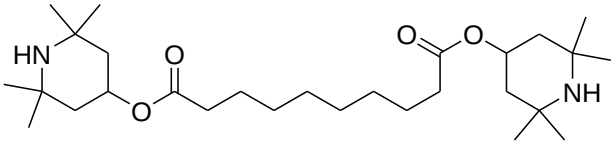
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	52829-07-9
Chemical Names	Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No ADME studies were available. However, based on the amphiphilic properties of bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate (further referred as bis-TMPS), the substance is expected to be well absorbed from the gastrointestinal tract and consequently bioavailable to some extent. Based on toxicodynamic data, metabolic degradation by Phase I hydrolysis is assumed, generating 2,2,6,6-Tetramethylpiperidin-4-ol (HTMP) and decanedioic acid as the main metabolites, leading to phase II reactions and rapid urinary and/or biliary elimination. Based on the results of the reproductive toxicity study, bis-TMPS or its metabolite(s) might be excreted via breast milk.

Bis-TMPS is of low acute oral and dermal toxicity. In rats, the oral LD_{50}-value was 3700 mg/kg bw. The substance caused salivation, diarrhoea and diuresis in all treated animals and a dose dependent decrease in body weight gain. The dermal LD_{50} in rats exceeded 3170 mg/kg bw after 24 hours of exposure. The substance caused some unspecific clinical signs in all animals. Bis-TMPS showed substantial acute inhalation toxicity with an acute inhalation LC_{50} value of 500 mg/m^3 (0.5 mg/L) in rats after a 4-hour exposure. Dyspnoea, salivation, trismus, tremor and sedation were observed in a dose dependent intensity in all treated animals.

Bis-TMPS showed minimal skin irritation in rabbits after 24 hours of exposure in a study lacking details regarding the application procedure of the test substance. Bis-TMPS caused serious eye damage in rabbits in a study conducted equivalent to OECD TG 405.

Based on the available information from two guinea pig studies (a maximization test equivalent to OECD TG 406 and a photosensitizing test), bis-TMPS is not considered to possess skin sensitizing properties.

In all repeated dose oral toxicity studies in rats and dogs, administration of bis-TMPS was associated with decreased body weight gain. In a study similar to OECD TG 407, bis-TMPS was administered to rats via gavage to 10 animals/sex/dose at 0, 50, 200 or 600 mg/kg bw/day for 28-days. A NOAEL for oral toxicity in rats of 50 mg/kg bw/day was derived based on decreased body weight gain and gross pathology (distensions of small intestine in some male and female animals). In a further repeated dose oral toxicity study (similar to OECD TG 408) in Sprague-Dawley rats, bis-TMPS was administered via the diet to 20 animals/sex/dose at 0, 26, 80 or 261 (males) and at 0, 29, 90 or 277 (females) mg/kg bw/day for 90 days. The NOAEL for males was 80 mg/kg bw/day and the LOAEL for females was 29 mg/kg bw/day (lowest dose tested) based on decreased body weight gain. In a repeated dose oral toxicity study (similar to OECD TG 408) in dogs, bis-TMPS was administered via the diet to 4 animals/sex/dose at 0, 27, 69 or 150 (males) and at 0, 27, 78 or 155 (females) mg/kg bw/day for 90-days. A NOAEL of 69-78 mg/kg bw/day was derived based on decreased body weight gain and liver hypertrophy.

In an Ames test (similar to OECD TG 471) with multiple strains of *Salmonella thyphimurium*, bis-TMPS was negative with and without metabolic activation. An *in vitro* chromosomal aberration test following OECD TG 473 with human lymphocytes was negative with and without metabolic activation. Based on these results, bis-TMPS is considered not to be mutagenic/genotoxic *in vitro*.

No data on carcinogenicity were available.

