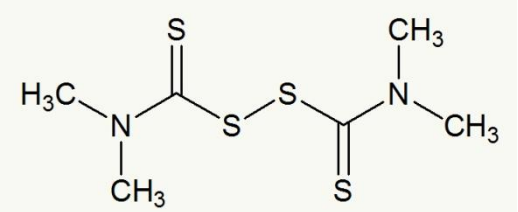
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	137-26-8
Chemical Name	Bis(dimethylthiocarbamoyl)disulfide; Thiram
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical and chemical properties

Bis(dimethylthiocarbamoyl)disulfide is a white or colourless to yellow crystalline powder with a melting point of 155.6 °C. Under normal atmospheric pressure, the substance decomposes before the boiling point is reached. It has a density of 1.29 g/cm^3 at 20 °C and a measured vapour pressure of 2.3 x 10^{-3} Pa at 25 °C. The measured octanol-water partition coefficient log K_{ow} is 1.73 and measured water solubility is ≤ 18 mg/L at room temperature.

Human Health

Bis(dimethylthiocarbamoyl)disulfide can be metabolised to toxic products such as carbon disulfide, hydrogen sulfide and dimethylamine. Experiments were carried out to investigate whether bis(dimethylthiocarbamoyl)disulfide is transformed by microsomal monooxygenase to carbon disulfide (CS_2) in rats. Adult male rats were given 15, 30 or 60 mg/kg of bis(dimethylthiocarbamoyl)disulfide in corn oil by intraperitoneal injection. The formation of CS_2 was dose dependant and was increased by pretreatment of rats with phenobarbital and decreased by SKF 525-A. Furthermore, measurement of the hepatic microsomal and serum enzymes activities at 5 hours and 24 hours following bis(dimethylthiocarbamoyl)disulfide treatment indicated significant loss of cytochrome P-450 and benzphetamine N-demethylase activity only at the 24 hour interval. Significant elevation of sorbitol dehydrogenase (SDH) and serum glutamic oxalacetic transaminase (SGOT) activity was observed at 5 and 24 hours after treatment.

A single oral dose of ^{14}C-bis(dimethylthiocarbamoyl)disulfide was administered to male and female rats to determine its absorption, excretion and final distribution. Only 32% of the administered dose was recovered, mainly from the urine (25%). About 3% was recovered from the various organs (blood, bone and liver). Only 3% of the administered dose was recovered in the faeces. Dose level or sex did not affect total recovery. Approximately 70% of the administered bis(dimethylthiocarbamoyl)disulfide, not recovered, may have been metabolized to CO_2 or other volatiles in the expired air or by bacterial action in the faeces or urine during the intervals between collections.

After 14 days of pretreatment with bis(dimethylthiocarbamoyl)disulfide at a dose level of 2 mg/kg bw/day, five rats/sex received a single dose of ^{14}C-bis(dimethylthiocarbamoyl)disulfide. The radioactivity was determined in urine, faeces and expired air at intervals up to 96 hours, and the radioactivity content in tissues was determined at 96 hours after dosing. ^{14}C-bis(dimethylthiocarbamoyl)disulfide was well absorbed by both sexes. Radioactivity was excreted in the urine (35-40% of dose within 96 hours), faeces (2-5%), and expired air (41-48%). Excretion was more extensive and rapid in urine and expired air within the first 12 hours post-dosing, while the majority of the faecal radioactivity was excreted after 24 hours. Trace levels of radioactivity were detected in all tissues: the highest in liver, blood cells and kidneys, and the lowest in brain, plasma, and skeletal muscle.

In an acute oral toxicity, bis(dimethylthiocarbamoyl)disulfide was administered via gavage to rats and mice. Ataxia and hyperactivity followed by inactivity, loss of muscular tone, and alopecia were observed. Deaths were occurred 2 to 7 days after exposure. Acute oral LD_{50} values for females and males were 1,900 and 4,000 mg/kg

bw, respectively, in rats and 3,800 and 4,000 mg/kg bw, respectively in mice.

No reliable studies of acute inhalation and dermal toxicity were available in experimental animals. A lower quality rat study indicated a 4-h inhalation LC_{50} value of 4.42 mg/L.

Bis(dimethylthiocarbamoyl)disulfide is reported as irritating to skin, eye and sensitising to skin in experimental animals.

