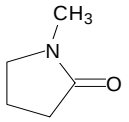
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	872-50-4
Chemical Name	1-methyl-2-pyrrolidone
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1-methyl-2-pyrrolidone (NMP; N-methylpyrrolidone) is rapidly and well absorbed following inhalation (40% - 60%), oral (~100%) and dermal (≤100% depending on conditions) routes of exposure. In rats, NMP is distributed throughout the organism and eliminated after hydroxylation to polar compounds *via* the urine. About 80% of the administered dose is excreted as NMP and NMP metabolites within 24 hours. The major metabolite is 5-hydroxy-*N*-methyl-2-pyrrolidone (5HNMP). Studies in humans show that NMP is rapidly biotransformed to 5HNMP, which is further oxidized to *N*-methylsuccinimide (MSI); this intermediate is further hydroxylated to 2-hydroxy-*N*-methylsuccinimide (2HMSI). The excreted amounts of NMP metabolites in the urine after inhalation or oral intake represented about 100% and 65% of the administered doses, respectively. Excretion of 5HNMP is useful as a biological marker for NMP exposure.

Dermal penetration through human skin has been shown to be very rapid and the absorption rate is in the range of 1 - 2 mg/cm^2/h, which is 2 to 3-fold lower than those observed in the rat. Prolonged exposures to neat NMP was shown to increase the permeability of the skin. Water inhibits dermal absorption while organic solvents (*e.g.*, d-limonene) can increase it. The dermal penetration of 10% NMP in water is 100-fold lower than that of neat NMP, while dilution of NMP with d-limonene can increase the absorption of NMP by as much as 10-fold. The dermal absorption of neat NMP indicated that dermal absorption 1 hour post-exposure was greatest under unoccluded (69%), followed by semi-occluded (57%) and occluded (50%) conditions.

Oral LD_{50} values range from 3605 - 7725 mg/kg bw in rats and mice and dermal LD_{50} values range from 5000 - 7000 mg/kg in rats. Reliable inhalation exposure studies were generally conducted with vapor/aerosol mixtures. The representative LC_{50} was >5.1 mg/l/4h in rats.

NMP is a mild skin and eye irritant in rabbits. In humans, NMP is not irritating to the eyes and upper respiratory tract but is a skin irritant. No valid animal data on skin sensitization exist. Experience at the workplace does not indicate such an effect. In rats, repeated exposure to aerosols under whole body conditions causes severe toxic effects (lethargy, respiratory effects and mortality at high exposures) as a consequence of mixed oral (grooming), dermal and inhalation exposure.

However, after 90-day head-nose aerosol exposures of NMP in rats, only high concentrations caused systemic effects including testicular damage and local respiratory tract irritation. The no observed adverse effect concentration (NOAEC) was 0.5 mg/l. Repeated dermal exposure to rabbits led to mortality at high dose levels without other signs of systemic toxicity. The no observed adverse effect level (NOAEL) was 826 mg/kg bw, while 413 mg/kg bw was the lowest observed adverse effect level (LOAEL) for local irritation. Repeated oral administration did not lead to the identification of a target

organ for systemic toxicity, although systemic effects were observed (decreased body weight, testicular atrophy, thymic atrophy, swelling of distal kidney tubuli). In all species tested, urine discoloration was the only indicator of systemic availability of NMP. In a 4 week feeding study in rats, unspecific signs and adaptive liver effects were observed. The NOAEL was 6000/18000 ppm (429/1548 mg/kg bw, males/females). In a 90-day oral study in rats, the liver and kidney weights were increased and hepatocellular hypertrophy in females was the only histopathological finding. Males exhibited slight and reversible neurological alterations in a few parameters (increase in foot splay, higher incidence in low arousal and slight light palpebral closure) mainly suggestive of a mild sedative effect, which is not considered an indication for specific neurotoxicity. The NOAEL was 3000 ppm for both sexes (169/217 mg/kg bw, males/females). In a 4 week dietary oral study in mice, renal impairment was observed. The NOAEL was 2500 ppm for both sexes (820 mg/kg bw). In a 90-day feeding study in mice, adaptive liver effects in the form of increased weight and histopathological findings were observed. The NOAEL was 1000 ppm (about 229/324 mg/kg bw, males/females). In dogs, no substance-related findings were observed. The NOAEL was the highest dose level tested (250 mg/kg bw).

