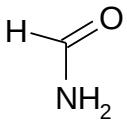
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	75-12-7
Chemical Name	Formamide
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Toxicokinetic and other toxicity studies show that formamide is readily absorbed after inhalation, oral and dermal application. Maximum plasma levels are reached within 1 – 2 hours in rats and mice. Elimination half-live from plasma is approx. 15 hours in rats and only 4 - 6 hours in mice. Approx. 30% of the dose is excreted unchanged in urine within 72 hours, a high fraction is excreted as CO_2 (rats about 30%, mice about 50%), and only minor quantities are excreted with the feces (1 – 3%). Protein binding increased with time in both species. The metabolism depended on the activity of microsomal enzymes, specifically CYP2E1, and in analogy to methylformamide it was proposed that formamide is oxidized to isocyanic acid, which reacts with nucleophils and decomposes in the presence of water to ammonia and CO_2. The formation of carbon monoxide during metabolism is unlikely. Toxicokinetic studies indicate presence of a first pass effect.

No signs of toxicity and mortality were noted in a rat Inhalation Hazard Test (8 hours, saturated atmosphere, 20°C). Clinical signs of toxicity (escape reaction, irritation of mucous membranes, dyspnea, apathy, and loss of weight) and mortality (one of 12 exposed rats) were seen after an 8-hour exposure when the saturated formamide atmosphere was generated at 150°C. Clinical signs were also seen in all rat groups when very high test substance concentrations were generated either at elevated temperature (100 to 210°C) or using a nebulizer (body weight losses, lethargy, hunched posture, clear or red ocular discharges, red nasal discharge, partially closed eyes, diarrhea, and brown-stained perineum). The inhalation LC_{50} is > 21 mg/L (4 hr, in the atmosphere generated using an evaporator heated to 100-210°C). The acute dermal LD_{50} in rats is estimated to be > 3000 mg/kg bw, based on two independent OECD TG 411 90-day repeated dose rat studies. Mortalities were 1/20 and 3/20, respectively, in the groups receiving 3000 mg/kg bw/day. The oral rat LD_{50} was approx. 5325 mg/kg bw in a pre-guideline study that was conducted similar to the method described in OECD TG 401; a LD_{50} of 3200 mg/kg bw was calculated in a less robust acute oral rat study.

There is no valid skin irritation study. Formamide was slightly irritating to the rabbit's eye in a test performed corresponding to OECD TG 405. The effects were described as reversible. No valid sensitization study is known to exist.

In a 4-week oral gavage rat study similar to OECD TG 407 male and female rats received 34, 113, 340, and 1130 mg/kg bw/day. No effects were noted at the lowest dose level, whereas 340 and 1130 mg/kg bw/day caused 50% and 100% mortality, respectively. Animals at 113 mg/kg bw/day and higher showed loss of appetite, extreme body weight loss (7 – 11% at 113 mg/kg bw/day and 44 - 51% at 340 mg/kg bw/day), and failure of reflexes. Along with prostration, general organ atrophy and tissue damage (especially of the gastrointestinal tract, testes, adrenal gland and kidney) was noted. Changes in hematological parameters were also observed at 113 mg/kg bw/d. Most of these effects were reversible as the effects were less

frequent and almost completely absent in the 14-day recovery group at 113 mg/kg bw/day. Histopathological findings were prominent at the dose of 340 mg/kg bw/day and above where a poor state of nutrition combined with general organ atrophy, gastric ulcerations, intestinal hyperemia, indication of lipid depletion of the adrenal glands including necrotic areas in the cortex and dilation of blood vessels, renal changes, fibrosis of spleen and thymus, and testes degeneration. The NOAEL was 34 mg/kg bw/day; the LOAEL was 113 mg/kg bw/day.

In a 14 day rat inhalation study (similar to OECD TG 412; measured concentrations 0, 190, 930, and 2800 mg/m^3, the high dose caused 30% mortality, significantly decreased body weight and body weight gain, and clinical signs of toxicity, weakness and hunched posture. No signs of toxicity or mortality were seen in the other dose groups. Hematology revealed mild thrombocytopenia in the mid and high dose group both during exposure and during recovery, and lymphopenia and hypocholesterolemia in the high dose group. Histopathology showed degeneration/ necrosis of the kidney and testicular degeneration in high dose rats. Based on the hematological findings the NOAEC was set at 190 mg/m^3; the LOAEC was 930 mg/m^3.

