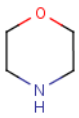
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	110-91-8
Chemical Name	Morpholine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

For human health endpoints, in some cases, the tested substance was a salt or acid of morpholine to avoid damage to the gastrointestinal tract following gavage administration due to the caustic mode of action. Testing the salt or acid also provides the ability to distinguish between symptoms caused by local effects and those that are due to systemic toxicity. Tested substances included morpholine hydrochloride (HCl), CAS No. 10024-89-2 (toxicokinetics and developmental toxicity); morpholine palmitate, CAS No. not available (toxicokinetics); morpholine oleic acid salt, CAS No. 1095-66-5 (MOAS; repeated dose toxicity), and morpholine fatty acid salt, CAS No. not available (mutagenicity). Note that the salts of morpholine used as analogues dissociate upon dissolution so that the tested chemical species *in vivo* is the same as the sponsored chemical. The counter ions are chloride and naturally occuring fatty acid substances and as such are not expected to contribute to the toxicological profile of morpholine.

Physical-chemical Properties

Morpholine is a liquid with a measured melting point of -4.9 °C, a measured boiling point of 128.3 °C at 1013 hPa and a measured vapour pressure of 9.8 hPa at 20.3 °C. The measured octanol-water partition coefficient (log K_{ow}) is -2.55 at 25 °C and pH 7, and the substance is completely miscible in water. The pKa of the protonated form is 8.49 at 25 °C (measured; expressed as the acidity of the conjugate acid).

Human Health

Absorption of morpholine by the dermal, oral and inhalation routes is expected because it has low molecular weight and is both water and lipid soluble. Based on the recovery of morpholine or morpholine salts in urine following inhalation or oral exposure, absorption is expected to be at least 55 or 90%, respectively. Morpholine (information from morpholine HCl) is well distributed following all routes of exposure, with distribution primarily to the kidney, intestine and muscle. The highest concentration is expected to be in the kidney. The major routes of metabolism of morpholine involve various oxidative processes, including N-oxidation and dealkylation followed by deamination and conjugation, and other enzyme-catalyzed reactions leading to detoxification and excretion. However, most of the administered dose is excreted in its non-metabolized form. The primary excretory pathway for morpholine (information from morpholine HCl or morpholine palmitate) is urinary excretion.

Acute inhalation studies are available for morpholine, although discrete LC_{50} values were not determined. There was no mortality in rats exposed to nominal concentrations of 24 mg/L for 4 hours (similar to OECD TG 403). There were signs of irritation, but there were no effects on body weight and no findings at gross necropsy.

There was 100% mortality in rats exposed to vapour concentrations of 21.14 mg/L (nominal) for 5.5 hours or 4.6 - 5.4 mg/L (measured) for 6 hours; 33% mortality was found in rats exposed to 28.8 mg/L (nominal) for 3 hours (similar to OECD TG 403). Clinical signs and findings at gross necropsy were consistent with generally severe local effects of eye and respiratory irritation, respiratory distress and lung damage. A dermal LD_{50} value (rabbit) of 500 mg/kg bw was determined following a 24-hour occluded exposure (similar to OECD TG 402); clinical signs were not reported in this study. Oral LD_{50} values were 1050 - 1900 mg/kg bw in rats (all studies similar to OECD TG 401). Clinical signs reported include breathing abnormalities, oral-nasal wetness and/or staining, effects on gait, postural abnormalities, and eye closure. Site of contact effects (irritation/corrosion) in the gastrointestinal tract were the only findings noted at gross necropsy. Based on the oral toxicity studies, females may be more sensitive than males.

Undiluted morpholine is corrosive to the skin (OECD TG 404) and the eyes (OECD TG 405) of rabbits. Respiratory irritation studies were not available. Signs of respiratory irritation were noted during an acute inhalation toxicity study in rats described above.

Morpholine was not sensitizing in a standard (Buehler) guinea pig sensitization study.

Systemic NOAECs following repeated whole body vapor inhalation exposure of rats to morpholine ranged from 0.543 mg/L (0, 0.036, 0.186 and 0.543 mg/L for 104 weeks; similar to OECD TG 453) to 0.89 mg/L (0, 0.089, 0.36, and 0.89 mg/L for 13 weeks; similar to OECD TG 413), which were the highest concentrations tested in each study. Local NOAECs following repeated inhalation exposure to morpholine ranged from 0.036 mg/L (104 weeks) to 0.36 mg/L (13 weeks). Focal erosion of the nasal turbinates was observed in rats following inhalation exposure to 0.89 mg/L for 13 weeks and necrosis of the nasal turbinates was observed in rats following inhalation exposure to 0.186 mg/L for 104 weeks.

