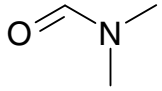
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	68-12-2
Chemical Name	N,N-dimethylformamide
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

N,N-dimethylformamide (DMF) is of low acute toxicity in mammals: LD_{50} rat (oral) 3040 mg/kg bw, LC_{50} rat (inhalative, 4 h) > 5900 mg/m^3, LD_{50} rat (dermal) > 3160 mg/kg bw. Main symptoms following exposure were apathy and staggering (oral) and irregular or intermittent respiration (inhalation). It was irritating to the eyes of rabbits but not irritating to the skin of rabbits and rats.

DMF did not show a sensitizing potential when used as a vehicle in a local lymph node assay. In repeated-dose toxicity studies in rats and mice with chronic exposure over 2 years (rats) or 18 months (mice) and subchronic exposure over 13 weeks by inhalation, or in rats treated by oral administration of DMF (90 day feeding study or administration by gavage for 28 days), the predominant target organ was the liver (NOAEC: chronic inhalation rat: 25 ppm (about 80 mg/m^3), LOAEC: chronic inhalation mouse: 25 ppm (about 80 mg/m^3); NOAEC: subchronic inhalation rat: 100 ppm, mouse: 400 ppm (about 300 mg/m^3 and 1210 mg/m^3 , respectively); NOAEL: rat, 90 days 200 ppm (about 12 mg/kg bw/day), 28 days about 238 mg/kg bw/day). In a 13-week inhalation study with a limited number of Cynomolgus monkeys no treatment-related effects occurred (NOAEC: 500 ppm (about 1500 mg/m^3)).

DMF does not induce chromosome aberrations or gene mutations in various test systems *in vivo* and *in vitro*. In addition, no increased tumor incidence was found in carcinogenicity studies in rats and mice that were exposed to 25, 100 and 400 ppm DMF (about 80, 300, and 1210 mg/m^3) by inhalation for 2 years or 18 months, respectively.

Reproductive toxicity was observed at the presence of some general toxicity in a continuous breeding study in mice, when DMF was administered orally in the drinking water at doses of 1000, 4000 and 7000 ppm (about 219, 820 and 1455 mg/kg bw/day). The maximal tolerated dose for generalized toxicity was 1000 ppm (about 219 mg/kg bw/day) for the F0 and the F1 generation, thus a systemic NOAEL could not be determined. Significant reproductive toxicity (e.g. reduced fertility and fecundity characterized by reduced pregnancy and mating index (the latter one only in the high dose group), reduced number of litters, reduced average litter size and for the F1 parental males by effects on prostate weight and epididymal spermatozoa concentration, the latter finding only in the high dose group) and developmental toxicity (e.g. reduced survival and growth of pups, increase in craniofacial and sternebral malformations) occurred at 4000 ppm and above. At 1000 ppm, reduced pup weights were found in F2 pups. Thus 1000 ppm (about 219 mg/kg bw/day) was the NOAEL for reproductive and developmental toxicity in F0 and F1, and the LOAEL for developmental toxicity in F2.

Developmental toxicity and teratogenicity occurred in rats and rabbits in various studies (inhalation, oral- or dermal

administration) and in mice (oral administration). In rats embryo-/fetotoxicity and teratogenicity were mostly seen at maternally toxic doses, whereas in mice and in rabbits embryo-/fetotoxicity and teratogenicity occurred also at dose levels without maternal toxicity. However, the rabbit appeared to be the most sensitive species to the developmental toxic effects of DMF.

Rabbit: NOAEC (inhalative) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 50 ppm (about 150 mg/m^3); NOAEL (oral, gavage) maternal toxicity and embryo-/fetotoxicity 65 mg/kg bw/day, teratogenicity 44.1 mg/kg bw/day; NOAEL (dermal) maternal toxicity and teratogenicity as well as embryo-/fetotoxicity 200 mg/kg bw/day).

In humans, DMF is absorbed by inhalation and through the skin. After high exposures (up to 60 ppm) headaches, abdominal pain, nausea, vomiting, dizziness, elevated liver enzymes, and alcohol intolerance (facial flashing and palpitations) were seen. Case reports of testicular cancer in aircraft repair and leather tannery facilities failed to be confirmed in further studies. Reports of DNA and chromosomal damage in peripheral lymphocytes of subjects exposed to DMF either failed to take into account smoking as a confounder or coexposure to other chemicals.

