SIDS INITIAL ASSESSMENT PROFILE

CAS No.	80-09-1				
Chemical Name	4,4'-Sulfonyldiphenol				
Structural Formula	но- - - - - - - - - - - - - - - - - - -				

SUMMARY CONCLUSION OF THE SIAR

Physical-chemical properties

4,4'-Sulfonyldiphenol is a white crystalline powder. Melting point is 240.5 °C. Boiling point is unmeasurable because the chemical decomposes at around 330 °C. An estimated value of boiling point is 422.5 °C. Density is 1.366 g/cm^3 at 15 °C. Measured value of vapour pressure is $< 3.41 \times 10^{-4}$ Pa at 80 °C, and calculated value is 6.29×10^{-8} Pa at 25 °C. Measured value of water solubility is 770 mg/L at 20 °C. Measured value of partition coefficient between octanol and water (log Kow) is 2.36 at 24.5 °C. Dissociation constant (pKa) of 7.02 at 25 °C shows that 4,4'-sulfonyldiphenol coexists as the neutral species and deprotonated phenolate anion in the aquatic environment.

Human Health

No specific studies are available on the absorption, distribution, metabolism, or excretion of 4,4'-sulfonyldiphenol. According to a 28-day repeat dose oral toxicity test of 4,4'-sulfonyldiphenol in rats, 2 males died in the 1000 mg/kg bw/day group. In pathological examinations, changes were observed in the cecum, liver, thymus, adrenal, spleen, bone marrow and kidney. Those findings suggest oral absorption and distribution to those organs in rats. In general human populations, 4,4'-sulfonyldiphenol (free plus conjugated) was found in 81% of 315 urine samples at concentrations ranging from below the LOQ (i.e.,0.02 ng/mL) to 21.0 ng/mL, with a mean value of 0.654 ng/mL (0.598 µg/g Cre).

Two limit dose studies estimated $LD_{50}s > 2000 \text{ mg/kg-bw}$ (similar to OECD TG 401) and >5000 mg/kg-bw (OECD TG 401), and a standard study estimated an LD_{50} of 2830 mg/kg-bw (OECD TG 401) in rats. Clinical signs included diuresis, salivation, sedation, dyspnoea, lateral and prone positions, decreased body weight gain, bad general condition, exophthalmus, ruffled fur and curved body position.

4,4'-Sulfonyldiphenol was non-irritant to rabbit skin (OECD TG 404) and did not show skin irritation potential in the EpiDermTM skin corrosion/irritation test (OECD TG 431). 4,4'-Sulfonyldiphenol was not irritating to eyes in rabbits (OECD TG 405). 4,4'-Sulfonyldiphenol was not a skin sensitizer in an LLNA with mice (OECD TG 429).

A repeated dose toxicity study was conducted according to the Japanese Guideline (similar to OECD TG 407). 4,4'-Sulfonyldiphenol was administered to male and female rats (6 or 12 animals/sex/dose) at dose levels of 0 (control group: 0.5% carboxylmethyl cellulose solution), 40, 200 and 1000 mg/kg bw/day orally by gavage for 28 days. For the control, 200 and 1000 mg/kg bw/day groups, a 14-day recovery group was provided separately. Two males in the 1000 mg/kg bw/day group died. Females in the 200 mg/kg bw/day group and males and females in the 1000 mg/kg bw/day group showed significantly suppressed body weight gain and food consumption. The hematological examination revealed anemic changes at 1000 mg/kg bw/day in both sexes. In the blood chemistry examination, significant effects were observed as follows: decrease in total cholesterol (both

sexes), an increase in alkaline phosphatase and a decrease in lactate dehydrogenase (males), and increases in total protein, Ca and albumin (females) were observed at 1000 mg/kg bw/day. In urinalysis, significant increases in the incidence of rats with decreased pH and increased protein and urobilinogen were observed at 200 and 1000 mg/kg bw/day in males and/or females. In the histopathological examination, the hypertrophy of centrilobular hepatocytes and atrophy of the thymus were significantly increased at 1000 mg/kg bw/day in both sexes. In the adrenal, hypertrophy of cortical zona fasciculata cells was significantly increased in males at 1000 mg/kg bw/day group. There were significant increases in mucosal hyperplasia and single cell necrosis in mucosal epithelium in the cecum in both sexes at 200 and 1000 mg/kg bw/day groups. In the recovery group, the changes in the kidney (weight of the kidney and urinary protein) and bone marrow (spongy cone) were still observed at 1000 mg/kg bw/day. In the spleen, a significant increase in extramedullary hematopoiesis was observed in the high-dose males at the end of recovery period. Based on suppressed body weight gain and effects in the kidney and cecum at 200 mg/kg bw/day, it was estimated that the NOAEL of 4,4'-sulfonyldiphenol was 40 mg/kg bw/day for both males and females.

