exposure is considered to be negligible.

Occupational exposure through inhalation of airborne dust and dermal contact is possible. Workers are using personal protective equipments to minimize intake.

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

Human Health: The chemical is of low priority for further work. The substance possesses properties indicating a hazard for human health (acute oral toxicity, repeated dose toxicity, and developmental toxicity). Based on data presented by the Sponsor Country, relating to production by one producer in one country which accounts for an unknown fraction of global production and relating to the use pattern in the Sponsor country, exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. 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 aquatic toxicity to fish, daphnids and algae are between 1 and 100 mg/L). Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.