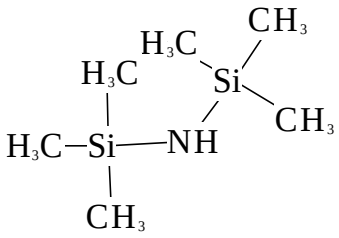
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	999-97-3
Chemical Name	1,1,1,3,3,3-Hexamethyldisilazane (HMDZ)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-Chemical Properties

Reduced Testing rationale

HMDZ undergoes rapid hydrolysis in the presence of water; the half life at pH 7 and 1.5°C is <0.5 minutes. Based on the chemical structure of HMDZ, this hydrolysis is expected to produce ammonia (CAS No. 7664-41-7) and trimethylsilanol (CAS No. 1066-40-6). Ammonia was previously assessed in the OECD HPV Chemicals Programme. Because HMDZ is hydrolytically unstable, water solubility and partition coefficient were not measured; modeled values are provided. In aqueous solutions, exposures to HMDZ are likely to be transient and observed toxicity is likely due primarily to the hydrolysis products.

The EPISuite program (v. 4.0) developed by the U.S. Environmental Protection Agency and Syracuse Research Corporation has not been validated for chemicals that contain silanes in their molecular structure (although some measured data are included in the training data set); therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported.

HMDZ is a liquid with a melting point of -76.2 +/- 1.9 °C, a boiling point of 125 °C at 1013 hPa and a measured vapour pressure of 22 hPa at 25 °C. The calculated octanol-water partition coefficient (log K_{ow}) is 2.62, and the water solubility is 761 mg/L at 25 °C. The water solubility and log K_{ow} values may not be applicable because the chemical is hydrolytically unstable.

Human Health

No data are available on the toxicokinetics, metabolism or distribution of HMDZ.

In an OECD TG 403 study, the 6-hr LC_{50} of HMDZ was 10 mg/L in rats, when exposed whole body to a vapour atmosphere. Clinical observations noted for the 7.8 mg/L group animals were consistent with respiratory and nervous system effects. Similar signs were also observed at 5.9 mg/L. In two studies conducted in a manner similar to OECD TG 402, the 24-hr dermal LD_{50} in rabbits was reported to be 547 (females) and 589 (males) mg/kg bw in one study and 1350 (combined sexes) mg/kg bw in the second study. Clinical signs were consistent with nervous system effects; local skin effects included severe irritation and necrosis. In a study conducted in a manner similar to OECD TG 401, the oral LD_{50} of HMDZ in rats was 1416 (males) and 1904 (females) mg/kg-bw, respectively. Clinical signs were consistent with nervous system effects and general signs of toxicity. The acute oral LD_{50} in another rat study was 774 mg/kg bw; clinical signs were consistent with nervous system effects and general signs of toxicity. In a final acute oral study in rats, the oral LD_{50} was determined to be 851 mg/kg bw. Clinical signs were consistent with nervous system effects at > 774 mg/kg bw, as well as reduction in body weight and a general poor condition.

HMDZ was not irritating to the skin in rabbits in an OECD TG 404 study. In three 4-hr studies conducted

under occlusive conditions according to U.S. Department of Transportation regulations, the substance caused necrosis of the skin; use of the occlusive cover is likely to have increased the severity of the effect. HMDZ was slightly or not irritating to the eyes in standard irritation studies (OECD TG 405 or similar) in animal tests. Acute inhalation studies with HMDZ suggest the substance is a respiratory irritant. In an OECD TG 403 test, rats exposed for six hours to 5.9 mg/L and above exhibited slow/noisy respiration. One group of five rats/sex was exposed for one hour at approximately 6.7 mg/L in a test conducted according to DOT guidelines. Clinical signs of toxicity were observed only during exposure and included respiratory difficulties (abdominal breathing). No experimental data are available for skin sensitisation in animals.

The repeated-dose toxicity of HMDZ has been investigated by the inhalation route in a combined repeated-dose/ reproductive/developmental toxicity screening study (OECD TG 422). The test article was administered to groups of 10 rats/sex via whole-body vapour inhalation for six hours/day, seven days/week to target concentrations of 0 (filtered air), 25, 100 and 400 ppm (0.16, 0.66, and 2.66 mg/L). Males were exposed throughout the 15 day pre-mating period and during the mating and post-mating periods, for a total of at least 4 weeks. Females were exposed throughout the pre-mating and mating periods and during pregnancy and lactation, until day 4 post-partum (or until sacrifice for un-mated females). Un-mated females were used in the repeated-dose portion of the study. Clinical signs were consistent with nervous system effects immediately after exposure at 2.66 mg/L. Significantly decreased body weight [15%] and food consumption were observed at 2.66 mg/L and absolute body weights of 0.66 mg/L females were decreased [7%; $p<0.02$]. Effects on haematology and serum chemistry parameters were noted at 2.66 mg/L. Decreases in absolute epididymides weight of 2.66 mg/L males and absolute lung weights of 2.66 mg/L females were observed. Increases in relative kidney weight were observed at 0.66 and 2.66 mg/L (females) and 2.66 mg/L (males). Increased relative liver weight was observed in 2.66 mg/L females. Centrilobular hypertrophy in the liver of 2.66 mg/L females was the only microscopic finding. Based on the clinical observations, body weight changes, serum chemistry, haematology and histological findings following whole body inhalation exposure, the systemic toxicity NOAEC was 0.66 mg/L and the LOAEC was 2.66 mg/L.