A one-generation reproduction toxicity study following OECD TG 415 was performed with male and female rats (24/sex/dose) at 0, 3, 30 or 300 mg/kg bw/day (gavage). Males were exposed 10 weeks before mating, during mating and up to termination (after delivery of litters). Females were exposed two weeks before mating, during post-coitum and during 20 to 22 days of lactation. Decreased body weight gain and food consumption as well as increased spleen (males only) and uterus weights were observed in parental animals at 300 mg/kg bw/day, thus the NOAEL for parental toxicity was established to be 30 mg/kg bw. The NOAEL for reproductive toxicity (fertility) was derived to be $\geq$ 300 mg/kg bw due to the absence of effects. The NOAEL for developmental toxicity was established at 30 mg/kg bw based on slightly reduced pup weight during lactation, which was not associated with any other developmental adverse effect. Bis-TMPs is not considered to be a specific developmental toxicant since the only finding in pups was marginal decrease in body weight at the end of lactation. This finding is not unexpected since such bodyweight effects were consistently seen in repeated dose toxicity studies.

In *in vitro* toxicodynamic studies, bis-TMPS was shown to block calcium channels and to act as an antagonist at the nicotinic acetylcholine receptors. In an investigational study in rats (5 weeks intraperitoneal), histopathologicial examinations revealed lesions in cardiomyocytes. However, no adverse effects in terms of neuro- or cardiotoxicity could be observed when bis-TMPs was orally applied.

Environment

Bis-TMPS is a white crystalline solid with a melting point of 210°C (calculated) and a vapor pressure of $5x10^{-8}$ Pa (calculated). It decomposes at 425°C. The substance has a solubility in water of 18.8 mg/l at pH 7.5 (measured, 22ºC) and a log Kow of 6.5. Bis-TMPS is predominantly protonated (positively charged) at environmentally relevant pH conditions. With the PALLAS program (v.3.0) pKa values of 9.6 and 10.2 have been calculated. At pH <9 the charged ionic species predominates. A log Kow of 6.5 (KOWWIN v.1.67) and 7.3 (ACD/Labs v.8.14) has been calculated for the neutral species. When considering the pH-dependency of the protonation the octanol/water distribution coefficient of bis-TMPS at 25°C is 3.22, 3.24, and 3.64 for pH 6, 7 and 8 respectively (ACD/Labs v.8.14). However, since the substance occurs as charged species in aqueous media at environmentally relevant pH, all results for physico-chemical properties and environmental fate that were obtained by QSAR modeling have to be regarded with caution because the calculations only consider the uncharged species which predominates only under high pH conditions (pH > 10).

In a modified Sturm test performed according to Directive 84/449/EEC C.5 (not GLP; corresponds to OECD TG 301 B with CO_2-evolution monitoring) bis-TMPS was not readily biodegradable. 10-24% of the test substance was degraded after 28 days. Based on abiotic hydrolysis testing according to the OECD TG 111 (GLP), bis-TMPS is not stable in water and is hydrolyzed, depending on pH conditions to form 2,2',6,6'-tetramethylpiperidin-4-ol (HTMP; CAS 2403-88-5), decan-1,10-dioic acid (CAS 111-20-6) (and the possible intermediary 9-(2,2,6,6-tetramethylpiperidin-4-yloxy)carbonyl nonanoic acid). A half-life of 206 days at pH 4, 57 days at pH 7 and 2 days at pH 9 was determined for bis-TMPS at 25ºC. One of the hydrolysis products of bis-TMPS, 2,2',6,6'-tetramethylpiperidin-4-ol (HTMP) has been evaluated under the OECD HPV Chemicals Programme at SIAM 14 (March 2002). The calculated half-life of bis-TMPS for the reaction with hydroxyl radicals in air is 0.847 hours and the overall OH rate constant is 151.67×10^{-12} cm^3/molecule-sec.

An OECD TG 106 adsorption/desorption study was performed with ^{14}C-labelled bis-TMPS at three concentration levels (4-5, 20-23, and 40-50 mg/L) for seven European soils and one soil-like mature compost. Apparent K'_{oc} (L/kg) values for adsorption were in the range of 800-16000 (log app. K'_{oc} 3-4) which indicates strong binding to soil. It was concluded that not only the organic carbon but also the clay content of the soils determined adsorption. Because significant degradation of bis-TMPS occurred, actual K_{oc} values can be expected to be even higher and the reported K_{oc} values can be considered worst case

with respect to leaching. Desorption occurred maximally for 17%.

