Thioperoxydicarbonic diamide ([(H2N)C(S)]2S2), tetramethyl-: Human health tier II assessment

25 November 2016

CAS Number: 137-26-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

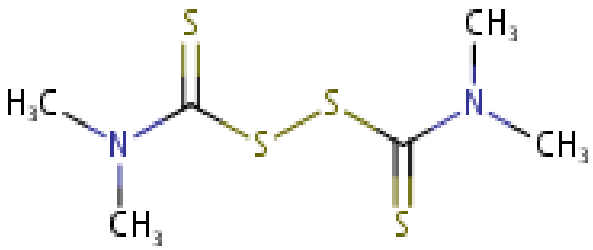
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	disulfide, bis(dimethylthiocarbamoyl) tetramethylthiuram disulfide Thiram
Structural Formula	
Molecular Formula	C6H12N2S4
Molecular Weight (g/mol)	240.4
Appearance and Odour (where available)	White or yellow, crystals or powder
SMILES	C(=S)(N(C)C)SSC(=S)N(C)C

Import, Manufacture and Use

Australian

No specific Australian industrial use, import, or manufacturing information has been identified.

The chemical has reported non-industrial use as a fungicide for seed treatment and to use on food crops (Australian Pesticides and Veterinary Medicines Authority—APVMA).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD)Screening information data set International Assessment Report (SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; and the OECD High Production Volume chemical program (HPV).

The chemical has reported domestic and/or commercial use as a preservative in paint.

The chemical has reported commercial or site-limited uses, including in:

- conductive agents;
- fillers;
- process regulators for polymerisation during production of resins, rubbers, polymers; and
- vulcanising agents.

The chemical has reported non-industrial uses including:

- as a biocide;
- in plant protection products;
- in fungicides; and
- in food/feedstuff flavourings.

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6 (SUSMP, 2016).

Schedule 6:

Thiram except in paint containing 0.5 per cent or less of thiram.

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2016).

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’);
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- US FDA Indirect Food Additives: Adhesives and Components of Coatings - Substances for Use Only as Components of Adhesives; and
- US FDA List of Indirect Additives Used in Food Contact Substances.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R20, R22 (acute toxicity)
- Xn; R48/22 (repeated dose toxicity via oral route)
- Xi; R36/38 (irritation)

- Xi; R43 (sensitisation)

Exposure Standards

Australian

The chemical has an exposure standard of 1 mg/m^3 time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 0.05–5 mg/m^3 TWA and 1–25 mg/m^3 short-term exposure limit (STEL)/MAK/occupational exposure limit (OEL) in different countries such as Austria, the USA (Alaska, Hawaii), Canada (Yukon), New Zealand and Switzerland.

Health Hazard Information

Toxicokinetics

In a study conducted according to the US EPA guideline OPP 85-1 (metabolism and pharmacokinetics), the absorption of the chemical in rats was reported to be rapid following a single oral dose (administered dose not available). Around 84–89 % of the administered dose was eliminated within four days (KEMI, 2015).

The metabolites were identified as dimethyldithiocarbamate, its alanine and glucuronide conjugates and methyl esters and thiosulfenic acid and 2-thioxothiazolidine-4-carboxylic acid (KEMI, 2015).

In an in vitro study with the chemical at 0.15 % and 62 % concentrations, dermal absorption through human skin was reported to be 12 % and 3 %, respectively (KEMI, 2015).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). The available data (OECD, 1978, IARC, 1992) generally support this classification.

Oral median lethal dose (LD50) values reported include (OECD, 1978; IARC, 1992; NTP, 2015; HSDB):

- 210 mg/kg bw in rabbits;
- 375–1000 mg/kg bw in rats; and
- 1350–2000 mg/kg bw in rats.

In addition to the above, LD50 values of 2500 mg/kg bw and 3700 mg/kg bw were reported in female and male Wistar rats, respectively (2600 mg/kg bw for female/male combined), indicating low acute toxicity (study performed according to the United State Environmental Protection Agency (US EPA) Acute Toxicity Study EPA OPP 81-1) (REACH). Reported signs of toxicity included lethargy, closed eyes, moist eyes, salivation, bloody eyes, nose encrustation and diarrhoea. Some females had additional signs of toxicity reported including tremors, emaciation, ungroomed appearance, reduced respiration, reduced faecal excretion and coma (REACH).