Two 90-day dermal rat studies were available. In the first study (OECD TG 411; applications of 0, 300, 1000, and 3000 mg/kg bw/day) hematological changes in all exposed groups (increased erythrocyte counts and hemoglobin) prevented to derive a NOAEL. Clinical signs (erythema, reduced general condition, apathy, reduced food consumption, decreased body weight) and pathological findings (decreased absolute weights of liver, kidney, spleen, adrenal glands and testes; increased relative weights of liver and kidneys) and an increased incidence of bilateral testicular tubular atrophy were limited to the high dose level. A follow-up study was conducted at lower dose levels (0, 30, 100, 3000 mg/kg bw/day). No substance related effect was seen in the groups at 30 and 100 mg/kg bw/day. Therefore, the NOAEL was 100 mg/kg bw/day based on the described adverse effects at higher doses.

Formamide was not mutagenic in bacterial mutation assays (*S. typhimurium* TA97, TA 98, TA 100, TA1535, and TA1537); *E.*coli WPuvrA both with and without metabolic activation up to 10000 µg/plate. Formamide did not induce micronuclei in the peripheral blood of male and female mice after oral doses of up to 160 mg/kg bw for 3 months, however, gave positive results in a Micronucleus Test using mouse bone marrow (OECD TG 474) following intraperitoneal dosing with 900 mg/kg bw or more. Formamide at 412 mg/kg bw was negative in a Dominant Lethal assay using male mice (OECD TG 478). In conclusion; formamide was not mutagenic in vitro, but showed clastogenicity in vivo at least at higher doses after intraperitoneal injection.

There are different results from in vitro cell transformation assays. Formamide was negative in a cell transformation assay using rat embryo cells at test concentrations of 0.01 to 100 µg/ml whereas a statistically significant and dose-related increase in the number of transformed colonies was obtained with Syrian hamster embryo cells which were exposed to formamide in the range 200 to 550 µg/ml without metabolic activation.

Oral gavage rat and mouse carcinogenicity studies, using formamide at 0, 20, 40, or 80 mg/kg bw, 5 days per week for 105 weeks and following OECD TG 451 under GLP, gave no evidence of a carcinogenic potential in male or female F344/N rats. There was clear evidence of carcinogenic activity of formamide in male B6C3F1 mice based on increased incidences of hemangiosarcoma of the liver. There was equivocal evidence of carcinogenic activity of formamide in female B6C3F1 mice based on increased incidences of hepatocellular adenoma or carcinoma (combined). Mineralization of the testicular arteries and tunic and hematopoietic cell proliferation of the spleen in male mice were also associated with administration of formamide.

In a continuous breeding study in mice with the substance in drinking water at concentrations of 0, 100, 350, and 750 ppm reproductive toxicity was observed at 750 ppm in drinking water (144-226 mg/kg bw/day) in the parental and offspring generation, mainly decrease in fertility rate and reduction in live litter size. In a crossover experiment, this was shown to be mainly due to impairment of reproduction in females. At 750 ppm (approx. 210 mg/kg bw/day) a prolongation of the time to litter from 22 to 26 days was seen. The estrous cycle of F1 mice at 750 ppm was extended (6.5 vs. 4.8 days in controls), and the high-dose group tended to be in estrous for a shorter time than controls, and to be longer in diestrous. At necropsy, histopathological examinations revealed no treatment related effect on the non-reproductive tissues. In the reproductive tissues a significant increase in relative corpus and caput epididymis and testis weight was

noted, and a decrease in relative seminal vesicle weight at the high dose level. The evaluation of sperm parameters (sperm concentration, motility, morphology, spermatid head count) revealed no treatment-related changes. The absolute and relative ovarian weight was reduced at the mid- and high-dose level. The NOAEL for generalized toxicity was 144 to 226 mg/kg bw/day for the F0 generation. The NOAEL for reproductive toxicity was 48-110 mg/kg bw/day for both generations.

