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Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology

SIDS INITIAL ASSESSMENT PROFILE

CAS NO. 107-46-0

The Joint Meeting is invited to agree on the declassification of this document, by 11 August 2017.

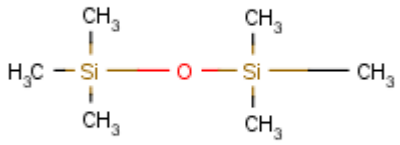
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SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-46-0
Chemical Name	Hexamethyldisiloxane (HMDS)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

Hexamethyldisiloxane (HMDS) is a liquid with a measured melting point of -68.2 °C and a measured boiling point of 100.5 °C at 1013 hPa. The measured vapor pressure is 44.51 hPa at 20 ºC. The measured water solubility is 0.93 ± 0.63 mg/L at 23 ºC. The measured log K_{ow} of HMDS is 5.20 at 20 ºC. Estimated log K_{oc} values using EPI Suite v 4.11 range from 2.5 (MCI method) to 4.5 (Kow method). As EPI Suite does not contain fragment corrections for siloxanes, since no data were available for use in training the log K_{oc} prediction algorithms, these log K_{oc} values should be treated with caution. The potential for hydrolysis of the test substance may have influenced the determination of partition coefficient and water solubility.

Human Health

The toxicokinetics of HMDS has been investigated; *in vivo* distribution in rats following nose only inhalation and *in vitro* percutaneous absorption in human skin have been evaluated. The primary route of elimination is in expired volatiles. The absorption of HMDS through the human skin is very low (0.023%). The major metabolites of HMDS identified in rat urine were $Me_2Si(OH)_2$; $HOMe_2SiCH_2OH$; $HOCH_2Me_2SiOSiMe_2CH2OH$ (predominant); $HOCH_2Me_2SiOSiMe_3$; $HOMe_2SiOSiMe_3$; Me_3SiOH. The presence of $Me_2Si(OH)_2$ and $HOMe_2SiCH_2OH$ clearly establish some demethylation at the silicon-methyl bonds. Considering the effective removal of HMDS through metabolism and exhalation, accumulation in the body after repeated exposures is unlikely despite its high lipophilicity. HMDS has been tested for acute toxicity by the inhalation, dermal and oral routes of exposure. The 4-hour LC_{50} of HMDS in rats is 15,956 ppm (106 mg/L; OECD TG 403). The dermal LD_{50} (24 hours) of HMDS ranges from greater than 2000 mg/kg bw in rats to 12,160 mg/kg bw in rabbits (similar to OECD TG 402). The oral LD_{50} of HMDS is greater than 2000 mg/kg bw in rats (similar to OECD TG 401). Undiluted HMDS produced no significant persistent irritation in several skin and eye (similar to OECD TG 405) irritation studies in rabbits. HMDS was not a skin sensitizer in studies in guinea pigs or humans. A positive control was not included in the guinea pig study.

HMDS has been tested for repeated dose toxicity using inhalation, dermal and oral routes of exposure in rats. Test durations ranged from 28-days up to 2 years and measured concentrations provided a range from 0.14 mg/L to 59.2 mg/L (inhalation), 100 to 1000 mg/kg bw/day (dermal) and 10 to 1000 mg/kg bw/day (oral). In a 4 week nose-only vapor inhalation study in rats, test substance-related changes were noted in clinical chemistry and target organs included lung, liver, ovaries, and kidney (male-specific). A NOAEC could not be determined as clinical chemistry and pathologic changes in the lungs occurred at all doses from 0.67 to 67 mg/L; the LOAEC was 0.67 mg/L. In a 13 week whole-body exposure in rats, minor alterations were noted in hematological and clinical chemistry but these

were not considered toxicologically relevant; target organs included kidney (male-specific changes) and testes. The NOAEC for male and female rats was reported to be 1.3 mg/L and 33.1 mg/L, respectively. Because the effects observed in male rats were considered to be alpha-2µ-globulin mediated and therefore not relevant to humans, the NOAEC for systemic toxicity is considered to be 33.1 mg/L. In another study, rats were exposed via nose-only inhalation exposure for 3 months to HMDS vapor (OECD TG 413) and a subset of animals was retained for a one month recovery period. Occult blood was observed in males of the two highest exposure groups and target organs included testes, lung, adrenal gland, vagina and kidney. Based on organ weight and histopathological changes in the lungs and testes, the NOAEC was not achieved in this study; the LOAEC for systemic toxicity was 0.14 mg/L. In a two-year combined chronic toxicity/carcinogenicity whole body vapour inhalation study in rats (OECD TG 453), the target organs were kidney, nasal cavity and testes. Effects in the kidneys were considered to be mediated by an alpha-2u-globulin mediated mechanism which is not relevant to humans. Effects in the nasal cavity were considered to be irritative. The no observed adverse effect level (NOAEL) for a 28-day repeated dose dermal toxicity study in rats (OECD TG 410) was 500 mg/kg bw/day in male rats based on reduced kidney and liver weights; there were no such effects in females. Based on a mechanistic study performed by the oral route to evaluate the alpha-2u-globulin induction, a NOAEL for specific kidney effects was < 10 mg/kg bw/day in male rats and > 1000 mg/kg bw/day in females. In a one-generation reproduction inhalation toxicity study (OECD TG 415), the parental NOAEC was 33.1 mg/L based on increased lung and liver weights. In a two-generation reproduction inhalation toxicity study with rats (OECD TG 416), the NOAEC for parental toxicity was 2.7 mg/L, based on the liver effect (pigment accumulation, chronic inflammation, bile duct hyperplasia).

