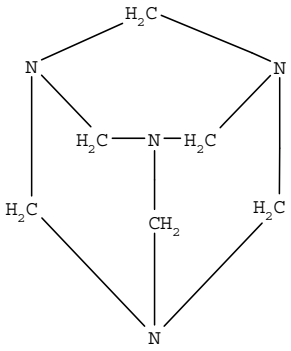
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-97-0
Chemical Name	Methenamine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Methenamine is rapidly absorbed and excreted (90% of the dose within 12 h) after oral uptake in man. The mean half-life in blood was reported as 4.3 h. Methenamine can pass the placenta and is detectable in breast milk of lactating women; however, no accumulation was seen. Toxicokinetic data were not available for dermal administration or inhalation exposure of methenamine.

Formaldehyde is formed via hydrolytic cleavage of methenamine at acidic pH values, thus formaldehyde formation occurs after oral administration at the acidic pH of the stomach. However, formaldehyde can be absorbed into the bloodstream, where it is converted to formic acid very rapidly. The half-life of formic acid is reported to be 90 min. It can be excreted through the kidneys or be further oxidised to carbon dioxide and water.

In limited studies, acute toxicity of methenamine in rats has been demonstrated by oral and dermal application (acc. to OECD TG 402) with LD_{50} values of > 20 g/kg bw and >2 g/kg bw, respectively. Data on acute inhalation toxicity are not available. Limited data on the acute toxicity of methenamine in humans show an acute dermatitis of the exposed surfaces as the main symptom.

Methenamine does not exhibit local irritation by contact with skin and eyes of rabbits under the conditions of tests according to OECD TGs 404 and 405. However, acute dermal exposure in humans causes local irritancy.

Guinea pigs exhibited strong skin sensitization in a maximization test according OECD TG 406. The substance does not clearly demonstrate skin sensitizing properties in humans. In a number of human cases, allergic symptoms such as wheezing and asthma were reported upon exposure to methenamine. However, in all cases simultaneous exposure occurred to other irritant and sensitizing chemicals. The respiratory hypersensitivity could not be specifically related to methenamine exposure.

In several early long-term studies with repeated application to rats and mice, no specific organ toxicity was recorded after oral administration of methenamine (gavage, feeding, or drinking water) up to doses of and including 2.5 g/kg bw/d. All in-life parameters, which included body weight gain, food consumption, and survival, were unaffected by exposure to methenamine. Similarly, post-mortem analyses, which included organ weights, gross pathology and histopathology, were unchanged. The systemic NOAEL values for methenamine derived in several experimental animal species for different durations ranged between 60-2500 mg/kg bw/d.

There are a number of studies on health of workers in the steel foundry, tire and rubber industry repeatedly exposed

to methenamine. Due to deficiencies in conducting, reporting, inadequate methenamine exposure data and/or mixed exposure to other chemicals, the effects could not be attributed clearly to methenamine. No complications were observed in patients receiving methenamine or its salts as a urinary antibacterial-antiseptic at dose levels of 2 to 4 g/d for weeks (corresponding to a NOAEL of 57 mg/kg bw/d). A higher therapeutic dose of 8 g/d (114 mg/kg bw/d) for 3 to 4 weeks produced bladder irritation, painful and frequent micturition, albuminuria and hematuria.

Methenamine was weakly positive in bacterial gene mutation assays at extremely high concentrations (10000µg/plate) and in an *in vitro* chromosomal aberration assay. The negative *in vivo* chromosomal aberration tests (2000/32/EC, B.11) and the negative dominant lethal test (87/302/EEC, part B) indicate that methenamine is unlikely to be genotoxic *in vivo*.

The carcinogenic potential of methenamine has been investigated in a number of old long-term/lifetime studies in a variety of strains of rats and mice, using the oral route. There was no indication of carcinogenic effects in rats and mice following prolonged exposure to high dosages up to and including 2.5 g/kg bw/d methenamine.

Results from retrospective and prospective epidemiology studies on workers in the steel foundry, tire and rubber industry did not show clearly the presence of a carcinogenic activity of methenamine in humans. The observed excess risks of skin, lung and bladder cancer reported in these studies could not be conclusively attributed to the exposure of methenamine because workers had also been exposed simultaneously to other chemicals. With respect to the extensive use of methenamine as a drug, there is no evidence for the formation of tumours in the urinary tract in humans.

In non-guideline fertility studies in Wistar rats administered high doses of methenamine in drinking water (1.5 - 2 g/kg bw/d for males and 2 - 2.5 g/kg bw/d for females), no adverse effects on fertility were observed. The dose of 1000 mg/kg bw/d is considered as the NOAEL for fertility.

In limited studies, methenamine induces developmental toxicity in experimental animals. In rats (at high gavage dosage of 1000 mg/kg bw/d) and in beagle dogs (30 mg/kg bw/d), effects were observed during the postnatal period of development in terms of pre-weaning mortality and postnatal growth retardation.