In a 13-week dietary study, bis(dimethylthiocarbamoyl)disulfide was administered at dose of 0, 0.05, 0.1 or 0.25% (equivalent to 0, 30, 58 or 132 mg/kg bw/day) to male rats (20 animals/dose). Treatment related reductions in body weight and food consumption were observed at all doses. Mortality was observed at 58 and 132 mg/kg bw/day. At 58 mg/kg bw/day a mild increase in blood urea nitrogen (BUN) was observed, and at 132 mg/kg bw/day mild elevations of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were noted. Moderate tubular degeneration of the testes with atypical spermatids in the epididymis occurred in some rats fed 132 mg/kg bw/day. Based on the testicular changes at 132 mg/kg bw/day and mild elevations of blood biochemical parameters at 58 and 132 mg/kg/day indicating renal or hepatic dysfunction, the NOAEL was 30 mg/kg bw/day.

In a 80-week study, groups of 24 male and 24 female rats were fed bis(dimethylthiocarbamoyl)disulfide at dosage levels of 0, 0.01, 0.04 or 0.1% (equivalent to 0, 5, 20 or 52 mg/kg bw/day for males and 0, 6, 26 or 67 mg/kg bw/day for females). Dose-dependent decreases in body weight and food consumption were observed in males at 5 mg/kg bw/day and in females at 26 mg/kg bw/day. In males, fatty infiltration in the pancreas was noted. The high-dose males and females also had slight increases in squamous metaplasia of the thyroid. Based on the slight growth depression and fatty infiltration of the pancreas, the chronic LOAEL was 5 mg/kg bw/day.

Bis(dimethylthiocarbamoyl)disulfide was administered via the diet to 64 rats/sex/dose at 0, 3, 30 and 300 ppm (equivalent to 0, 0.1, 1.2 or 11.6 mg/kg bw/day for males and 0, 0.1, 1.4 or 13.8 mg/kg bw/day for females, respectively) for 104 weeks. Increased mortality rate was observed at mid and top dose in females only. Decreased body-weight gain and reduced food intake were observed in both sexes at the high dose. Anemia and regressive changes in the sciatic nerve accompanied by atrophy of the calf muscle were seen in females at 13.8 mg/kg bw/day. In high-dose groups, progression of myocardial lesions of the heart and chronic nephrosis of the kidney were depressed in males and females, respectively. Mid and top dose female rats had decreased development of skin mass. Based on the effect on mortality, anemia, nerve degeneration, muscle atrophy and skin mass, the NOAEL of 0.1 mg/kg bw/day was determined in rats.

In an oral repeated dose study, dogs (4/sex per group) were treated orally via capsule with the compound at 0, 0.4, 4, or 40 mg/kg bw/day for 104 weeks. Top dose animals showed severe toxic signs, including nausea or vomiting, salivation, and occasional clonic convulsion, and all were subjected to unscheduled necropsy before Day 203 of treatment. The dogs also had ophthalmological changes such as fundal hemorrhage, miosis, and desquamation of the retina which were consistent with the retinal lesions shown by histopathology. Anemia was evident in the 4 and 40 mg/kg bw/day groups. All mid and top dose animals developed liver failure, and mid and top dose females also showed kidney damage. Based on the anemia and the effects on the liver, the NOAEL was 0.4 mg/kg bw/day.

In a bacterial reverse mutation assay [OECD TG 471] with multiple strains of *Salmonella typhimurium* and *E. coli* WP*uvr*A, bis(dimethylthiocarbamoyl)disulfide showed equivocal results both with and without metabolic activation (S9 mix). An *in vitro* chromosomal aberration test with mammalian cell was negative both in the absence and presence of metabolic activation (S9 mix). An *in vivo* micronucleus assay with male and female hamsters was negative up to the maximum tolerated dose (500 µg/kg bw). An *in vivo* germ cell cytogenetics assay and spot test, both in mice, were also negative. Overall, the substance is not genotoxic. Further *in vitro* and *in vivo* studies were reported with equivocal results, probably due to evidence of impurities in the test substance.

In an oral carcinogenicity study in rats, the test substance was administered via the diet to 50 animals/sex/dose at 0, 0.05 or 0.1 % for 104 weeks. Calculated total intake of bis(dimethylthiocarbamoyl)disulfide in the diet were 18.3 mg/kg/day and 39.2 mg/kg/day for males and 20.2 mg/kg/day and 42.3 mg/kg/day for females in the low and high dose groups, respectively. There was no significant difference in survival between treated and control animals. Except for dose-dependent reduction of spontaneous leukaemia in both sexes and slightly reduced incidences of pituitary and thyroid adenomas in females, no significant lesions or tumor induction attributable to the treatment were observed.