HMDS did not induce chromosome damage in a rat bone marrow chromosome aberration test *in vivo*. HMDS did not induce gene mutations in bacteria (with and without metabolic activation) *in vitro* and, excepting one assay (a positive response without a dose-response relationship was observed in mouse lymphoma L5178Y cells only in the presence of metabolic activation), was not mutagenic with or without metabolic activation in a variety of *in vitro* mammalian assays. HMDS is not expected to be genotoxic. In the two-year combined chronic toxicity and oncogenicity whole-body inhalation study in Fischer 344 rats, there were no neoplastic effects. The target organs of HMDS were kidney, nasal cavity and testes. Effects in the kidneys were considered species-specific (alpha-2µ globulin-mediated mechanism). Effects on the testes (Leydig cell tumors) were increased following exposure to all concentrations, but they are considered to be spontaneous findings as they are common to Fischer 344 rats and were also observed in control animals. It was thought that HMDS might accelerate progression to this common tumor.

In a one-generation reproduction inhalation toxicity study (OECD TG 415), the NOAEC for maternal and reproductive/developmental toxicity of HMDS in the rat via whole body inhalation exposure was 33.1 mg/L and the paternal NOAEC was 33.1 mg/L based on increased lung and liver weights in parental males. In a two-generation reproduction inhalation toxicity study with rats (OECD TG 416), the NOAEC for parental toxicity was 2.7 mg/L, based on the liver effect (pigment accumulation, chronic inflammation, bile duct hyperplasia). The NOAEC for reproductive toxicity was 33.1 mg/L (the highest concentration tested). The NOAEC for developmental toxicity was 2.7 mg/L due to decreased offspring weights at 10.6 and 33.1 mg/L. In the same study, developmental landmarks (balanopreputial separation and vaginal patency) were evaluated for the selected F1 and F2 rats. The NOAEC for developmental neurobehavioral endpoints was 10.6 mg/L. The NOAEC for neuropathologic endpoints was 33.1 mg/L (the highest concentration tested). There were no gross anomalies in pups. Based on decreased offspring weights, the NOAEC for developmental toxicity was 2.7 mg/L.

Hexamethyldisiloxane may possess properties indicating hazard for human health (based on repeated dose toxicity and developmental toxicity at high concentrations). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Not all programs within EPI Suite have been validated for chemicals that contain the element Si, but recent upgrades to the Kow and water solubility modules, found in the EPI Suite (v4.11), may improve estimates of these properties for silanes and siloxanes. However, estimates of other properties that rely on measured or estimated Kow or water solubility should be used with caution whenever they are reported, because siloxanes may exhibit different relationships with these properties compared with the compounds used to train the models (e.g., Koc).

HMDS is hydrolytically unstable over a range of environmentally relevant pH and temperature conditions (OECD

TG 111), and results in the production of trimethylsilanol. The silanols condense to siloxane oligomers under certain conditions; this condensation of silanols is affected by both concentration and pH, and since both change over time it is not feasible to isolate specific silanols for analysis other than trimethylsilanol (the structures continue to evolve until they either reach equilibrium or precipitate out of solution). At environmentally relevant concentrations, condensation is not expected to occur. Basic pH accelerates condensation of silanols. The hydrolysis half-lives were 1.5, 120 and 12 h at pH 5, 7 and 9 and at 25 °C. HMDS in air undergoes indirect photolysis through hydroxyl radical oxidation. The dominant photochemical loss process of HMDS in the atmosphere is by gas-phase reaction with OH radicals. By use of a tropospheric OH radicals concentration of 7.7 x 10^5 molecule/cm^3 over a 24h period, a half-life of 7.5 days is calculated. The O_3 reactions are of negligible importance as a tropospheric removal process for HMDS, and that the NO_3 radical reactions are, at most, of minor significance Level III Fugacity modeling, using equal releases to air, soil, and water (loading rates of 1000 kg/hour to each medium), shows the following percent distribution of HMDS: air = 48.5%, soil = 0.62%, water = 50.1%, and sediment = 0.72%. The log Koc used for the modeling is 2.5 (KOCWIN MCI method). There is a range of estimated and measured Koc values and this uncertainty in the selected Koc may affect the results of the distribution modeling. In addition, the expected hydrolysis rate of HMDS in natural waters could be reduced due absorption to sediments. However, due to the range and uncertainty of Koc estimates the significance of this effect of absorption for HMDS is not known. The estimated Henry's Law constant of is 5.1x10^5 Pa m^3/mole at 20 °C suggests that volatilization from the water phase for HMDS is expected to be high. In two studies, HMDS achieved a breakdown rate of 0-4% and 0-2% after 28 days, indicating that it is is not readily biodegradable. In one biodegradation study, 20% of the parent substance was converted into trimethylsilanol, which is expected to reflect hydrolysis of HMDS rather than biodegradation.

