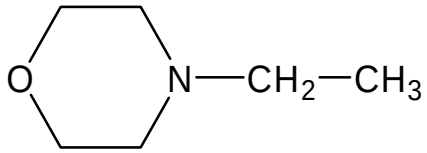
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-74-3
Chemical Name	Morpholine, 4-ethyl-
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information of morpholine, 4-ethyl- on toxicokinetics, metabolism or distribution.

In the acute oral toxicity study [OECD TG401], rats (5 animals/sex/dose) were given morpholine, 4-ethyl- by gavage at 0, 500, 1000, 1500 or 2000 mg/kg bw. Death was observed in three males and two females at 2000 mg/kg bw, one male at 1500 mg/kg bw, and one female at 1000 mg/kg bw. Most of males and females at 1000 mg/kg bw and higher showed tonic and/or clonic convulsions and decreased locomotor activity. The body weight gain of both sexes was suppressed at 1500 mg/kg bw and higher. No abnormalities were found at necropsy in surviving animals, although edema and red area in the glandular stomach were found in the dead animals. The LD_{50} values are considered to be approximately 2000 mg/kg bw in rats. Groups of 6 rats were exposed to atmospheres saturated with this chemical. Strong irritation of the eyes and mucous membranes were observed during exposure, and 5 of the 6 rats died after 30-minutes exposure.

This chemical is an irritant to the eye and respiratory tract in humans, and skin and eye in rabbits. No information is available regarding sensitisation.

In a repeated dose toxicity study [OECD TG407], male and female rats were given this chemical by gavage at 0, 50, 200 or 800 mg/kg bw/day for 28 days. The initial numbers of rats were 10/sex at 0 and 800 mg/kg bw/day, and 5/sex at other doses. Five rats/sex from each group were killed on day 29, and the remaining 5 rats/sex at 0 and 800 mg/kg bw/day were kept without treatment for 14 days (recovery period). No death was observed in any group. Cage-licking and chewing were observed at 200 and 800 mg/kg bw/day in both sexes. The following toxicological changes were noted at 800 mg/kg bw/day with action tremors, decrease in movement, crouching position, eyelid closure, salivation, and suppression of body weight gain accompanied by reduced food consumption were observed in males and females. In urinalysis, increased level of ketone bodies and urobilinogen and decreased specific gravity in females were found. Blood biochemical examinations revealed increased levels of inorganic phosphate and decreased levels of chloride in both sexes, increased levels of calcium and blood urea nitrogen and decreased level of albumin in males, and increased levels of glucose and triglyceride and decreased level of total bilirubin in females. Increases in relative weights of the liver and kidney in both sexes and of brain, adrenal glands and testes in males were observed. Histopathological examinations revealed hypertrophy of the centrilobular hepatocytes and vacuolation of the epithelium in distal and Henle's loop. Based on clinical signs, the LOAEL and NOAEL for repeated dose toxicity are considered to be 200 and 50 mg/kg bw/day, respectively, in male and female rats.

This chemical was not mutagenic at concentrations up to 5000 ug/plate in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2*uvrA* with or without metabolic activation [OECD TG471]. Even at the highest concentration tested (10 mmol/L), there was no effect on growth, polyploidy or the incidence of chromosome aberrations after 6- or 24-hr incubation, with or without metabolic activation [OECD TG473].

No information is available for carcinogenicity.

In a reproductive/developmental toxicity screening study [OECD TG421], rats (13 animals/sex/dose) were given this chemical by gavage at 0, 50, 150 or 500 mg/kg bw/day. Males were dosed for a total of 42 days beginning 14 days before mating. Females were dosed from 14 days before mating to day 3 of lactation throughout the mating and pregnancy period. No death was found in males. One female at 500 mg/kg bw/day died on day 2 of lactation. Tremors were noted in dead females. Salivation was observed in surviving males and females at 150 mg/kg bw/day. Decrease in body weight gain accompanied by a reduced food consumption was detected in males at 500 mg/kg bw/day and females at 150 mg/kg bw/day and higher. No effect on absolute and relative weights of the testes and epididymides was found. Necropsy and histopathological examinations revealed no changes related to this chemical. Histopathological examinations of the testes, epididymides and ovaries revealed no toxicological changes. There were no adverse effects on estrous cyclicity, copulation index, fertility index, precoital interval, gestation length, gestation index or number of corpora lutea. No significant changes were observed in numbers of implantations and pups or live pups, or in indexes for implantation, delivery, birth or live birth. No treatment-related changes in body weight, external appearance or necropsy findings were found in offspring. Based on clinical signs and decreased body weight gain and food consumption, the LOAEL and NOAEL for general toxicity are considered to be 50 mg/kg bw/day in males and females. The NOAEL for reproductive and developmental toxicity is considered to be 500 mg/kg bw/day.

