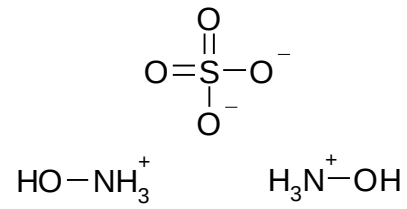
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	10039-54-0
Chemical Name	Bis(hydroxylammonium)sulphate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue rationale

Depending on the pH, bis(hydroxylammonium)sulphate is dissociated into SO_4^{2-} and NH_3^+-OH. Therefore in case of few or missing data read across from hydroxylamine (CAS-No. 7803-49-8) or its hydrochloride (CAS-No. 5470-11-1) has been performed eg. mutagenicity and sensitisation.

Physical-chemical properties

Bis(hydroxylammonium)sulphate (BHAS) is a white crystalline powder (relative density 1.883 at 20°C) which decomposes above 120 °C. The vapour pressure was not determine because of the salt character. The measured partition coefficient (log Kow) is -3.6 (at pH 3.2), and the water solubility is 587,000 mg/L at 20 °C.

Human Health

For bis(hydroxylammonium)sulphate (BHAS) no in vivo data are available on absorption, distribution or excretion, and only few *in vitro* studies exist. Hydroxylamine is formed as an intermediate during cellular metabolism. Hydroxylamine reductase is detected in the mitochondria of livers from mice, rats and pigs. Its activity appears to be age-dependent. An *in vivo* rat study described partial metabolic oxidation of hydroxylamine to nitrate. Absorption via oral and inhalation uptake is expected to be high, because of experimental data Based on physical-chemical data of BHAS, animal data on systemic effects and occupational dermal exposure scenario under non-occlusive conditions, dermal uptake is assumed to be low.

Human data on the acute toxicity of BHAS are not available. In tests with rats, cats and rabbits BHAS caused methaemoglobin formation by the oral and the dermal routes. Respective data after inhalation are not available. Oral LD_{50} values are 545-652 mg/kg bw for rats and appr. 200 mg/kg bw for female cats; dermal LD_{50} values are over 500 mg/kg bw for rats and between 100 mg/kg bw and 500 mg/kg bw for rabbits. In two inhalation studies in rats saturated vapours of BHAS did not cause any toxic effects. After dermal exposure toxicity is significantly higher under occlusive compared to semi-occlusive conditions. A dose of 1 mg/kg bw can be considered as NOAEL for occlusive application of the substance in the rabbit. A dermal NOAEL of 500 mg/kg bw can be derived for semi-occlusive exposure.

Information from non-standard animal data demonstrate moderate to severe irritating and even corrosive properties of BHAS depending on the time of exposure. Brief exposures of 15 minutes to an 80% BHAS solution caused some irritation, and a longer exposure of 20 hours caused more severe reactions. Limited information in humans indicates that concentrations of 1% and above caused skin irritation. Limited information from experimental animals indicates that BHAS is an eye irritant.

Skin sensitising properties of BHAS and hydroxylamine were demonstrated in animal experiments and in humans. Limited information from experimental animals indicates that BHAS is not a respiratory sensitiser.

In a subchronic oral toxicity study similar to OECD TG 408 (no recovery period), groups of 10 male and 10 female rats received BHAS (purity ≥99%) in the drinking water at concentrations of 0, 10, 50, or 250 ppm for 90 consecutive days. The doses administered corresponded to a mean daily BHAS intake of about 0, 0.9, 4 or 21 mg/kg bw/d. Repeated administration of 50 and 250 ppm BHAS (equivalent to about 4 and 21 mg/kg bw/d respectively) to rats via the drinking water for 3 months led to toxicity in male and female rats at both dose levels. In the males and females of the 50 and 250 ppm groups the administration of BHAS led to hemolytic anemia (dose-related) with methaemoglobinemia and to organ weight increases in the spleen and liver together with the specific histopathological findings in the liver and spleen seen as increased hemosiderin deposits in both sexes. The NOAEL for all adverse effects of this rat study was 10 ppm (equivalent to about 0.9 mg/kg bw/d) for both sexes.