In mice exposed to MOAS in drinking water (~ 0, 140, 200, 400 and 700 mg/kg bw/day) for 91 days, cloudy swelling of the proximal tubules of the kidneys was observed at 700 mg/kg bw/day in drinking water. The NOAEL for oral systemic toxicity for morpholine in mice was 400 mg/kg bw/day.

In mice exposed to MOAS in drinking water (~ 0, 0.4 and 1.5 g/kg bw/day for males; ~ 0, 0.5 and 1.5 g/kg bw/day for females) for 96 weeks, followed by 8 weeks of tap water, reduction in body weight was observed in both sexes given 1.5 g/kg bw/day and in females given 0.5 g/kg bw/day. Water consumption was also decreased in both sexes at 1.5 g/kg bw/day compared to controls consuming tap water. Significant increases in blood-urea nitrogen concentrations were only observed in the 1.5 g/kg bw/day male group. A NOAEL was not identified based on a reduction in body weights in females at 0.5 g/kg bw/day and both sexes at 1.5 g/kg bw/day.

Moderate adiposis of the liver was observed in rats administered 500 mg/kg bw/day morpholine (only dose tested) in the diet for 56 days; this was the established LOAEL.

In rats administered morpholine by gavage (0, 160, 320 and 800 mg/kg bw/day) for 30 days, swelling, congestion, necrosis and/or desquamation of the liver, kidneys, lungs and stomach were observed; the LOAEL was 160 mg/kg bw/day. In guinea pigs administered morpholine by gavage (0, 90, 180 or 450 mg/kg bw/day) for 30 days, clinical signs of toxicity included prostration, sneezing and coughing. Effects on the kidney (cloudy swelling, congestion, necrotic tubules), liver (cloudy swelling, congestion, necrosis and fatty degeneration), spleen and stomach (necrosis) were seen at all treatment levels; the LOAEL was 90 mg/kg bw/day.

Morpholine did not increase reverse mutations in *E. coli* or *S. cerevisiae* or in three studies with *S. typhimurium* (including one study conducted with morpholine fatty acid salt) *in vitro* (all similar to OECD TG 471). However, weak positive results for gene mutations were noted in another study with *S. typhimurium* (Ames test) and in an *in vitro* study of mammalian (mouse lymphoma) cells (similar to OECD TG 476) at high and/or cytotoxic doses. One negative and one positive result were observed in two *in vitro* mammalian (BALB/3T3 mouse) cell transformation assays (EU Method B.21). No increases in the frequency of sister chromatid exchanges (CHO cells; similar to OECD TG 479) or unscheduled DNA synthesis (rat hepatocytes; similar to OECD TG 482) were observed in *in vitro* studies of mammalian cells. Morpholine fatty acid salt did not induce chromosome aberrations in mammalian (CHL cells; no guideline specified) cells *in vitro*. In an *in vivo* study, morpholine did not induce chromosomal aberrations or micronuclei in hamster embryos (no guideline specified). Based on the weight of evidence, with special regard to the equivocal findings of the gene mutation studies conducted at high doses *in vitro*, and the negative results for clastogenicity *in vitro* and *in vivo*,

morpholine is not considered to be genotoxic.

Carcinogenicity studies conducted via the inhalation (similar to OECD TG 453) and oral (no guideline specified) routes of exposure indicate morpholine is not carcinogenic.

A standard toxicity to fertility study was not located. There were no effects of morpholine on the reproductive organs examined in 13-week (exposure concentrations of 0, 0.089, 0.36, and 0.89 mg/L; similar to OECD TG 413) or 104-week (exposure concentrations of 0, 0.036, 0.186 and 0.543 mg/L; similar to OECD TG 453) repeated dose vapour inhalation studies with rats; the NOAEC for effects on reproductive organs was 0.543 mg/L (NOAEC from longest duration study). In a prenatal developmental toxicity study (OECD TG 414), pregnant rats were administered morpholine HCl by oral (gavage) at doses 0, 75, 250 and 750 mg/kg bw/day for gestation day 6 - 19. The maternal NOAEL was 75 mg/kg bw/day based on hematological changes. There were no effects on gestational parameters and fetal examinations revealed no effects on sex distribution of the fetuses, fetal body weights or placenta weights. Fetal findings in this study were primarily limited to skeletal variations (slight increase in delayed ossification) in the mid- and high-dose groups, and are considered to be transient in nature, and secondary to maternal toxicity. These findings were regarded to be of no toxicological relevance and are not considered adverse. The NOAEL for prenatal development toxicity was 750 mg/kg bw/day (highest dose tested).