NMP showed no mutagenic/genotoxic potential in several bacterial and mammalian test systems *in vitro,* covering different genetic endpoints (point mutations, DNA damage and repair). *In vivo* no clastogenic or aneugenic potentials of NMP were reported for somatic or germ cells. NMP showed no oncogenic potential in the rat after long-term exposure *via* inhalation or dietary administration. However, in mice, NMP revealed an oncogenic potential (liver tumors) at very high oral dose levels exceeding 1,000 mg/kg bw.

Two oral reproduction toxicity studies in Sprague-Dawley and Wistar rats caused pup mortality at parental toxic dose levels (350 mg/kg bw and higher). No effects on fertility parameters were noted including histopathological examinations of the male/female reproductive systems. The NOAEL for reproduction was 350 mg/kg bw and the NOAEL for developmental toxicity was 160 mg/kg bw. In an inhalation reproduction toxicity study there was no effect on reproductive performance or fertility to rats exposed to 116 ppm. The NOAEC was 116 ppm for reproductive toxicity and 50 ppm for maternal and developmental toxicity (decreased fetal weight). NMP, but not its metabolites, was embryotoxic (whole embryo culture test) *in vitro* and *in vivo* (oral rat). Several studies addressed prenatal developmental toxicity *via* the inhalation, dermal and oral exposure routes in rats and rabbits. No adverse effects were observed at the highest achievable vapor concentration of 120 ppm. When administered *via* the dermal route, malformations in rats but not rabbits were observed at high dose levels (NOAEL 235 mg/kg bw). Via the oral route, embryotoxicity and malformations were noted with NOAELs of 125 mg/kg bw in rats and 175 mg/kg bw in rabbits in the presence of maternal toxicity. However, the developmental effects are not considered secondary to maternal toxicity.

Environment

The colorless liquid 1-methyl-2-pyrrolidone (NMP) has a melting point of -23.5 °C, a boiling point of 204.1-204.4 °C at 1013 hPa and a vapor pressure of 0.32 hPa at 20 °C. The solubility of NMP in water is 1,000 g/l. The measured log P_{ow} of -0.46 (25 °C) and the calculated BCF of 3.16 do not indicate a potential for bioaccumulation. The estimated Koc is 20.94. The Henry´s law constant of 3.2*10-4 Pa*m³/mol was measured at 20 °C and indicates low volatility from water. The SPARC-calculated pKa of 0.93 indicates that at environmentally relevant conditions, the molecule will occur almost entirely as uncharged species. According to Mackay Level I modeling, NMP will distribute almost completely into water (99.9 %). With Mackay Level III modeling using equal distribution to all compartments, NMP partitions to soil (56.4 %), water (43.2 %) and air (0.4%). NMP is readily biodegradable according to OECD criteria. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-life for a 12-hour day and 1.5E06 OH/cm³: 5.8 hours; for a 24-hour day and 0.5E06 OH/cm³: 17.5 hours). Hydrolysis in water is not expected to occur due to the lack of hydrolyzable functional groups.

Results on acute aquatic toxicity were available for fish (*Oncorhynchus mykiss*; LC_{50} (96 hours) > 500 mg/l, nominal, based on analytical verification), invertebrates (*Daphnia magna*; EC_{50} (24 hours) > 1,000 mg/l, nominal), and algae (*Scenedesmus subspicatus*; EC_{50} (72 hours, nominal) > 500 mg/l). In a chronic toxicity test on reproduction of the water flea *Daphnia magna*, the NOEC (21 days) was 12.5 mg/ l (nominal, based on analytical verification).