Formamide was found to be embryotoxic and teratogenic in several guideline conform oral gavage studies using rabbits, rats, and mice. The NOAEL values for maternal toxicity, embryo toxicity, and teratogenicity were 70, 70, and 140 mg/kg bw/day, respectively, in a recent rabbit study. In rats NOAELs ranged from 100-529 mg/kg bw/d for maternal toxicity, 50-529 mg/kg bw/d for embryo/fetotoxicity and 177 mg/kg bw/d or above for malformations. In mice treated during gestation, embryotoxicity and teratogenicity was seen in the absence of maternal toxicity. The NOAELs were 198 mg/kg bw/day for maternal toxicity and 133 mg/kg bw/day for embryotoxicity and teratogenicity. Mechanistic studies identified susceptible stages during gestation in both rats and mice.

Environment

The colorless to yellowish liquid formamide is slightly viscous, odorless, and hygroscopic. It has a nearly unlimited solubility in water (1000 g/l at 25°C) and a vapor pressure of 0.08 hPa at 20°C. The measured log K_{OW} of -0.82 (25°C) and the calculated BCF of 3.16 do not indicate a potential for bioaccumulation. At 25°C, the estimated Koc is 8.5 and the Henry's Law Constant was calculated to be 0.0016 Pa*m^3/mol. According to Mackay Level I, formamide will distribute almost completely into water (99.99%). Formamide is readily biodegradable according to OECD criteria. In the atmosphere, it will be photodegraded by reactions with OH radicals (calculated half-lives: 8.0 days for a 24 hour day with 5.0E05 OH/m^3 and 5.4 days for a 12-hour day with 1.5E06 OH/m^3).

The rate constant (k) for reaction with photochemically-produced OH radicals in water was measured to be 5.0E+08 l/mol*sec at pH 5.5. Based on best and worst case conditions of OH-radical concentrations in water as measured in a natural lake in Switzerland, half-lives of 64.2 days and 14.7 years, respectively, can be calculated for the aquatic photolysis. Hydrolysis is expected to be slow at neutral conditions. A water rate constant (kw) of 1.1E-10 s^{-1} ($t_{1/2}$ = 199 years) at 25°C was estimated. Acidic and basic conditions as well as elevated temperatures accelerate the hydrolysis. The pKa of -0.48 at 20 °C indicates that at environmentally relevant pH of 6 – 9 the molecule will be present as uncharged species.

Results on acute aquatic toxicity are available for fish (*Leuciscus idus*; 96-h LC_{50}: 6569 mg/l), invertebrates (*Daphnia magna*; 48-h EC_{50}: > 500 mg/l), and algae (*Scenedesmus subspicatus*; renamed to *Desmodesmus subspicatus* 96-h E_rC_{50}: > 500 mg/l). Based on the acute toxicity studies, formamide is considered of low acute toxicity to aquatic organisms. In a test with embryos of *Danio rerio* a 96-h LC_{50} of 9135 mg/l and a 96-h NOEC of 1080 mg/l was determined. Effect concentrations are based on nominal values because none of the tests was supported by analytical monitoring. According to the EU risk assessment procedure, a PNECaqua of 0.50 mg/l was obtained by applying an assessment factor of 1000 on the lowest endpoint.

Ion leakage resulting from membrane damage due to formamide exposure was examined in the aquatic plant *Lemna minor* and in the algae *Desmodesmus subspicatus*. The 24-h EC_{50} was 81.2 mg/l for *Lemna minor* and > 2000 mg/l for *Desmodesmus subspicatus*.

The pooled 96-h LC_{50}/EC_{50} values for mortality and malformation in the embryos of the South African clawed frog *Xenopus laevis* corresponded to 11400 mg/l and 12800 mg/l, respectively. Multiple malformations like cephalic abnormalities, ocular abnormalities, gut abnormalities, and reduction or lack of pigmentation at exposure concentration ≥ 5870 mg/l were observed. Abnormal swimming behavior was observed at concentrations > 5870 mg/l, growth retardation (reduced length) was observed at concentrations ≥ 8500 mg/l.