Acute oral gavage exposure to the chemical at 150 mg/kg bw/day in female Wistar derived rats caused a reduction in motor activity (KEMI, 2015) (see **Other Health Effects *Neurotoxicity***).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure.

The LD50 in male and female New Zealand White rabbits is >2000 mg/kg bw in a study performed according to US EPA Acute Toxicity Study EPA OPP 81-2 (Acute Dermal Toxicity) (REACH).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS (Safe Work Australia). The available data support this classification

Median lethal concentration (LC50) values of 3.46 and <5.04 mg/L/4-hours were reported in female and male Sprague Dawley (SD) rats, respectively, following exposure to the chemical as an aerosol (combined LC50 for rats = 4.42 mg/L/4-hours) (REACH).

Corrosion / Irritation

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). Although the available data do not support this classification, as only the summarised study data are available and the chemical has a EU harmonised classification for skin irritation, the existing classification is recommended to remain the same.

In an acute dermal irritation study (conducted according to US EPA OPP 81-5), the chemical was applied (semi occlusive, applied amount not indicated) on intact clipped skin of six New Zealand White (NZW) rabbits for 4 hours. At 24-hour observation following treatment, slight erythema (mean score = 0.16; maximum score = 1) and no oedema (mean score = 0) were reported. Erythema was fully reversible after 48 hours. The chemical was reported as not irritating (REACH).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification.

In an eye irritation study (conducted according to US EPA OPP 81-4 and similar to OECD Test Guideline (TG) 405) in NZW rabbits, the chemical caused conjunctivitis (mean score = 2.17 and maximum score = 3 for redness; mean score = 2.1 and maximum score = 3 for chemosis) and marked to dense corneal opacity at 24, 48 and 72 hours after application. Effects were reversible within 15 days (KEMI, 2015; REACH).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’(R43) in the HSIS (Safe Work Australia). The available data support this classification.

In a split adjuvant test for skin sensitisation (US EPA OPP 81-6), female Dunkin-Hartley guinea pigs (n=10 control and n=20/test group) were induced epicutaneously with 25 % (w/w) of the chemical in petrolatum and challenged epicutaneously (timing not available) with the same concentration of the chemical. During the challenge phase, clinical observations including red spots and moderate and diffuse skin reactions were reported in 8/20 animals at 24 hours and, in 6/20 animals at 48 hours (REACH).

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful: Danger of serious damage to health by prolonged exposure if swallowed' (Xn; R48/22) in the HSIS (Safe Work Australia). The available data support this classification.

In a 90 day sub chronic oral toxicity study (EU Method B.26), CD(SD)BR rats (n=10/sex/dose) were administered the chemical at 0, 3.5, 38 or 67 mg/kg bw/day in males and 0, 4, 38 or 80 mg/kg bw/day in females. Haemolysis was reported in both sexes in the mid and high dose groups and the lowest observed adverse effect level (LOAEL) was reported as 38 mg/kg bw/day. The affected parameters included: lower red blood cell count, haemoglobin and haematocrit and higher leukocyte count in females. Changes in urinary parameters were reported in both sexes in the mid and high dose groups. The affected parameters included: lower albumin and higher urea nitrogen and chloride in the females, and lower total protein and glucose in both sexes. A no observed adverse effect level (NOAEL) of 3.5–4 mg/kg bw/day was established (REACH).

In a 90-day dog study (US EPA OPP 82), Beagle dogs (n = 4/dose/sex) were administered the chemical in the diet at 0, 75, 250 and 500 ppm (actual ingested doses were: 0, 1.94–2.58, 6.17–7.85, 10.55–14.69 mg/kg bw/day for males and 0, 2.14–2.55, 6.67–8.01, 11.75–13.42 mg/kg bw/day for females). The chemical induced significant changes in blood parameters. Red blood cell count was reduced in all treated dogs (statistically significant at 75 and 500 ppm males and 250 and 500 ppm females). Lower albumin levels were observed in all treated groups (statistically significant compared to controls, except in females at 75 ppm). A NOAEL of around 2 mg/kg bw/day was reported based on changes in blood parameters from around 6 mg/kg bw/day (REACH).