Morpholine possess properties indicating a hazard for human health (acute toxicity; corrosive to skin, eyes, respiratory tract, and/or the site of contact; repeated-dose toxicity [liver and kidney)]). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Morpholine is considered resistant to hydrolysis because it does not contain labile functional groups; hydrolysis is not expected under environmental conditions. Morpholine is expected to exist in its protonated form at pH 5 - 7. At pH 8 and pH 9 the degree of ionization was estimated at 65% and 15%, respectively, using SPARC v4.2.

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.9 hours ($1.5x10^6$ OH/cm³; 12-h day). Morpholine was considered readily biodegradable, fulfilling the 10-d window criteria, in a biodegradation test according to OECD TG 301E (92.6 % in 22 days) after a lag phase of 15 days. Supporting studies according to OECD TG 302B confirm that morpholine is inherently biodegradable under aerobic conditions when morpholine-degrading organisms are present and after acclimation of these organisms is achieved.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that morpholine will distribute mainly to the soil (57.9%) and water (41.7%) compartments with a negligible amount in the air and sediments compartment. Henry's Law constants of 1.15 x 10^{-2} Pa-m^3/mole for the neutral molecule and 3.60 x 10^{-4} Pa-m^3/mole for cationic morpholine at pH 7.0 suggest that volatilization of morpholine from the water phase is not expected to be high. A K_{oc} of 7.4 for neutral morpholine and a pH-corrected K_{oc} of 76 for the charged molecule at pH 7.0 was estimated; these Koc values suggest that morpholine will be mobile in soils. However, cationic forms of molecules generally bind more strongly to soils that contain organic carbon and clay than the neutral form of morpholine.

Morpholine is not expected to bioaccumulate in the aquatic environment based on measured bioconcentration factors of < 2.8 (0.5 mg/L) and < 0.3 - 0.65 (5 mg/L) in an OECD 305C study.

The following acute toxicity test results have been determined for aquatic species, e.g.:

Fish

Species	**Results (mg/L) (nominal/measured)**
Oryzias latipes	96-h LC_{50} >100 (nominal, verified by measurement)

Invertebrates

Species	**Results (mg/L) (nominal/measured)**

Daphnia magna	48-hr EC_{50} = 45 (nominal, verified by measurement)

Algae

Species	**Results (mg/L) (nominal/measured)**
Pseudokirchneriella subcapitata	72-hr E_rC_{50} = 58, 72-hr E_bC_{50} = 51, 72-hr NOE_rC = 30.9; 72-hr NOE_bC = 30.9 (nominal, verified by measurement)

The following chronic toxicity test results have been determined:

Species	**Result (mg/L)**
Daphnia magna	21-day NOEC (reproduction) = 5, 21-day EC_{50} (reproduction) = 12 (nominal, verified by measurement)

Morpholine possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 10 and 100 mg/L for invertebrates and algae). Morpholine is readily biodegradable and is not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Morpholine is commercially produced with a 2005 production volume of 4536 – 22,680 tonnes in the sponsor country (United States). Morpholine is used in industry as a versatile intermediate for chemical synthesis, e.g. for the production of rubber chemicals, pharmaceuticals, pesticides and optical brighteners. Functionally, morpholine is used as a solvent (which becomes part of product formulation or mixture) in industrial gas manufacturing and in other chemical product and preparation manufacturing.

Furthermore, formulations containing morpholine are used by professionals in many applications e.g. coatings, adhesives, paints, cement/asphalt and lubricants.

In addition, morpholine is used in commercial or consumer soaps and detergents.

The most likely route of human occupational exposure is either via dermal contact or inhalation; morpholine is corrosive and adequate protective equipment is required. In addition, employee health and safety training is recommended to provide employees with an understanding of the potential for skin and eye damage from direct contact.

Consumer exposure can occur through the use of commercial or consumer soaps and detergents.

Environmental releases of morpholine could occur through fugitive air emissions and on-site land disposal.