With respect to the metabolism of DMF the following conclusion can be drawn: DMF is readily absorbed via all exposure routes. N-hydroxymethyl-N-methylformamide is the main urinary metabolite and to a minor extent, but with greater toxicological relevance the metabolite mono-N-methylformamide (MMF) occurs which may partially be conjugated to glutathione forming S-methylcarbamoylglutathione. The GSH and its sequel adducts (S-methylcarbamoylcystein and the corresponding mercapturic acid S-methylcarbamoyl-N-acetyl-cysteine) seem to be responsible for developmental toxic effects.

At higher doses, DMF inhibits its own metabolism, i.e. the formyloxidation to MMF which precedes the GSH binding.

Persons who repeatedly inhaled DMF excreted the mercapturic acid at levels of ~ 13% of the dose with a total half-life (i.e. DMF biotransformation and excretion) of 23 hours.

Ethanol and probably the metabolite acetaldehyde inhibit the breakdown of DMF and conversely, DMF inhibits the metabolism of ethanol and acetaldehyde. Furthermore, ethanol induces cytochrome P450 2E1 which facilitates the initial hydroxylation of DMF. Thus, exposure to DMF can cause a severe alcohol intolerance.

Environment

N,N-dimethylformamide (DMF) is a colorless liquid, which is miscible with water in all proportions and has a vapour pressure of 3.5 hPa (at 20°C). The log Kow was measured to –0.85 (at 25°C).

Distribution modelling using Mackay Level I indicates water to be the main target compartment for DMF (98.7%). In the atmosphere DMF is indirectly photodegraded by reacting with hydroxyl radicals with $t_{1/2}$ = 2 hours. According to OECD criteria the substance is readily biodegradable. Hydrolysis is not expected under environmental conditions. Bioconcentration factor in fish was measured to 0.3 – 1.2.

In short term tests with fish, daphnids and algae DMF showed an acute toxicity EC/LC50 >100 mg/l. Hence DMF is not regarded as harmful to aquatic organisms. In the following the lowest valid EC/LC50 data of different aquatic species are summarized:

Lepomis macrochirus: LC50(96h) = 7100 mg/l
Daphnia magna: EC50(48h) > 100 mg/l; EC50(48h) = 15700 mg/l
Scenedesmus subspicatus: EC10 and EC50(96h) > 1000 mg/l (biomass and growth rate).

Long term reproduction studies with *Daphnia magna* resulted in NOECs of 1140 mg/l (28 days) and 1500 mg/l (21 d).

Applying an assessment factor of 50 on the lowest available NOEC of 1140 mg/l a $PNEC_{aqua}$ = 22.8 mg/l can be

derived according to the EU risk assessment procedure.

Exposure

In Germany 50,000 to 100,000 t DMF were produced in 2000 at BASF AG, Ludwigshafen. Further producers are located in Belgium, Korea, Japan, Spain and USA. The total production volume in the EU (including Germany) is in the range of 50,000 to 100,000 t/a. In Asia, the production volume is 100,000 to 500,000 tonnes per year and in North America it is 50,000 to 100,000 tonnes per year. DMF is predominately used as a solvent in synthesis of fine chemicals, in polyacrylonitrile fibre production, polyurethane coating and in the electronics industry. The remaining is split into various applications like varnishing, surface coating, polyamide coating, absorbents, cleaners and extractants. In addition, DMF is also used as a solvent in crop protection agents.

Releases into the environment may occur during production of DMF and during its use as solvent or cleaning agent. In 1991 the maximum annual release of DMF into the hydrosphere from production and processing in pre-unification Germany was estimated to 352 t. Approximately 9000 t/a were emitted into the atmosphere. More recent data about environmental releases are not available. Releases into the terrestrial compartment may occur from use of DMF as solvent in plant protection products. However, this release is not quantifiable.

Product register information indicates that there are several products that contain the substance in significant amounts (up to 100 %). The product types are solvents, intermediates, paints, lacquers and varnishes. Among the products there are some products for private use. Therefore consumer and occupational exposure can not be excluded. Exposure to workers during production is well controlled in the industry of the sponsor country (Germany).

NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. In occupational settings where exposure is not controlled and, due to information of European product registers, exposure to consumers and workers cannot be excluded. As the extent of exposure cannot be estimated and the substance is a developmental toxicant, a human exposure and if then indicated a risk assessment should be performed.

Environment: Concerning the aquatic compartment, DMF is of low concern due to the low toxicity to aquatic organisms, the low bioaccumulation potential and the classification as readily biodegradable. However, high releases of DMF into the atmosphere are described in the BUA report from 1991. Although the substance has a half-life in the atmosphere of 2 hours, these very high emissions may pose a local problem in the vicinity of point sources. In addition releases into the soil result from the use of the substance in plant protection products. Therefore, exposure data gathering should be performed. Depending on the exposure information further information on toxicity to terrestrial organisms may be required, for example a plant fumigation test.