The chemical is also reported to cause neurotoxicity (KEMI, 2015) (See **Other Health Effects *Neurotoxicity***). In a 90-day repeated dose oral toxicity study, adult rats exposed to the chemical in the diet showed low brain weights (compared with controls) and increased incidence of rearing and hyperactivity during weeks 8 and 13, at doses around 21–44 mg/kg bw/day (KEMI, 2015).

Dermal

Based on the available data, the chemical is not considered to cause severe systemic effects from repeated dermal exposure.

In a repeated dose toxicity study (US EPA OPP 82-2), NZW rabbits (n=5/sex/dose) were topically (occlusive) applied the chemical at 0, 100, 300 or 1000 mg/kg bw/day for 6 hours a day, for 21–22 days. No systemic toxicity effects were reported due to treatment and the lowest observed adverse effect level (LOAEL) was reported as 1000 mg/kg bw/day. Local irritation (slight to well defined erythema with or without oedema) was observed in all treatment groups. The intensity and frequency of the irritation increased proportionally with time and dose (REACH).

Inhalation

No data are available.

Genotoxicity

The weight of evidence indicated that the chemical could cause mutations in vitro and in somatic cells (in vivo). Germ cell studies were mostly negative. The available data support classification of the chemical as a Category 3 mutagen.

In vitro genotoxicity studies showed mixed results for the chemical (IARC, 1991; REACH):

- positive for gene mutation in *Salmonella typhimurium* strains (US EPA OPP 84-2) at 333.3 µg/plate (TA98) and 1000 µg/plate (TA98, TA100, TA1537 and TA1538), with or without metabolic activation;
- positive for gene mutation in Chinese hamster lung (V79) cells tested at 5.0 µg/mL, without metabolic activation;
- positive for unscheduled DNA synthesis in human lymphocytes tested at 5 µg/mL, with metabolic activation;
- positive for sister chromatid exchanges in human lymphocytes tested at 15 µg/mL, with metabolic activation.
- weakly positive for chromosomal aberrations in Chinese hamster lung cells at 0.4 µg/mL, with or without metabolic activation;
- negative for chromosomal aberrations in Chinese hamster ovary (CHO) cells (OECD TG 473) at 0.003 - 3 µg/mL concentrations, with or without metabolic activation;
- there were no significant increase in mutant frequency at the HPRT-locus in Chinese hamster lung (V79) fibroblast cells (OECD TG 476) up to 10 µg/mL (cytotoxic concentration; cell survival was less than 20 %) without metabolic activation and, at or above 30 µg/mL (cytotoxic concentration) with metabolic activation; and
- negative results in a DNA damage and repair unscheduled DNA synthesis assay (OECD TG 482) in hepatocytes of male Wistar rats exposed to the chemical at 1 - 10 µg/mL. However, several grains were observed over nuclei from cells devoid of cytoplasm at 10 µg/mL and this was reported as probably irrelevant as it occurred above the EC50 cytotoxicity value (concentration resulted 50 % decrease in the number of viable cells) of 1 µg/mL.

There were mixed results from in vivo genotoxicity studies using the chemical (IARC 1991; REACH):

- positive for micronucleus formation in bone marrow cells of BALB/c mice that were exposed to the chemical by two intraperitoneal (i.p.) injections at 500 mg/kg bw;
- positive for micronucleus formation in bone marrow cells of (CBAxC57C1/6J)F1 mice that were exposed to the chemical by one i.p. injection at 100 mg/kg bw;
- negative for micronucleus formation in Chinese hamsters exposed to the chemical by one i.p. injection at 0.5 mg/kg bw; and
- no micronucleus formation in polychromatic erythrocytes (PCE) of bone marrow from CD-1 mice intraperitoneally administered the chemical once, at 38, 189 or 377 mg/kg bw (US EPA OPP 84-2). At the highest dose, 15/38 animals died and the others showed clinical signs and bone marrow toxicity (reduced ratio of PCE to total erythrocytes). Some animals in the mid-dose group also showed toxic effects.

Mostly negative results were seen in germ cell tests (IARC, 1991; REACH):

- negative results for gene mutation in a mouse spot test (EU Method B.24) when female (NMRI) and male (DBA/2) mice were exposed with a single oral gavage dose of the chemical at 75 or 750 mg/kg bw;
- Swiss mouse spermatocytes tested positive for chromosomal aberrations and morphologically abnormal sperm when exposed to the chemical at 80 mg/kg bw/day with three oral gavage doses;
- morphologically abnormal sperm in mice was induced after exposure to the chemical by one i.p. injection at 50 mg/kg bw, or five i.p. injections at 30 mg/kg bw; and
- no chromosomal aberrations in spermatogonia cells (OECD TG 483) in male NMRI mice exposed to the chemical once, at 75, 250 or 750 mg/kg bw by oral gavage dosing (no mortalities observed).