In a 104-week study, bis(dimethylthiocarbamoyl)disulfide was administered via the diet to 64 rats/sex/dose at 0, 3, 30 or 300 ppm (equivalent to 0, 0.1, 1.2 or 11.6 mg/kg bw/day for males and 0, 0.1, 1.4 or 13.8 mg/kg bw/day for females). Death was observed in the 1.4 and 13.8 mg/kg bw/day females. No evidence of carcinogenic potential

was observed.

Simultaneous feeding to rats of bis(dimethylthiocarbamoyl)disulfide with sodium nitrite was carried out to assess the possibility of formation of carcinogenic N-nitroso derivatives *in vivo*. Groups of 24 male and female rats/dose were fed 0 or 500 mg/kg bw/day (750 mg/kg bw/day for the first three weeks) of bis(dimethylthiocarbamoyl)disulfide alone in diet or in combination with 2,000 mg/kg of diet sodium nitrite in diet for 104 weeks. Fifteen percent of the rats receiving bis(dimethylthiocarbamoyl)disulfide alone had died. No evidence of carcinogenic potential was observed in rats treated with bis(dimethylthiocarbamoyl)disulfide. Based on these results, bis(dimethylthiocarbamoyl)disulfide alone was not carcinogenic in rats. However, high incidence of papillomas of the forestomach was also seen in the rats of both sexes given the combined treatment.

In a two generation dietary reproduction and fertility study, rats (26/sex/dose/generation) received bis(dimethylthiocarbamoyl)disulfide at 0, 20, 60, or 180 ppm through 2 generations (2 litters/generation). Average dose-treated daily intake calculated for the F0 and F1 premating periods was 1.4-1.8, 4.2-5.4 and 12.2-16.4 mg/kg bw/day at 20, 60 and 180 ppm, respectively. Body weights decreased in both sexes of F0 parents at 180 ppm and F1 parents at > 60 ppm. Mean body weight decreased in F0 females (F1a generation) during gestation and lactation at 180 ppm. Decreases, though statistically significant, were minimal (< 10%, except day 0 lactation). These effects were not seen with the F0 females (F1b generation) during gestation or lactation. F1 females (F2a generation) had statistically significantly, but minimally decreased body weights during gestation and lactation at 180 ppm. Food consumption decreased in both sexes of F0 and F1 parents at 180 ppm. Because of lack of toxicologically relevant effects, the reproductive NOEL was 180 ppm (equivalent to 12.2-14.9 mg/kg bw/day in males and 14.0-16.4 mg/kg bw/day in females). Based on decreased body weight in pups at 180 ppm (F0) and > 60 ppm (F1) throughout lactation, the pup NOAEL was 20 ppm (equivalent to 1.4-1.7 mg/kg in males and 1.6-1.8 mg/kg in females).

In a dietary reproduction toxicity study, bis(dimethylthiocarbamoyl)disulfide was administered at doses of 0, 30, 58 or 132 mg/kg bw/day for male rats and 0, 30 or 96 mg/kg bw/day for female rats (20 animals/sex/dose). Weanling males were treated for at least 13 weeks before mating with untreated females. Virgin females were treated for at least 14 days, and then mated with untreated males. After mating, all females were fed the control diet. Death occurred in 70% of the male rats in the 132 mg/kg bw/day group, and the absence of fat was noted at necropsy. Average body weight and food consumption was depressed in both sexes.

At the high dose, decreased fertility in male rats was observed after 13 weeks of treatment; high dose females for 14 days treatment had prolonged the diestrous phase of the oestrus cycle. At 30 mg/kg bw/day, decreased litter size was observed. Based on the decreased the litter size, bis(dimethylthiocarbamoyl)disulfide was considered to adversely affect fertility at doses of 30 mg/kg bw/day and above.

In a developmental toxicity gavage study, the test substance was administered to pregnant female rats at doses of 0, 40, 90, 136, 164 or 200 mg/kg bw/day during gestation days 6-15 (10-32 animals/sex/dose). Average body weight gain and food consumption decreased in treated dams. A significant decrease in the number of implants per dam at doses of 164-200 mg/kg bw/day was observed. The number of fetuses per dam decreased, accompanied by a corresponding increase in resorptions at doses of 136-200 mg/kg bw/day. Fetal body weight was decreased in all treated groups. The following teratogenic effects were seen in the group given 136 mg/kg bw/day, domed cranium, hydrocephalus, unossified sternebrae, incompletely ossified supraoccipital, and centra split or lobed. Based on the fetal mortality, the fetal body weight reduction and increased incidence of abnormalities in fetuses, the LOAEL was 40 mg/kg bw/day.