Another study was conducted according to the OECD guideline (TG421) under GLP assurances as a preliminary reproduction toxicity screening test. 4,4'-Sulfonyldiphenol was administered by gavage at doses of 0, 10, 60 and 300 mg/kg bw/day to rats (12 animals/group/sex). Male rats were treated from 14 days before mating to the day before necropsy (including the mating period; 45 days in total) and female rats from 14 days before mating to day 3 of lactation (including the mating period, gestation period, and delivery; a total of 40 to 46 days). In the 300 mg/kg bw/day group, both males and females showed significantly suppressed body weight gain and food consumption. The relative weight of the pituitary was increased at 300 mg/kg bw/day. Males showed a significant increase in the relative weight of the liver, and both males and females showed hypertrophy of centrilobular hepatocytes in histopathological examination at 300 mg/kg bw/day. Cecum distension and diffuse hyperplasia of the mucosal epithelium were observed in both sexes of the 60 and 300 mg/kg bw/day groups although not all animals were examined histopathologically. Effects on the cecum were observed at lower doses in this test than in the repeated 28 day study due to the longer dosing period. Based on the effects on the cecum, the NOAEL for repeat dose toxicity is considered to be 10 mg/kg bw/day for both sexes.

4,4'-Sulfonyldiphenol did not induce gene mutation in bacterial reverse mutation tests in *Salmonella typhimurium* TA100, TA1535, TA98,TA1537 and TA1538 and *Escherichia coli* WP2 *uvrA* with or without exogenous metabolic action (OECD TG 471). 4,4'-sulfonyldiphenol was found to be negative in mammalian cell gene mutation tests (OECD TG 476) both with and without S9 mix. The test substance induced structural chromosome aberration of CHL/IU cells and CHO cells without exogenous metabolic activation (OECD TG 473). However, in two *in vivo* micronucleus assays in mice (OECD TG 474), 4,4'-sulfonyldiphenol showed no micronucleus inducibility up to 2000 mg/kg bw (single or twice gavage dose). Based on these results, 4,4'-sulfonyldiphenol is considered to be non genotoxic *in vivo*.

No data were available on the carcinogenicity of 4,4'-sulfonyldiphenol.

One study of reproductive and developmental toxicity was conducted according to the OECD guideline (OECD TG 421). 4,4'-Sulfonyldiphenol was administered by gavage to rats at doses of 0, 10, 60 and 300 mg/kg bw/day. Male rats were treated from 14 days before mating to the day before necropsy (including the mating period; 45 days in total) and female rats from 14 days before mating to day 3 of lactation (including the mating period, gestation period, and delivery; a total of 40 to 46 days). There were significant prolongation of estrous cycle and diestrus period, and a significant decrease in the implantation index at 300 mg/kg bw/day. A decrease in the fertility index was also observed at 300 mg/kg bw/day, although this effect was not statistically significant. In offspring in the 300 mg/kg bw/day group, the total number of offspring delivered, number of live offspring and the number of offspring alive on day 4 of lactation tended to be low, but these effects were considered to be due to decreased implantation index. The NOAEL of reproductive and developmental toxicity is considered to be 60 mg/kg bw/day based on prolongation of estrous cycle and diestrus period, decreased fertility index and decreased implantation index.

4,4'-Sulfonyldiphenol has uterotrophic potency in a *in vivo* uterotrophic assay. The number of in vitro studies indicated that 4,4'-sulfonyldiphenol can activate the estrogen receptor. In addition, significant prolongation of estrous cycle and diestrus period in the reproductive and developmental toxicity study (OECD TG 421)

suggested a potential endocrine mediated effect. According to these *in vivo* and *in vitro* studies, there is an indication that the substance has an endocrine modulating activity.

4,4'-sulfonyldiphenol possesses properties indicating a hazard for human health (repeated-dose toxicity, and reproductive toxicity, (potential endocrine modulating activity)). Adequate screening level data are available to characterize the human health hazard for the purpose of the Cooperative Chemicals Assessment Programme.

Environment

4,4'-Sulfonyldiphenol in the atmosphere is expected to be degraded by hydroxyl radicals. Using AOPWIN (ver. 1.92a), a calculated half-life time of 8.833 hours and a rate constant of 14.5×10^{-12} cm³/molecule-sec are obtained for the indirect photo-oxidation of 4,4'-sulfonyldiphenol by reaction with hydroxyl radicals in air. It is assumed that the concentration of hydroxyl radicals in air is 1.5×10^6 OH/cm³ and that the hydroxyl radicals are available to react with 4,4'-Sulfonyldiphenol for 12 hours/day. The results of the study of the photodegradation of 4,4'-sulfonyldiphenol in aqueous solutions showed that degradation of 4,4'-sulfonyldiphenol occurred under UV light.

A study according to OECD test-guideline 111 showed no hydrolysis of 4,4'-sulfonyldiphenol in water at pH 4, 7 and 9 at 50 °C after five days. 4,4'-Sulfonyldiphenol is not hydrolyzed due to the lack of hydrolysable functional groups.