Although mutagenicity of the chemical was not evaluated, the KEMI report states that, 'The available *in vitro* data shows that thiram is cytotoxic.' (KEMI, 2015).

Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

In a carcinogenicity study, SPF Fischer 344 (F344) rats (n=50/sex/dose) were exposed to the chemical via feed at 0, 0.05 or 0.1 % (the maximum tolerated dose was estimated at >0.06 %) for 104 weeks. No significant difference was noted between the survival of control and test animals. The incidences of leukaemia were lower in both test groups compared with the control groups (males: 10/50, 4/49 and 2/50; females: 14/49, 6/50 and 2/50 for 0, 0.05 and 0.1% respectively). The incidences of pituitary chromophobe adenomas in females were significantly lower in the test groups compared with the control group (22/49, 11/50 and 10/50 for 0, 0.05 and 0.1% respectively) and C-cell adenomas of the thyroid were significantly lower in the high dose females (0/50) compared with the control group (7/49). No statistically significant difference in the occurrence of tumours at other sites was reported (IARC 1991).

Rats (F344, n=24/sex) administered the chemical in the diet at 500 mg/kg diet (750 mg/kg diet for the first three weeks) for 104 weeks had a significant decrease in the incidence of monocytic leukaemia (treated females 1/24; control females 11/24; treated males 4/24; control males 12/24). The number of animals used in the study was reported to be low (IARC, 1991).

Workers (42 men and 181 women) involved in the manufacturing of the chemical for more than three years in the Union of Soviet Socialist Republics (USSR) were studied and only one worker (out of 105 examined) was found to have a malignant thyroid lesion (IARC, 1991).

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Not classifiable as to its carcinogenicity to humans’ (Group 3), based on inadequate evidence for carcinogenicity in humans and in experimental animals (IARC 1991).

Reproductive and Developmental Toxicity

Based on the available animal data, the chemical is not considered to cause reproductive or developmental effects up to 9 mg/kg bw/day. Old studies (IARC, 1991) have indicated reproductive effects in animals exposed to the chemical at higher doses.

In a two generation reproductive toxicity study (according to the US EPA OPP 83-4 guidelines), Charles River Crl:CD VAF/Plus rats (n = 26/sex/dose) were exposed to the chemical via the diet at 0, 1.52, 2.94 and 8.88 mg/kg bw/day and 0, 2.27, 4.61 and 13.89 mg/kg bw/day, for the parent (F0) male and female rats, respectively. Offspring of the parent generation rats (F1) were exposed to the chemical via the diet at 0, 1.82, 3.82 and 11.37 mg/kg bw/day and 0, 2.39, 5.12 and 16.21 mg/kg bw/day, for males and females, respectively. Reduction in the body weight of the F0 females was observed during the gestation period in the mid and high dose groups. Decreases in the mean body weight were observed in the F1 generation up to 10 and 13 weeks for males and females, respectively. Statistically significant reductions in body weight were observed in the high dose F2 (offspring of F1 generation) females. Reductions in food consumption were noted across the generations in the mid and high dose groups. Treatment related effects were not reported for organ weight, reproductive performance, stillborn rates or for clinical observations; although reduced pup body weight (degree of reduction not specified) was reported in both generations at the high dose. The NOAEL for reproductive toxicity was reported to be >9 mg/kg bw/day (the highest dose tested in F0 males) in rats (KEMI; 2015).

In a developmental toxicity study (OECD TG 414), female NZW rabbits (n = 20/dose) were treated with the chemical by oral gavage doses of 0, 1, 5 and 10 mg/kg bw/day from gestation day (GD) 7 to 19. No treatment related malformations were observed in the foetuses up to the highest dose tested. The NOAEL for developmental toxicity was reported to be > 10 mg/kg bw/day (KEMI, 2015).