In a combined chronic toxicity/carcinogenicity study according to OECD TG 453, BHAS (purity commercial grade) was administered to groups of 50 male and 50 female rats in the drinking water at concentrations of 0, 5, 20 and 80 ppm for 24 months (main groups). In order to define the hematotoxic potential of the test substance, groups of 10 animals per sex and dose were treated for 12 months (satellite groups). In these satellite animals, assays of blood parameters were performed every three months. The doses administered corresponded to a mean daily BHAS intake in the main groups of about 0, 0.2, 1.0, and 3.7 mg/kg bw/d in males and 0, 0.4, 1.6, and 6.2 mg/kg bw/d in females; and in the satellite groups of about 0, 0.3, 1.1, and 4.5 mg/kg bw/d in males and 0, 0.4, 1.6, and 6.2 mg/kg bw/d in females. In conclusion, the prolonged oral administration of 80 ppm BHAS via the drinking water to male and female rats caused hemolytic anemia, characterized by significant reduced counts of erythrocytes, haemoglobin concentrations and hematocrit values, increases in MCV, MCH, and furthermore, increased number of Heinz bodies, Howell-Jolly bodies, and reticulocytes in the peripheral blood. These adverse effects were associated with increases of spleen weights, increased red blood cell regeneration by the bone marrow and increased extramedullary hematopoiesis in the spleen and the liver. At 20 ppm (equivalent to about 1.0 mg/kg bw/d in males and 1.6 mg/kg bw/d in females), hemosiderin storage in the spleen, sign of hemolysis, were significantly increased when compared with controls in male rats after 12 months of treatment and in female rats after 24 months of treatment, respectively. No hematotoxic effects were detected in animals given 5 ppm. Therefore, the NOAEL for systemic effects was 5 ppm, corresponded to a mean daily BHAS intake of about 0.2/0.3 mg/kg bw/d in males and 0.4 mg/kg bw/d in females.

BHAS was negative in a bacterial test in Salmonella typhimurium. In mice, a bone marrow micronucleus test (OECD TG 474) and a screening for dominant lethal mutations were negative. Hydroxylamine and its hydrochloride were mainly negative in bacterial genotoxicity tests; hydroxylamine hydrochloride was weakly positive in mouse lymphoma assays. However, clearly negative results were obtained concerning UDS in rat hepatocytes and chromosomal aberrations in rodent bone marrow cells. Further data were of relatively low reliability or significance. Overall, BHAS has no genotoxic potential.

There are no data in experimental animals available for the inhalation and dermal route of exposure and there are no human data on carcinogenicity. In a standard combined chronic toxicity/carcinogenicity toxicity study according to OECD TG 453 (24 month drinking water study, details see description under repeated dose toxicity). BHAS treatment was associated with an increased incidence of hemangiosarcomas in males treated at ≥ 5 ppm, equivalent to about ≥0.2 mg/kg/bw/d and hemangioma development in females treated at 80 ppm, equivalent to about 6.2 mg/kg bw/d, both in the spleen. Angiomatous hyperplasia in the spleen considered as a precursor lesion of angiomatous tumours (hemangioma, hemangiosarcoma) was observed in animals of both sexes at 80 ppm. The LOAEL was 5 ppm. Although the database for mice is insufficient, the data available did indicate that BHAS may induce spleen tumours as it does in the rat. It was considered that BHAS has no genotoxic potential, and the carcinogenicity observed in experimental animals is mediated via a non-genotoxic mechanisms involving especially erythrotoxicity.

Guideline-compliant generation studies, respectively fertility studies for BHAS are presently not available. Regarding a subchronic oral repeated dose toxicity study with rats no indications for an impairment of male and female reproductive organs could be revealed up to and including the highest tested dose level of about 21 mg/kg bw/d (NOAEL). Data from oral repeated dose toxicity studies in mice and rats showed that in female animals BHAS induced impaired ovarian functional state and morphology and in addition impaired development and morphology of mammary gland tissues. In an oral repeated dose toxicity study with rats a LOAEL of about 67 mg/kg bw/d was determined based on retardation of the development of the mammary gland.

In a guideline compliant prenatal toxicity study (OECD TG 414) in rats groups of 22-24 pregnant rats had been

treated with BHAS at dosages of 1,3,10,and 20 mg/kg bw/d from day 6 to day 15 post coitum. A NOAEL (oral) for embryo-/fetotoxicity of 20 mg/kg bw/d (highest dose) was derived due to the absence of any relevant treatment effects. No human data are available.