In a teratology study, 4 groups of 25 female rats were administered dose levels of 0, 7.5, 15 or 30 mg/kg bw/day by gavage on day 6-15 of gestation. At 15 and 30 mg/kg bw/day a transient, dose-related, loss of body-weight was observed. There were no adverse effects upon implantation or upon fetal survival, but fetal and placental weights were significantly reduced at 30 mg/kg bw/day. At 30 mg/kg bw/day there was evidence of fetal immaturity e.g., reduced skeletal ossification and increased incidence of space between the body wall and organs, and there was a slightly increased incidence of subcutaneous oedema. Three fetuses with diaphragmatic hernia were observed, two at 7.5 and one at 30 mg/kg bw/day. The toxic effects on fetuses (immaturity and increased incidence of 13th ribs of reduced size) at higher doses were considered a result of maternal toxicity. The NOAEL for fetal toxicity was 7.5 mg/kg bw/day. Based on the reduced maternal body weight and placental weight, the NOAEL for maternal toxicity was 7.5 mg/kg bw/day.

Overall, the developmental adverse effects were observed in the range of maternal toxic doses

In a neurotoxicity study, bis(dimethylthiocarbamoyl)disulfide was administrated via diet to 24 male and female rats. In the first experiment (duration of 80 weeks) active bis(dimethylthiocarbamoyl)disulfide intake were around

0, 5.3, 20.4 or 52.0 mg/kg bw/day for male rats and 0, 6.1, 25.5 or 66.9 mg/kg bw/day for female rats. In a second experiment (duration of 36 weeks) active bis(dimethylthiocarbamoyl)disulfide intake was around 0 or 65.8 mg/kg bw/day for female rats. Top dose females from first experiment and females from second experiment developed ataxia and paralysis. Abnormal nerve conduction, neuropathology and behavioural effects were observed in top dose rats from the first experiment and females from second experiment. The walking pattern of the hind legs was altered with decreases in stride width and the angle between contra lateral steps. These rats required significantly more shock-motivations and cleared a lower height in a jump/climb ability test. An open-field study indicated that this substance caused hyperactivity in the non-ataxic rats of both sexes. Based on the results, the NOAEL for neurotoxicity was 20 (and 26) mg/kg bw/day

In a subchronic diet neurotoxicity study, rats (15/sex/dose) were exposed to bis(dimethylthiocarbamoyl)disulfide at doses of 0, 1.74, 7.3, or 28.63 mg/kg/day for male rats and 0, 2.04, 8.07, or 31.82 mg/kg bw/day for female rats. Significant decreases in weight gain in both male and female rats were observed at 28.6 mg/kg bw/day dose level. Functional observational battery observations revealed an increased incidence of hyperactivity along with significantly increased occurrences of rearing events in male rats at 8 and 13 weeks at the high dose and females at mid and high doses. Necropsy and histopathology examinations of the highest dose animals revealed no compound related abnormalities. Based on these results, LOAEL was 8.1 mg/kg bw/day (based on increased numbers of rearing events and elevated incidences of hyperactivity in female rats). The NOAEL was 2.04 mg/kg bw/day for female rats, and 7.3 mg/kg bw/day for male rats.

In an acute neurotoxicity gavage study rats (15/sex/dose) received 0, 5, 150, or 600 mg/kg bw of bis(dimethylthiocabamoyl)disulfide, and were subsequently evaluated in functional observational battery (FOB) at 2 hours and 7 and 14 days, and motor function observations were conducted at 3 hours, and 7 and 15 days. FOB effects occurred at the two highest dose levels two hours post dosing. FOB findings at 7 and 14 days indicated nothing remarkable. Male and female rats from the mid and top doses showed reduced mean motor activities at 3 hours, and 7 and 14 days. Absolute mean brain weights in 150 and 600 mg/kg male rats were significantly decreased. Mean brain weights for females from mid and top dose were also lower than those of their controls, but there was no statistical significance. There were no indications of any other adverse neuropathological effects in the brains or in any of the central or peripheral nervous system tissue which were examined following sacrifice. The NOAEL for neurotoxicity was 5 mg/kg bw and the LOAEL (FOB effects at 2 hours post-dosing; reduced motor activity at 3 hours, and at 7 and 14 days post treatment) was 150 mg/kg bw.