Environment

Morpholine, 4-ethyl- is a transparent and flammable liquid with a slight ammonia-like odour. Water solubility is 303 g/L at 20 °C, a melting point of – 68.4 °C, a boiling point of 138.6 °C at 1013 hPa, a vapour pressure of 1.12 hPa at 25 °C and a relative density of 0.8996 at 20/20 °C are reported. Based on the measured log Kow value of 0.08 (non-ionised form, pH at 11.9) bio- or geoaccumulation of this chemical is unlikely. Environmental distribution using Mackey level III suggests that when morpholine, 4-ethyl- is released into the environment, it distributes mainly into water and soil. A calculated Henry's Law constant of $4.3x10^{-7}$ atm.m^3/mole indicates that only limited volatilisation of morpholine, 4-ethyl- from water may occur. Morpholine, 4-ethyl- is not readily biodegradable and no abiotic degradation is expected. A measured dissociation constant value of 7.57 suggests that some portion of the substance is present as an ionized form in the environment. In the atmosphere morpholine, 4-ethyl- is indirectly photodegraded by reaction with OH radicals with a half-life of 0.1 days.

Eco-toxicity data of this chemical are available in aquatic species. For fish a 96 h LC_{50} of > 100 mg/L (OECD TG 203, *Oryzias latipes*, semi-static), and a 96 h LC_{50} of 280 mg/L (DIN 38412, Part 15, *Leuciscus idus*, static) are available. For daphnids, a 48 h EC_{50} of > 92 mg/L (OECD TG 202, *Daphnia magna*, semi-static) and a 48 h EC50 of > 580 mg/L (DIN 38412, Part 11, *Daphnia magna*, static) were reported. For algae, two reliable test results are available. For *Pseudokirchneriella subcapitata* (OECD TG 201, open system), the (0-72 h) ErC_{50} and the (0-72 h) EbC_{50} were > 53 mg/L and 52 mg/L, respectively. In addition, for *Scenedesmus subspicatus* (DIN 38412, Part 9), a (0-72 h) ErC_{50} of 580 mg/L and a (0-72 h) EbC_{50} of 270 mg/L were reported.

In a chronic study, for daphnids, a 21 d EC_{50} of > 100 mg/L and a 21 d NOEC of 99 mg/L on reproduction were reported (OECD TG 211, *Daphnia magna*, semi-static). For algae, the (0-72 h)

NOECs were 23 mg/L by both growth rate and biomass methods (OECD TG 201, *Pseudokirchneriella subcapitata*, open system).
Regarding the toxicity towards microorganisms of morpholine, 4-ethyl- the EC_{50} for *Pseudomonas putida* was > 1800 mg/L, and the EC50 for activated sludge (OECD TG 209, a limit test) was > 600 mg/L.

Exposure

Morpholine, 4-ethyl- is commercially produced by at least three manufactures in Japan with an annual production volume of approximately 110-115 tonnes (2002-2004). Worldwide production capacity outside Japan is not known. In Japan whole production process is operated in a closed system and all the residual non-reacted raw materials and bi-products are recovered from the reactor tank and applied for re-distillation and/or incineration.
Although no exposure scenario outside Japan is available, it is known that morpholine, 4-ethyl- is used as an intermediate (indirect use) for dyestuffs, pharmaceuticals, rubber accelerators, emulsifying agents and as a solvent (direct use) for dyes and resin oils. In some facilities, morpholine, 4-ethyl- is used to adjust pH values of industrial water which also affects rust preventer.

Under certain use conditions, e.g. pH adjustment and/or solvents, morpholine, 4-ethyl- is expected to be released mainly into the water compartment.

Morpholine, 4-ethyl- is liquid with moderate vapour pressure, occupational exposure through inhalation and dermal route is possible at production sites and user sites. An occupational exposure standard of 5 ppm is adopted in many countries. An OEL for this chemical is not established in Japan. In one production site personal protective equipments are used to prevent exposure. Based on the limited information available, it can be considered that the exposure to workers is not significant in the sponsor country.

The general population may be exposed through dermal contact via industrial water contaminated with morpholine, 4-ethyl-. Another route would be the inhalation of vapour under conditions where morpholine, 4-ethyl- is used as a solvent in certain applications. In addition multiple applications including end use products also suggest that direct exposure to consumers are possible to some extent in the sponsor country.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses a hazard for human health (repeated dose toxicity, irritation). Exposure to general public is expected through dermal contact and inhalation. This chemical is produced in a closed system in a company in Japan, but used to formulate various products. Occupational exposure through inhalation and dermal route is possible in both production and user sites. Therefore, an exposure assessment and, if necessary, risk assessment for workers and consumers are recommended.

Environment: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment (acute toxicity in algae). Although these hazards do not warrant further work as they are related to aquatic acute toxicity which may become evident only at high exposure level, they should nevertheless be noted by chemical safety professionals and users.