Human data on potentially adverse effects to development are available from investigations on women that had been treated with methenamine salts during pregnancy. No indications for a specific impairment of pregnancy outcome or of the development of the children were observed at therapeutic doses of 2 g methenamine hippurate or 4 g methenamine mandelate per day (corresponding to about 13 or 27 mg methenamine/kg bw/d, respectively).

Environment

At 20°C, methenamine is a white crystalline powder with a density of 1.33 g/cm^3. At 230°C, the substance starts to sublime, and the melting temperature is > 270°C. The vapour pressure is 0.05 Pa at 20°C. The Henry's Law Constant was calculated to be 1.051×10^{-5} Pa m^3 mol^{-1}. With a solubility of 667 g/l (25°C) the substance is highly soluble in water which is also the target compartment in the environment. The n-octanol water partition coefficient (log Kow) was calculated as -4.15 indicating a low bioaccumulation potential.

The information on environmental fate and behaviour indicates no tendency to volatilize into air or to be distributed into sediment. The target compartment is the water-phase of aqueous systems. Once released into air, methenamine will degrade rapidly by photo-oxidation. The half life estimated using the different models was 30 – 45 minutes. In water, methenamine is degraded hydrolytically to ammonium and formaldehyde, which is further degraded biologically (ready biodegradable). The extent of hydrolysis is dependent on the pH of the medium. At acidic pH-levels degradation within a few hours could be expected. At neutral and basic pH-levels the half life might increase to several days. In the studies on biological degradation, between 28% and > 100% was degraded. This can be explained by hydrolysis of methenamine to ammonia and formaldehyde followed by complete biological degradation.

The available ecotoxicological studies indicate that methenamine is non-toxic for aquatic organisms following short term exposure (tests performed at pH>7 ==> hydrolysis of methenamine was minimised). In a test on inhibition of microbial nitrification, no effects could be observed up to 100 mg/l. Using *Lepomis macrochirus,* a LC_{50} (96 h) of 41 g/l, and using *Pimephales promelas* a LC_{50} (96h) of 49.8 g/l were determined. The EC_{50} (48 h) for *Daphnia magna* was 36 g/l and for the crustacean *Nitrocra spinipes,* the LC_{50} (96 h) was 92.5 g/l. A 14 day algae test with *Selenastrum capricornutum* (formally not valid, but reliable) was used to estimate an ErC_{50} of 3g/l from the growth

curve. The EC_{50} of a 96-h test with *Scendesmus quadricauda* was > 10g/l. Since acute aquatic toxicity data for three trophic levels are available, the Predicted No Effect Concentration (PNECaqua) can be calculated with an assessment factor of 1000. Hence, the PNECaqua is 3 mg/l.

The information available for the main metabolite formaldehyde (CAS-No. 50-00-0) indicate that fish, invertebrates and algae are more than three orders of magnitude more susceptible to this metabolite than to methenamine (formaldehyde was assessed in the OECD HPV Chemicals Programme). However, it could be assumed that following hydrolysis of methenamine, formaldehyde is degraded rapidly by microbiological activity.

The other degradation product is ammonia (ammonia CAS No. 7664-41-7 was assessed in the OECD HPV Chemicals Programme as part of a category).

Reliable data about the effects of methenamine on terrestrial organisms were not available. However, according to the environmental fate and behaviour, no relevant exposure of the terrestrial compartment is to be expected. In addition to that the available information indicate that the substance is non-toxic and of low environmental concern.

Exposure

Methenamine is produced in several EU-Member states with a total amount of approximately 30,000 t in 2001. With 95 % of the total production, the main use (non-dispersive) is in the polymer and rubber industry to produce powdery or liquid preparations of phenolic resins, urea resins, and phenolic resins moulding compounds to which methenamine is added as a curing or a vulcanisation agent. Additional minor uses are as intermediate in nitration reactions (production of explosives) and as fuel tablets for camping stoves.

In general, methenamine is expected to be released into the environment during production, formulation and processing via waste water and exhaust dust. Due to the negligible sorption potential and the incineration of the sludge at the production sites, direct releases to the soil compartment via sludge application can be excluded. Residual contents in final phenolic resins and rubber products are not expected due to complete decomposition during processing. Since the fuel tablets are pressed in a dry process and burned without residues, no environmental releases are expected from this use.

The main route of potential consumer exposure is assumed to be via dermal contact. Exposure of consumers to methenamine results from the use of cosmetics containing the substance as a preservative (maximum allowed concentration 0.15%) and in addition, from the use of solid fuel tablets. Oral exposure may result from the intake of provolone cheese (according to the German law 25 mg methenamine/kg (calculated as formaldehyde) are allowed in provolone cheese. It is not allowed in other food).

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 properties indicating a hazard for human health (skin sensitisation, repeated dose toxicity and developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary, a risk assessment.
Note: A risk assessment in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is in progress.

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