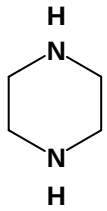
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-85-0
Chemical Name	Piperazine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In pigs, piperazine is readily absorbed from the gastrointestinal tract, and the major part of the resorbed compound is excreted as unchanged piperazine during the first 48 hours. The principal route of excretion of piperazine and its metabolites is via urine, with a minor fraction recovered from faeces (16 %). In humans the kinetics of the uptake and excretion of piperazine and its metabolites with urine appear to be roughly similar to that in the pig, and the nature and extent of conversion to metabolites has not been determined.

Piperazine has demonstrated a low acute toxicity (LD_{50} = 1-5 g/kg bw) by the oral, dermal, and subcutaneous route of administration to rodents, whereas adequate inhalation toxicity data have not been found. However, there are findings of EEG (electroencephalogram) changes in 37 % of 89 children administrated 90-130 mg/kg piperazine (two doses during one day), corroborated by a proposed GABA (γ-aminobutyric acid) receptor agonism exerted by piperazine. Since clinical symptoms of neurotoxicity may occur after exposure to higher doses, a LOAEL of 110 mg/kg piperazine base for acute neurotoxicity in humans after acute exposure is proposed.

Piperazine, as concentrated aqueous solution, has strongly irritating properties with regard to skin, and should be regarded as corrosive with respect to the eye. Exposure to piperazine and it salts has been demonstrated to cause allergic dermatitis as well as respiratory sensitisation in humans. As shown by the LLNA, piperazine has a sensitising potential in animals. Although piperazine is clearly sensitising, no NOAEL can be set for this effect from the present database.

A NOAEL of 25 mg/kg/day of piperazine for liver toxicity in the beagle dog has been chosen after repeated exposure. A LOAEL of 30 mg/kg/day of piperazine for neurotoxicity is proposed based on documentation of (rare cases) of neurotoxicity from human clinical practice. Neurotoxicity also appears in other species (e.g., rabbits, dogs, cats, tigers, and horses), but not in rodents.

For reproductive effects of piperazine, there is a NOAEL of 125 mg/kg/day for effects on fertility, i.e., reduced pregnancy index, decreased number of implantation sites, and decreased litter sizes in rats. The teratogenic properties have been investigated in rats and rabbits in adequate studies. In rabbit, such effects may be elicited at a dose level that is also toxic to the mother animal. The maternal LOAEL is 94 mg/kg/day, and the NOAEL 42 mg/kg/day piperazine base. In the rat study, there were decreases in body weight of both dams and offspring at the top dose (2100 mg/kg/day piperazine base), but there were no signs of any malformations.

The genotoxic properties have been investigated both *in vitro* (in the Ames test, in a non- standard study on

saccharomyces cervisiae and in Chinese hamster ovary cells) and *in vivo*, a micronuclei assay on mice, all with negative results. There are no solid indications of a carcinogenic effect of piperazine, either in animal studies, or from the investigation on humans. In view of lack of genotoxic action, it appears unlikely that piperazine poses a carcinogenic risk.

Environment

Piperazine has a vapour pressure of 44 Pa (at 24.2 °C), the solubility in water is 150 g/l (at 20 °C) and the partition coefficient (n-octanol/water) is log P_{OW} -1,24 (at 25 °C). For calculations in the EUSES the lowest possible log P_{OW} is –1, in the SIMPLETREAT model the lowest possible log P_{OW} is 0, therefore these values are also used.

At neutral pH piperazine is positively charged, it would therefore theoretically bind to soil particles and humus, which are most commonly negatively charged. There is one adsorption study available, resulting in Kd values between 7.9 and 20 mL/g. These results indicate that sorption of piperazine to soil is not correlated to the organic carbon content of the soils. For sewage treatment plants, the distribution was calculated with SIMPLETREAT, resulting in distribution to the water phase.

Piperazine can be assumed to be rapidly photolysed in the atmosphere, the half-life was calculated to be 0.8 hours. In natural water it is considered to be stable towards photolysis. From non-standard studies it can be expected that piperazine is hydrolytically stable under environmentally relevant conditions. Piperazine is not readily biodegradable but can be considered to be inherently degradable.

There is no considerable potential for bioaccumulation, a BCF of < 3.9 for *Cyprinus carpio* is reported.

Short-term effect studies on aquatic organisms are available for algae, aquatic invertebrates and fish. For algae (*Selenastrum capricornutum*) the NOEC (72 h growth inhibition test) is determined to be > 1000 mg/l. For *Daphnia magna* the EC_{50} 48 h is 21 mg/l and for fish (*Poecilia reticulata*) the LC_{50} 96 h is > 1800 mg/l. A long-term study for *Daphnia magna*, which is the most sensitive of the species tested in short term studies, results in a NOEC (21 d semi static reproduction study) of 12.5 mg/l.

Exposure

In 1999, three plants in Europe produced piperazine. The United States and Japan are known to produce piperazine and export to the EU. The tonnage (production + import – export) of piperazine handled within the EU in 1997 was < 5000 tonnes.

Piperazine, as such or as salts, is mainly used as an intermediate in chemical industry including production of pharmaceuticals. Piperazine, as such or as salts, is used also for human and veterinary medicinal drugs, as formulation in gas-washing (scrubbers), and as a catalyst in urethane production.

Releases to the environment can be expected during production, processing and formulation of the substance as such or as salts, and during the use and disposal of products containing piperazine.
Sources of potential human exposure are at workplaces producing or handling piperazine or its salts.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemical possesses properties indicating a hazard for human health. Due to the use pattern of the substance member countries are invited to perform an exposure assessment, and if necessary a risk assessment for human health. Note: A risk assessment performed in the EU in the context of the EU Existing Chemicals Regulation has concluded that there is a need for limiting the risks for workers, especially considering skin and respiratory sensitization, but in some scenarios also due to neurotoxicity and reproductive toxicity.

Environment:

Although this chemical possesses properties indicating a low hazard for the environment, in a risk assessment performed in the EU in the context of the EU Existing Chemicals Regulation, risks were identified at a local level from gas washer processing and other industrial sites. Other countries are invited to perform an exposure assessment, and if necessary a risk assessment for the environment.