The bioconcentration behavior of HMDS with common carp (*Cyprinus carpio*) was evaluated in separate water exposures with nominal aqueous HMDS concentrations of 0.004 (10 weeks) or 0.040 mg/L (8 weeks) (similar to OECD TG 305c); no depuration period was conducted and the sampling regime did allow attainment of a steady-state condition to be demonstrated. Steady state was reached by day 42 for the lower concentration and day 13 for the higher concentration. The empirical steady state BCF values at the lower concentration were 1181 L/kg (1374 L/kg when lipid normalised), and 1683 (1957 L/kg lipid normalised) at the higher concentration. As no growth data were available in this study, no further calculation could be done.

When the HMDS/carp BCF values were placed in a biota/water fugacity ratio ($F_{biota/water}$. i.e. lipid-normalised BCF / Kow) context, the values at the two dose levels ranged from 0.16 to 0.22, with a mean value of 0.19. Currently, there is no global consensus on how these calculations can be used to inform the bioaccumulation potential of a chemical.

Due to the hydrolysis of HMDS, the aquatic organisms are likely exposed to a mixture of the parent and its hydrolysis products. The following acute toxicity test results with HMDS have been determined for aquatic species:

Fish [*Oncorhynchus mykiss*] 96-h LC_{50}= 0.46 mg/L (flow-through; measured)
[*Pimephales promelas*] 14-d LC_{50} >0.093 mg/L (flow-through; not specified)
Algae [*Pseudokirchneriella subcapitata*] 70-h E_rC_{50} >0.55 mg/L (measured), NOEC = 0.01 mg/L (nominal),
Algae [*Pseudokirchneriella subcapitata*] 95-h E_rC_{50},> 0.55 mg/L (measured); 95-h NOEC growth rate = 0.15 mg/L (measured)
95- E_bC_{50} = 0.22 mg/L (measured); 95- LOEC growth rate = 0.28 mg/L (measured)
Where: E_bC_{50} = EC_{50} based on biomass; E_rC_{50} = EC_{50} based on growth rate

The following chronic toxicity test results with HMDS have been determined for aquatic species:
Invertebrate [*Daphnia magna*] 21-d EC_{50} = 0.45 mg/L (semi-static; measured)
NOEC = 0.25 mg/L (mortality)
NOEC = 0.08 mg/L (reproduction)
LOEC = 0.14 mg/L (reproduction)
NOEC = 0.25 mg/L (condition)
LOEC = 0.44 mg/L (condition)

Hexamethyldisiloxane possesses properties indicating a hazard for the environment (acute and chronic aquatic toxicity values below 1 mg/L). HMDS is not readily biodegradable and has the potential to bioaccumulate (based on the GHS criterion). Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

The 2010 production and import volumes in the United States (sponsor country) are 9072 tonnes and 454 to 4536 tonnes, respectively. The 2010 production and import volumes in Europe are 8210 tonnes and 45 to 454 tonnes, respectively. The 2010 production and import volumes in Japan are 227 to 680 tonnes and 227 to 680 tonnes, respectively. HMDS is used as a chemical intermediate in the production of monomers and polymers, and also in personal care applications (cosmetics), in insulating materials, and as part of construction material additives.

In production, this material is handled in closed systems. Necessary engineering controls during production include local ventilation. HMDS is stored on site in large outside storage tanks connected by piping to the manufacturing facility. Worker exposure may occur via inhalation or dermal exposure, which can be mitigated through the use of personal protective equipment (PPE), particularly during drum transfers.

Consumer exposure can occur through the use of HMDS in personal care products; concentrations are generally less than 10 percent. Environmental exposure through the use of consumer products is likely.

Note: At the time of finalisation of this document, HMDS is being further investigated within the EU framework of REACH Substance Evaluation. Information on prenatal developmental toxicity, additional information to support the environmental exposure assessment, information on the PBT assessment and information on sediment toxicity should be submitted to ECHA by September 2018.