No measured data on bioaccumulation is available for bis-TMPS. At environmentally relevant pH conditions the substance is almost completely ionised. A BCF in the range between 17.2 (pH 6) and 45.1 (pH 8) is calculated by using pH-dependent log D_{ow} values of 3.22 and 3.64. Therefore, bis-TMPS is not expected to accumulate in biota.

Based on fugacity modeling (Level I and III) uncharged bis-TMPS will partition primarily into soil and sediment. Surface water is considered to be a minor target compartment for the neutral species and partitioning into air is negligible. However, partitioning into water may be underestimated by fugacity calculations, since the chemical occurs as a protonated cationic species under neutral pH conditions.

Aquatic toxicity testing has resulted in a 96-h LC_{50} in fish (*Oncorhynchus mykiss* and *Lepomis macrochirus*) of 4.3 mg/l (measured concentration), a 24-h EC_{50} in aquatic invertebrates (*Daphnia magna*) of 17 mg/l (nominal concentration), and a 72-h EC_{50} in aquatic plants (*Scenedesmus subspicatus*) of 1.9 mg/l (NOEC = < 1.23 mg/l; nominal concentrations), based on growth rate. A 21-d EC_{50} in aquatic invertebrates (*Daphnia magna*) of 1.31 mg/l (NOEC for reproduction = 0.23 mg/l; measured concentration). The 3-h EC_{50} of bis-TMPS was found to be above 100 mg/l in a 3-hour activated sludge study.

Exposure

The estimation of the global production of bis-TMPS is 11,000 tonnes per year where 6,500 tonnes per year is estimated to be produced in Europe. Bis-TMPS is used to prevent or slow down spontaneous changes in and ageing of polymers; it belongs to the hindered amine light stabilisers (HALS), the most important chemicals used in light stabilisation for polymers. The substance is used in concentrations between 0.1 and 0.5% – depending on the substrate, processing conditions and application – for industrial applications demanding particularly high light stability. Bis-TMPS is incorporated in thermoplastics by extrusion compounding and is not reacted with the polymer but may be degraded partially by photochemical reactions during service life of the product. Compounding with plastics is done in closed systems.

Synthesis of bis-TMPS takes place in dedicated equipment. It is estimated that workers, during production and industrial use, can be exposed, in particular during filling activities, weighing, cleaning and maintenance work. If emission occurs into the workplace atmosphere, appropriate protective equipments are in place (e.g. local exhaust ventilation, gloves, eye protection and protective clothing). From the synthesis process, the substance is obtained in the form of a melt that is transferred in a closed system to a melt granulation tower to yield the test substance shaped as granules. The granulate form of the test substance reduces the possible exposure concentration of inhalable dust significantly compared to powder (particle size < 100 µm: 3-5 %). Therefore exposure of workers is expected to be minimal. Estimated workplace exposure by inhalation of bis-TMPS is 0.01-0.1 mg/m^3 (for granules) and 1-10 mg/m^3 (powder). Consumers may be exposed when they are in contact with the end products. However, as the concentration of the substance is relatively low (maximum 0.5 %) and as the substance is mostly immobilized in the polymer matrix, consumer exposure is regarded as negligible.

Exposure of the environment may occur during production and industrial use of the substance and by leaching waste at landfills. Emission to wastewater from contact of extruded plastics with cooling water and cleaning of equipment at sites of industrial production and use is considered the most relevant route of exposure of the environment. The measured emission factor for crude waste water from production of bis-TMPS is 3.53×10^{-4}. Local emission to wastewater from compounding with polyolefins for a representative scenario has been estimated to be 1.08×10^{-2} kg/day for a production of 50,000 tonnes polyolefin per year. Therefore, exposure of the environment from production and industrial use of bis-TMPS is considered to be very low.

RECOMMENDATIONS 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 (serious eye damage, acute inhalation toxicity and reduced bodyweight gain after repeated exposure and in pups during lactation). However, based on data presented by the Sponsor Country, relating to production by one producer in one OECD country, which accounts for 27% of global production, exposure to humans is anticipated 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, non-ready biodegradability and relatively slow hydrolysis). However, based on data presented by the Sponsor Country, relating to production by one producer in one OECD country, which accounts for 27% of global production, exposure to the environment is considered to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor Country.