In a 30 min respiration inhibition test with activated sludge from a laboratory waste water plant treating municipal sewage a 30-min EC_{50} of > 1000 mg/l was determined. In a 17-h cell growth inhibition test with *Pseudomonas putida* the 17-h EC_{50} was > 10000 mg/l.

The nitrogen fixation of *Azotobacter* sp. was reduced by 75 - 100% after 21 days of incubation with

500 mg/l formamide.

Exposure

In the sponsor country formamide is manufactured in a two stage process in which carbon monoxide and methanol are reacted in the presence of catalytic sodium methoxide to form methyl formate, which is then reacted with ammonia to yield formamide.

The annual world production capacity in 2004 for formamide was estimated at 70,000 - 110,000 tons, subdivided into 50,000 - 80,000 for the sponsor country, 60,000 - 90,000 tons for Europe, 10,000 - 20,000 tons for Asia/Pacific.

In the sponsor country most of the produced formamide is internally converted to hydrogen cyanide (captive use approx. 80%). In addition formamide is used as a starting material in the synthesis of agrichemical and pharmaceutical products and as a solvent in the manufacture of synthetic leather in China.

Formamide is generally known to be used as an intermediate in the chemical industry to produce heterocyclic compounds, copolymers, pharmaceuticals, and crop protection agents such as fungicides as well as many other chemicals. Further, it is applied as softener in the production of pastes and paper and has a wide range of solvent applications. Formamide can also be used as an additive in lube oil or hydraulic fluid, as a component of deicing fluids for airport runways, a curing agent for epoxy resins, a plasticizer, an affinity enhancer for dyes, and a component of liquid fertilizers.

Some of the above mentioned applications have, however, already been published a couple of years ago and may not be representative of, or comparable to, current conditions. In the European Union formamide is classified as toxic to reproduction Cat 2 (may cause harm to the unborn child). As a consequence formamide or preparations containing it in concentrations equal or higher than 0.5% may not be placed on the EU market for sale to the general public.

The Swiss Product Register of 2001 has listed two formamide-containing products, both for industrial usage. According to the SPIN database extract for 2004, 8 preparations with a total volume of 2.0 tons are registered in Denmark and 3 preparations in Sweden with a total volume < 0.1 tons. Finland reported that formamide preparations are registered in the national industrial use categories. Consumer preparations containing formamide are not mentioned in the database.

At the production sites it is technically ensured that exposure of workers to formamide is minimized. Significant exposure is normally not expected during production, transportation, and sampling, because these processes are largely enclosed. Occupational exposure is limited to situations of maintenance and accidental spills. Due to the low vapor pressure of formamide, the potential for inhalation exposure is minimized, with dermal exposure to be the most likely route.

Between 01 Jan 2003 and 31 Dec 2005, 31 workplace measurements have been carried out by personal air sampling at BASF AG in Ludwigshafen/Germany. Twenty-five of the 31 measurements were time-weighted averages of 8-hour work shifts. The measurements took place at six locations for production, processing, bottling, shipping, storing and chemical analysis of formamide. All measured values were below the limit of quantification. A significant worker exposure due to inhalation could therefore not be demonstrated.

Natural occurrence of formamide is not known. It may be emitted to the environment as a result of its manufacture and use as an intermediate and solvent. For example, formamide was detected at 2.0 mg/l in condensate retort water of an oil-shale retort, but was not detected in the process retort water. It was also detected in wastewater from a polyamide production plant as well as in the waste streams from an acrylonitrile plant as a result of a detoxification process for cyanide-containing wastewaters. Formamide may also be detected in waste streams due to chemical hydrolysis of cyanide.

According to the data reported to the German Emission Register 2004, during production and processing at BASF AG in Ludwigshafen/Germany less than 1 kg of formamide was emitted to air in 2004. Data regarding emission via wastewater treatment effluent are not available from BASF AG production and

processing sites.

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 properties indicating a hazard for human health (genotoxicity, carcinogenicity, toxicity to reproduction and developmental toxicity). Based on data presented by the sponsor country (related to production by one producer in the sponsor country), exposure to humans is anticipated to be low and adequate risk management measures are in place. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

Environment: The chemical is currently of low priority for further work. The chemical has a low hazard profile.