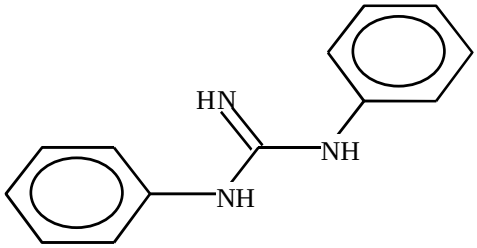
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	102-06-7
Chemical Name	1,3-Diphenylguanidine
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,3-Diphenylguanidine is absorbed rapidly after oral uptake but only slowly after dermal application. The substance is metabolised quickly and eliminated in the urine and faeces. No information is available on the mode of action.

1,3-Diphenylguanidine has an acute oral LD50 of 350-460 mg/kg b.w. for the rat. By dermal route, the dermal LD0 is > 2,000 mg/kg b.w. in the rabbit. After oral administration, the symptoms were normally of a nervous character, but post mortem examination revealed liver effects (dark colour) and severe irritation of the gastro-intestinal tract.
Sub-chronic (90-day) feeding studies in rats have shown an increase in mortality rate at 181 mg/kg bw/d, and a decrease in body weight gain (>10%) and food consumption (>12%) at 32 mg/kg bw/d and above. In a 90-day feeding study in mice, a decrease in body weight gain (>7%) was seen at 114 mg/kg bw/d and above. Decreases in rat body weight gain are considered to be due to the poor palatability of 1,3-diphenylguanidine. No treatment related effects were seen on organs, haematological and clinical-chemistry parameters, or urinalysis. Thus, from this data, a NOAEL of 17 mg/kg bw/d was determined in the rat for decreases in body weight gain and food consumption.

1,3-Diphenylguanidine gave negative results in numerous Ames and *in vitro* mammalian cell assays. An equivocal response was observed in a single Ames test, along with a positive result in a host mediated mutagenicity assay that was not reproducible. *In vivo*, negative results were seen in a (oral) rat bone marrow cytogenetic test and a (oral) mouse micronucleus assay. Thus, the data indicate 1,3-diphenylguanidine is not genotoxic.

The only available carcinogenicity studies are of insufficient rigour to determine whether or not DPG is carcinogenic.

1,3-Diphenylguanidine, with a purity of 97.7% to 99.9%, representative of the industrial product, did not affect the fertility of male mice when administered by gavage up to the maximal tested dose level of 16 mg/kg/d. In addition to the results of the feeding sub-chronic studies on the rat and mouse, special studies for recognising reproductive toxic effects were also performed. Comparisons of the parameter changes with the results of tests with feed withdrawal infer that the effects observed in the 1,3-diphenylguanidine-treated animals in high concentration groups

are a result of the poor general state of health (malnutrition, exhaustion) of the animals and not a direct toxic effect on the reproductive organs. Very conservative NOAELs, based on the effects on the reproductive organs, secondary to malnutrition and exhaustion, can be established at 32 mg/kg bw/d for rats and from 16 to 114 mg/kg bw/d for mice.

In female rats and mice foetotoxic, but not teratogenic, effects were seen after gavage administration of maternotoxic doses. In the rat study, based on a decrease of the maternal body weight gain at 25 mg/kg bw and above, and a decrease of the foetal body weight at 50 mg/kg bw, the NOEL was given as 5 mg/kg bw for the dams and 25 mg/kg bw for the foetuses. In the mouse study the NOEL was given as 4 mg/kg bw for the dams based on a decrease of mean number of implants and > 10 mg/kg bw for the foetuses. 1,3-Diphenylguanidine is irritating to the eye and non-irritating to the skin. Human cases have shown that contact dermatitis patients, for whom a rubber intolerance was often present, occasionally reacted positively to 1,3-diphenylguanidine in the patch test. Taken into account the negative Guinea pig maximisation assay, it can be infer that the positive reactions observed in human patients with contact dermatitis reflected cross-reactions rather than a direct sensitising effect of 1,3-diphenyl guanidine. In man, earlier and unconfirmed studies described the following symptoms after workplace exposures to 1,3-diphenylguanidine: eye and mucous membrane irritation, gastric and bilious complaints and disturbed liver metabolism.