In bacterial reverse mutation assays with *Salmonella typhimurium* and *E. coli*, HMDZ was negative both with and without metabolic activation. Mammalian gene mutation assays with L5178Y mouse lymphoma cells were negative both with and without metabolic activation. An *in vitro* chromosomal aberrations test using HMDZ was negative both with and without metabolic activation. Based on these results, HMDZ is considered to be non-genotoxic *in vitro*.

No data are available regarding the carcinogenicity of HMDZ.

In the combined repeated-dose/reproductive/developmental toxicity screening study [OECD TG 422] with HMDZ, the NOAEC for reproductive/developmental toxicity for HMDZ was 2.66 mg/L (highest dose tested). The NOAEC for maternal toxicity was 0.66 mg/L. Overall, HMDZ did not show evidence of reproductive/developmental toxicity based on screening level data.

HMDZ possesses properties indicating a hazard for human health (acute and repeated dose toxicity, skin and respiratory irritation). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

The hydrolysis half-life for HMDZ is <0.5 minutes at 1.5 °C and pH7 following OECD TG 111. HMDZ is expected to form ammonia and trimethylsilanol. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 11.9 days. The biodegradation of HMDZ was investigated following EU Directive 92/69/EEC, C.4-E; HMDZ achieved a breakdown rate of 15.3% in 28 days, indicating the test substance is not readily biodegradable. This result is more likely to reflect the biodegradation potential of trimethylsilanol than it is parent substance.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that HMDZ will distribute mainly to the soil (70.8%) compartment with minor distribution to the water compartment (21.8%) and negligible amount to the air (7.08%) and sediment (0.31%) compartments. However, HMDZ is unlikely to be found in the environment, as this material is hydrolytically unstable. Henry's Law constant of 8.69×10^{-5} atm-m3/mole (8.8 Pa-m^3/mole) suggests that volatilisation from the water phase for HMDZ is not expected to be high. The bioaccumulation potential of the parent compound is considered to be low based on the chemical reactivity of HMDZ. The estimated BCF value is 24.77 L/kg wet-wt

using BCFBAF v3.00.

No information on the environmental fate of trimethylsilanol was found. Trimethylsilanol is relatively stable. Although at high concentrations (>5%) trimethylsilanol is known to condense forming hexamethyldisiloxane,at environmentally relevant concentrations this is not expected to be a significant reaction pathway. However, based on studies of related monomeric silanols, the adsorption of trimethylsilanol onto surfaces is expected. Trimethylsilanol is expected to partition primarily to water, soil, and sediment due to its high water solubility and have the potential to bind to mineral surfaces. Slow biodegradation in water and soil might also occur.

Due to the rapid hydrolysis of HMDZ, aquatic organisms are likely exposed primarily to its hydrolysis products, ammonia and trimethylsilanol. The following acute toxicity test results have been determined for aquatic species:

Fish [*Brachydanio rerio*]	96 h LC_{50} = 88 mg/L (measured as Total Organic Carbon; (TOC); EU Directive 92/69/EEC, C.1)
Aquatic invertebrate [*Daphnia magna*]	48 h EC_{50} = 80 mg/L (measured as TOC; EU Directive 92/69/EEC, C.2)
Algae [*Scenedesmus subspicatus*]	72 h EbC_{50}=19 mg/L (biomass) (measured as TOC; EU Directive 92/69/EEC, C.3)
Algae [*Scenedesmus subspicatus*]	72 h ErC_{50}=50 mg/L (cell growth)(measured as TOC; EU Directive 92/69/EEC,C.3)

HMDZ possesses properties indicating a hazard for the environment (acute aquatic toxicity values between 1 and 100 mg/L). The substance is not readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

HMDZ is commercially produced with an annual production volume of 454 - 2268 tonnes in 2005 in the United States of America. Worldwide production volume was estimated to be 2722-11340 tonnes/year in 2005.

Industrial uses of HMDZ include surface treatment of silica, as an intermediate; sold into the semiconductor industry as an adhesion promoter or silylating agent; chemical modification of inorganic fillers; water scavenger in some silicone sealants. HMDZ is a universal silylating agent used for the dervatization of alcohols, carboxylic acids, amines, amides, mercaptans and other compounds. HMDZ is a popular monofunctional silane that many researchers have found useful for deactivating and coating HPLC or GC chromatographic supports. HMDZ is a popular choice for silylation of sugars and related substances. HMDZ is also used for deactivating glass wool and for treating GC injection port glass inserts. HMDZ, used as a blocking agent by the pharmaceutical industry to produce antibiotics, is completely consumed and does not become part of the final product. In other applications, the sponsored substance is reacted during use and is not expected to be present in the final product.

HMDZ is manufactured in closed systems (hard-piped); engineering controls are routinely used. Dermal and inhalation are possible routes of occupational exposure (manufacturing and industrial consumer).

HMDZ is added to several silicone home maintenance sealants at 1-5% as a scavenger for free water or methanol. During use as a sealant applied to a substrate, HMDZ is expected to very rapidly react with moisture and no longer be available unless used in environments with unusually low moisture or in cases where there is excess HMDZ.

Some healthcare adhesives are manufactured using HMDZ as the endcapping (chain terminating agent) of the polymer. During the manufacture of these polymers residual HMDZ is removed by vacuum stripping. There is no residual HMDZ expected to remain in the pressure-sensitive adhesives.

There are no intentional releases to the environment.