Bis(dimethylthiocarbamoyl)disulfide possesses properties indicating a hazard for human health (skin and eye irritation and skin sensitization, oral repeated-dose toxicity, reproductive toxicity and neurotoxicity). 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 measured for bis(dimethylthiocarbamoyl)disulfide at pH 3.8, 5.7, 7 and 8 were 9.5, 108, 1,123 and 3,316 hours, respectively. The photolysis half-life of bis(dimethylthiocarbamoyl)disulfide in water was 4.3 hours. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.03 days. No biodegradation was measured by biochemical oxygen demand (BOD) testing and the percentage biodegradation of bis(dimethylthiocarbamoyl)disulfide observed by HPLC analysis was 42.9% after 28 days at pH 7.8~8.0 [OECD TG 301C]. Bis(dimethylthiocarbamoyl)disulfide is not readily biodegradable under aerobic conditions.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that bis(dimethylthiocarbamoyl)disulfide will distribute mainly to the soil (80.4%) and water (19.0%) compartments with minor distribution to the sediment compartment (0.6%) and negligible amount in the air compartment. If released only to the soil compartment, bis(dimethylthiocarbamoyl)disulfide stays in the soil compartment (99.0%) with negligible amounts in other compartments. A Henry's law constant of 3.26×10^{-7} atm-m^3/mole suggests that bis(dimethylthiocarbamoyl)disulfide is expected to be essentially non-volatile from moist soil and water surfaces. A K_{oc} value of 676 has been measured for bis(dimethylthiocarbamoyl)disulfide. This K_{oc} value suggests that bis(dimethylthiocarbamoyl)disulfide is expected to have low mobility in soil.

Bis(dimethylthiocarbamoyl)disulfide is not expected to bioaccumulate in the aquatic environment based on bioconcentration factors of 1.1-4.4 and <3.4 which were measured in carp at concentrations of 25 and 2.5 μg/L, respectively.

Acute aquatic and terrestrial toxicity of bis(dimethylthiocarbamoyl)disulfide was performed with OECD test guidelines (TGs).

The following acute toxicity test results have been determined for aquatic species:

Fish [OECD TG 203, *Oryzias latipes*]	96 hours LC_{50} = 0.17 mg/L
Invertebrate [OECD TG 202, *Daphnia magna*]	48 hours EC_{50} = 0.036 mg/L
Algae [OECD TG 201, *Pseudokirchneriella subcapitata*]	72 hours E_rC_{50} = 0.19 mg/L
	72 hours E_yC_{50} = 0.060 mg/L

The following acute toxicity test results have been determined for terrestrial species:

Plant [OECD TG 208, *Lactuca sativa*]	7 days EC_{50} = >32 to <100 µg/g soil
Plant [OECD TG 208, *Lactuca sativa*]	14 days EC_{50} = 54 µg/g soil

Bis(dimethylthiocarbamoyl)disulfide possesses properties indicating a hazard for environment (acute aquatic toxicity lower than 1.0 mg/L for fish, invertebrates and algae, toxicity to terrestrial plants). The substance is not readily biodegradable and has a low bioaccumulation potential. Adequate screening-level data are available to characterize the environmental hazard for the purposes of the OECD HPV Programme.

Exposure

In the Republic of Korea (sponsor country), the production, use and import volume of bis(dimethylthiocarbamoyl)disulfide was 604, 836 and 694 tonnes, respectively in 2006. Bis(dimethylthiocarbamoyl)disulfide is used for vulcanising agents in the rubber industry, complexing agents, adhesive agents, binding agents, intermediates, catalyser, oxidising agents and as a fungicide on turf, fruit and vegetables in the Republic of Korea. It is also used as a seed disinfectant as well as an animal repellent for rodents and certain large animals that cause damage to field crops and as a bacteriostat in soap and antiseptic. Environmental exposure through its use as a fungicide is anticipated. Maximum residue levels of thiram on fruit and vegetables are regulated by European Commission Directive 2007/57/EC of 17 September 2007 (EU).

In the tire industry, bis(dimethylthiocarbamoyl)disulfide is handled in closed system facilities in the Republic of Korea. Occupational exposure is managed with local ventilation systems and personal protective equipments such as dust masks, gloves and goggles. According to the monitoring data, the 8hr-TWA (Time Weighted Average) concentrations of dust for workplaces were 0.05 - 1.07 mg/m^3, which were less than occupational exposure limit of 10 mg/m^3. Occupational exposure is considered to be negligible in the sponsor country.