Environment

1,3-Diphenylguanidine has three forms: unionised, primarily protonated and secondarily protonated. The pKa at which the first protonation occurs is 10.12 while the pKa for the second protonation is unknown and as this will be less than 10.12 it is not known whether this state will be reached at normal environmental pHs between 6 and 8. This leads to problems in determining the environmental fate of the substance.

Due to the relatively high solubility (approx. 0.5 g/l) at environmental pHs (6 to 9), low octanol water partition coefficient (<3) and low volatility of 1,3-diphenylguanidine the substance is not expected to adsorb to sediment and will mainly be present in the aqueous phase although, due to the positive charge of the ionised form of the molecule, adsorption to material with a high capacity for ion exchange (e.g. clay) may occur. Although not readily biodegradable, the substance has been shown to mineralise rapidly in the presence of adapted micro-organisms. A bioconcentration test on fish provided a BCF of <20 (LOQ). Based on the above the substance can be considered inherently biodegradable while bioaccumulation in biota is not expected for this substance.

1,3-Diphenylguanidine has been shown to be toxic to fish and algae and harmful to daphnia in several acute studies (fish : 96 h LC50 = 4.2-11 mg/l; algae : 72 h EC50 = 7.5 mg/l; 96 h EC50 = 1.7 mg/l; daphnid : 24 h EC50 = 73.6 mg/l; 48 h EC50 = 17mg/l).

The PNEC can be determined using the NOECs from the algae (0.3 mg/l) and daphnid chronic 21 d (0.6 mg/l) studies (excluding the EbC50 results), by applying an uncertainty factor of 50. The resulting PNEC would be 6 µg/l.

A terrestrial plant study conducted on monocotyledons and dicotyledons did not show a high level of concern for DPG in these species (*Brassica rapa*: EC50 = 358 mg/kg; *Avena sativa*: EC50 = 1169 mg/kg). In an avian study performed on three species of song bird at a limit concentration of 100 mg/kg, no effects were observed.

Exposure

1,3-Diphenylguanidine is a solid with a melting Point in the region of 147-150°C. Its boiling point is greater than 200°C. Vapour pressure is relatively low (1.74×10^{-7} kPa at 20°) and solubility in water varies greatly with the pH of the medium from 475 mg/l at pH 7 and 20^{o} C, to 519 g/l at strongly acid pH and 20°C. At higher pHs the solubility does not appear to decrease significantly. The change in solubility is due to the ionisation state of the substance. There are two protonation steps. The log pKa of the first protonation occurs at 10.12 but the second is unknown. The log Kow is measured as 1.69 but the pH of test is unknown. Probably this result relates to the protonated molecule but whether in cationic or di-cationic form not known. A calculated value is 2.9

The expected production volume of 1,3-Diphenylguanidine in year 2000 is 2400 tonnes/year in Europe, 2400 tonnes/year in the USA, an amount of 5300 tonnes/year for Asia and 11100 tonnes per year for the world.

1,3-Diphenylguanidine is used as a primary accelerator in vulcanisation of rubber, as secondary accelerator for sulfur-containing compounds such as thiazoles, sulfenamides and thiurams and as a minor use as a primary material for standardising acids.

Depending on the specific application, the concentration of 1,3-diphenylguanidine used in the production of rubber compounds may vary from 0.25% to 2.0% by weight.

1,3-Diphenylguanidine can be absorbed into the body by inhalation. Accidental exposure can occur by ingestion or contact with the eyes. Dermal exposure is probably minimal due to the low skin penetration.

NATURE OF FURTHER WORK RECOMMENDED

Human health: The substance is a candidate for further work (post-SIDS) due to the high toxicity profile. In occupational settings where exposure is not controlled, exposure to workers cannot be excluded. As the extend cannot be estimated, a human exposure assessment and, if then indicated, a risk assessment should be performed.

Environment: Based on current information no clear conclusion can be drawn. While the fate properties suggest that the substance will not bioaccumulate in the environment and that degradation will occur, the PNEC, be it based on flora or fauna is relatively low and the downstream use is such that the substance is likely to be found (within or outside polymer matrix) in the environment mainly due to abrasion from car tyres.

In the absence of knowledge on the leaching behaviour of the substance from abraded rubber compounds, further work to provide a reasonable estimate of the environmental concentration is considered necessary.