An OECD test guideline 301C test was conducted with 4,4'-sulfonyldiphenol with activated sludge for four 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 matter. The test result showed 0 % degradation by BOD. According to a research oriented study which is a kind of river-die-away method, the biodegradability of 4,4-sulphonyldiphenol was 0% after 22 days' incubation under aerobic conditions. BIOWIN (ver. 4.10) prediction indicates limited biodegradability of 4,4'-sulfonyldiphenol. According to these results, 4,4'-sulfonyldiphenol is considered to be not readily biodegradable.

In a study performed according to OECD test guideline 305 with carp exposed to 4,4'-sulfonyldiphenol, steadystate bioconcentration factors of ≤ 2.2 and ≤ 0.2 were obtained for the concentration of 50 µg/L and of 500 µg/L respectively for a 6-week exposure period. Using an octanol-water partition coefficient (log K_{ow}) of 2.36, a bioconcentration factor of 16.8 was calculated with BCFBAF (ver. 3.01). This chemical is not expected to bioaccumulative.

Fugacity level III calculations show that 4,4'-sulfonyldiphenol is mainly distributed in soil (83.0 %) and water (16.0 %) compartments if equally and continuously released to the air, soil and water. This is a result for only the neutral species of the chemical which is the dominant species at pH values below 6. At pH 8 and higher, deprotonated charged phenolate anions dominate. A Henry's law constant of 2.73×10^{-10} Pa.m³/mole at 25 °C suggests that 4,4'-sulfonyldiphenol is non-volatile from water. A soil adsorption coefficient of log Koc = 3.26 indicates that 4,4'-sulfonyldiphenol has moderate adsorption potential to soil and sediment.

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

Fish [Oryzias latipes]:	96 h LC ₅₀ >100 mg/L (nominal, semistatic), OECD-TG 203					
Daphnid [Daphnia magna]:	48 h EC ₅₀ = 100 mg/L (nominal, static), OECD-TG 202					
Algae[Pseudokirchneriella subcapitata]:	72 h $\text{ErC}_{50} = 65 \text{ mg/L}$ (nominal, growth rate, static), OECD-TG 201					
	72 h EbC ₅₀ = 16 mg/L (nominal, area method, static), OECD-TG 201					
The following chronic toxicity test results have been determined for aquatic species:						
Daphnid [Daphnia magna]:	21 d LOEC = 8.8 mg/L (measured, semistatic), OECD-TG 211					
	21 d NOEC = 2.7 mg/L (measured, semistatic), OECD-TG 211					

Algae[Pseudokirchneriella subcapitata]:	72 h NOErC = OECD-TG 201	5 mg/L	(nominal,	growth rate,	static),
	72 h NOEbC = 2 OECD-TG 201	.2 mg/L,	(nominal,	area method,	static),

In the human health section, it is mentioned that the substance has a potential endocrine modulating activity. The relevance of this for the environment is unknown.

4,4'-sulfonyldiphenol possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for invertebrate and algae). This chemical is not readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Total amounts of production and import of 4,4'-sulfonyldiphenol in Japan (the sponsor country) were reported to be 4,913, 4,222 and 2,962 tonnes in fiscal years 2005, 2006, 2007, respectively. In the 2010 fiscal year, production and import volumes of 4,4'-sulfonyldiphenol in Japan were reported to be 4,000 tonnes/year according to the notification of annual manufactured and/or imported quantities under the Chemical Substances Control Law. In the United States, the total amount of production and/or import was reported to be 1 - 10 million pounds (454 to 4,540 tonnes) in 2006. Production volume in the world is not available.

4,4'-Sulfonyldiphenol is manufactured by oxidation of 4,4'-thiodiphenol or dehydration reaction with phenol and sulfuric acid.

4,4'-Sulfonyldiphenol is manufactured in a closed system in Japan. Dusts generated during processing are collected by local exhaust ventilation system followed by appropriate treatment as industrial wastes. Therefore, release to the environment from industrial sites is considered to be negligible in Japan.

4,4'-Sulfonyldiphenol is used as an intermediate or used for product modification. 4,4'-Sulfonyldiphenol is reported to be used in thermal paper, such as cash register receipts and in can linings and plastics for food storage. The substance was identified in indoor dust and detected in urine samples from New York and seven Asian countries. In Japan, 4,4'-Sulfonyldiphenol is used as a raw material for vinyl chloride plastic, colour developer for thermal paper, dye fixative. 4,4'-Sulfonyldiphenol is also used as dyeing aid, flame retardant or raw materials for photographic coupler in Japan.

Occupational exposure through inhalation of dust and dermal route is anticipated when a worker handles this chemical directly.

4,4'-Sulfonyldiphenol is used as a raw material for industrial chemicals. On the other hand, 4,4'-sulfonyldiphenol is used in thermal paper, in can linings and plastics for food storage. The substance was identified in indoor dust and detected in urine samples in some countries. Therefore, it is consider that consumer exposure exists.

Note: Further test data for sub-chronic oral toxicity and developmental toxicity for this substance should become available in 2014.