Environment

BHAS is a crystalline powder. In the aqueous environment, the salt dissociates completely and rapidly to $[NH_3OH]^+$ and $[SO_4]^{2-}$. Depending on the pH, the hydroxyl-ammonium ion is rapidly converted to hydroxylamine which could be degraded further by abiotic and biotic processes. In the pH range 6 to 9 representative of most aquatic ecosystems, the free hydroxylamine base is very reactive and is expected to decompose further by abiotic processes and nitrification. The expected ultimate degradation products are ammonia, nitrogen and water.

Due to the structure of the substance, degradation by photolytic mechanisms can be excluded.

Normally, distribution of a substance in the environment can be estimated using a Mackay-type model. Since BHAS is an inorganic substance dissociating in water, it is not reliable to estimate the distribution using a Mackay-type model.

The substance does not exhibit any measurable vapour pressure. Taking into account the inorganic character of BHAS and its high solubility in water, a complete distribution to the aqueous compartment can be expected. In the aqueous phase, the substance is expected to dissociate, and hence not volatile. According to these findings, volatilisation from the aqueous phase can be excluded.

Due to the specific properties of the substance it can be expected that the adsorption to organic matter is negligible.

Although the QSARs for adsorption estimation are not valid for inorganic substances, an approximate estimation was carried out using a QSAR for Nonhydrophobics and the measured partition coefficient octanol/water. Using this correlation, a Koc of 0.141 $L.kg^{-1}$ was estimated indicating a very low adsorption to organic matter.

The Log K_{OW} determined experimentally for bis(hydroxylammonium)sulphate is -3.6 indicating no potential for bioaccumulation. No accumulation in organisms and the food chain is expected.

The following acute toxicity test results have been determined for aquatic species (with nominal concentrations):

e.g.,Fish *Pimephales promelas*	96-h LC_{50} = 7.2 mg/L (not reliable)
Invertebrate *Daphnia magna*	48-h EC_{50} = 1.6 mg/L
Algae *Scenedesmus subspicatus*	72-h ErC_{50} = 0.8 mg/L (growth rate method)

The following chronic toxicity test results have been determined:

Daphnia magna	21-d, semi-static,	NOEC = 0.31 mg/L (length); NOEC ≥ 0.62 mg/L (reproduction weight) [mean of the measured concentrations]

The inhibition of oxygen consumption of activated sludge was investigated according to OECD 209. After 3h at a test concentration ≤ 5 mg/L the test substance did not inhibit respiration (EC_{20}, corresponds to NOEC), at 50.4 mg/L 56% inihibition was observed (EC_{50}).

Exposure

BHAS is commercially produced at three sites with an annual production volume of approximately 490,000 tonnes in the EU 15. Worldwide production volume is not available. BHAS is mainly produced by catalytic hydrogenation of nitric oxide.

BHAS is used as intermediate for the production of cyclohexanone oxime or caprolactam (large-scale chemical industry). In addition, bis(hydroxylammonium)sulphate is used in many branches of the chemical industry.

BHAS is an intermediate for the production of pharmaceuticals, e.g. antibiotics and tranquilizers, Intermediate for the production of active ingredient for plant protection products, like insecticides and herbicides, and of sweeteners for the food industry.

In the Photographic industry BHAS is used as a stabilizer for developers, additive in emulsions for colour films (containing 1 – 30 % BHAS).

BHAS is also used in the Rubber industry (accelerator for the vulcanizing of synthetic rubber, antioxidant for natural rubber), for soaps (auxiliary for refining fats for soap production), plastics (regulator and inhibitor in various polymerisations) metallurgy (additive for surface treatment of steel), nuclear industry (auxiliary for separation of uranium and plutonium) and textile industry (auxiliary for specific dyeing processes; fixative for textile dyes).

Monitoring data for effluents are available from two of the production sites in the EU.

Occupational exposure by inhalation or dermal contact is possible but controlled.

Exposure of consumers is assumed to be negligible.

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 (acute toxicity, skin sensitisation, repeated dose toxicity and carcinogenicity). Based on data presented by the sponsor country, exposure is controlled and anticipated low. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

Environment

The chemical is a candidate for further work. The substance has properties indicating a hazard for the environment (aquatic toxicity < 1 mg/l for algae). Member countries are invited to perform an exposure assessment and, if necessary, a risk assessment.

Note: A risk assessment performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is available.