Exposure

Large-scale production of NMP is predominantly carried out in a continuous process by reaction of gamma-butyrolactone with methylamine. The annual world production capacity of NMP in 2003 was estimated at 100,000 to 150,000 tons, subdivided into 30,000 – 50,000 tons/year for Europe (3 production sites), 60,000 – 80,000 tons/year for USA (3 production sites), and 10,000 – 20,000 tons/year for Asia/Pacific (4 production sites). During 2005, the European production capacity was reduced to about 20,000 – 30,000 tons. NMP is used as an intermediate and as a solvent by a wide variety of industries such as petrochemical processing, producers of electronics, cleaners, coatings, pharmaceuticals, agricultural and photographic chemicals. Most of the NMP-containing consumer products are household and car cleaning agents, paints, adhesives and sealants, paint removers, and coated fabrics. The NMP content varies from 1 – 100 %.

The Swedish Product Register of 2003 quantifies the total number of registered NMP-containing products with 471, resulting in a total volume of 1,264 tons NMP/a. The total number of consumer products is given with 73. The Danish Product Register of 2004 includes 809 products with a total quantity of 609 tons NMP per year. The Swiss Product Register from 2005 states 2018 registered NMP-containing products for industry and 414 products for consumer use.

Environmental release of NMP occurs from industries such as textile, paper, furniture, printing, chemicals, plastics, and leather. Depending on the industrial leachate site, NMP was found in waste water concentrations ranging from 0.001 to 5 mg/l. Due to the ready biodegradability, NMP is quickly eliminated from water. This is confirmed by measurements of NMP levels in the influent and effluent of the waste water treatment plant of BASF AG (Ludwigshafen, Germany). Results from the year 2000 showed NMP levels in the effluent that were always below the limit of quantification. The elimination was calculated to be > 95 %. During production and internal processing at BASF AG (Ludwigshafen, Germany), 112 kg/a were emitted into the air in 2004. According to the information in the U.S. Environmental Protection Agency (USEPA) Toxics Release Inventory database for 2004, the total reported emissions of NMP were 6,311,272 lbs (2,862 tons). In the United States, NMP is registered as a pesticide inert and exempt from the requirement of tolerance by the USEPA, as described by 40 C.F.R. 180.920. NMP is also regulated by Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) and Section 6607 of the Toxic Chemicals and the Pollution Prevention Act.

Occupational exposure to NMP is most likely via the dermal route of exposure. However, manufacturing and distribution processes utilize closed system engineering practices to eliminate/reduce potential exposure to NMP. In addition, adequate ventilation and chemical-specific personal protective equipment (PPE) is utilized for additional protection. Depending on the type of industry and work place, breathing zone samples showed airborne NMP concentrations in the range 0.01 – 25 ppm with peak concentrations of up to 70 ppm. The American Industrial Hygiene Association (AIHA) has established a Workplace Environmental Exposure Level (WEEL) 8-hr time-weighted average (TWA) of 10 ppm for skin exposure.

In the United States, consumer exposure to NMP may result from the use of products containing NMP. However, NMP use in consumer products in the European Union is under review. In the European Union, NMP is classified as Category 2 for reproductive toxicity (may cause harm to the unborn child). Consumers may be exposed to NMP from tobacco smoke or other NMP emitting sources like floor varnish, sealants and wall paints. Consumer exposure to NMP containing products has been evaluated by the USEPA, and its use as a pesticide inert is regulated. Private and public indoor air sample analyses revealed NMP concentrations of up to 0.3 mg/m^3. In Berlin, Germany, the arithmetic mean of 744 indoor air samples was 0.015 mg/m^3. The median of < 0.002 mg/m^3 indicated that NMP was often not found in indoor air samples above the limit of detection.

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 a hazard for human health (skin/eye/respiratory irritation, repeated dose toxicity and reproductive/developmental effects). Based on data presented by the Sponsor country, adequate

risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: This chemical is currently of low priority for further work because of its low hazard profile.