Pregnant Sprague-Dawley rats (n = 25/dose) were treated with the chemical by oral gavage at 0, 7.5, 15 or 30 mg/kg bw/day on GD 6–15. Maternal weight loss occurred in groups treated at =15 mg/kg bw/day. Increased incidences of foetuses with reduced 13th ribs were reported but without dose response (3.2, 6.2, 13.1 and 9.5 in the control, low, mid and high dose groups, respectively). The NOAEL for foetotoxicity was reported to be 15 mg/kg bw/day based on slightly reduced foetal weight at this dose level, but within the historical control range (KEMI, 2015; REACH).

In studies conducted prior to 1980, there are some adverse systemic and/or reproductive effects reported in animals exposed to the chemical at higher doses during the gestation period (IARC, 1991):

- pregnant NMRI mice which received oral doses of the chemical at 10-30 mg/animal on GD 5 to 15 or 6 to 17 showed increased resorptions and foetal malformations;

- Syrian hamsters exposed to the chemical at 250 mg/kg bw and higher on GD 7 or 8 had increased rate of resorptions and decreased foetal weights;
- daily administration of the chemical at 132 mg/kg bw/day in diet for 13 weeks decreased fertility in male Charles River CD rats.
- female Charles River CD rats exposed to the chemical at 96 mg/kg bw/day for 14 days were reported to have prolonged dioestrous phase of the oestrus cycle and weight loss; and
- female rats exposed to the chemical by oral gavage doses at 136–200 mg/kg bw/day during GD 6–15 showed increased foetal mortality rates.

When Swiss-Webster mice exposed to the chemical by oral gavage dosing at up to 300 mg/kg bw/day on GD 6–14, a number (not indicated) of dams died during the study. However, there were no significant developmental effects up to 300 mg/kg bw/day (IARC, 1991).

Other Health Effects

Neurotoxicity

Neurotoxic effects were observed in rats following acute or repeated oral exposure to the chemical.

KEMI (2015) stated 'Thiram caused functional developmental neurotoxicity at maternally toxic doses and adult neurotoxicity. Some histopathological data and an *in vitro* study suggest thiram causes neuronal cell death.'

In an acute toxicity study (OECD TG 424, without histopathology), Wistar derived rats (n = 10/sex/dose) were exposed to the chemical at 0, 10, 25, 60 or 150 mg/kg bw via oral gavage dosing. No clinical effects were observed. Reduced body weight and food consumption were reported at 60 and 150 mg/kg bw. A reduction in motor activity was observed in females at 150 mg/kg bw (KEMI, 2015; REACH). Male rats orally exposed to a single dose of the chemical were reported to have a significant reduction in orientation hypermotility at 240 mg/kg bw, reduced subcortical electroencephalography (EEG) activity at 40 and 240 mg/kg bw, and decreased reformation of norepinephrine at 60 mg/kg bw (KEMI, 2015).

In a 90 days repeated oral toxicity study, adult male rats were treated with the chemical in the diet at 1.5–2.3, 5.9–10.2 or 22.8–40.2 mg/kg bw/day and adult female rats were exposed to the chemical via feed at 1.8–2.6, 6.9–10.1 or 21.6–43.9 mg/kg bw/day. In the high dose groups lower brain weights were reported. The high dose males showed increased incidence of rearing and hyperactivity during weeks 8 and 13. Similar effects were observed in week 8 across all treated females. No treatment-related effects on motor activity or histopathology were observed (KEMI, 2015).

In a chronic exposure study, female rats exposed (length of exposure not available) to the chemical at 13.8 mg/kg bw/day showed regressive changes to the sciatic nerve and atrophy of the calf muscle (KEMI, 2015). In another study to investigate neurotoxic and behavioural effects, rats were exposed to the chemical for 80 days at 5.3/6.1, 20.4/25.5 and 52/66.9 mg/kg bw/day for males and females, respectively. Neurotoxic effects, characterised by ataxia and paralysis of the hind legs, were observed in the high dose females. The neuropathology of two female rats in the high dose group showed demyelination, degeneration of the axis cylinders, macrophages in the nerve bundle of the sciatic nerve and degeneration in the ventral horn of the of the lower lumbar region of the spinal cord. The non-ataxic rats at mid and high dose groups showed behavioural effects characterised by altered walking patterns of the hind legs and hyperactivity (KEMI, 2015).

In a developmental neurotoxicity study (US EPA guideline OPPTS 870.6300) pregnant rats were exposed to the chemical in the diet at 1.6–4.1, 3.8–9.2 or 6.6–18 mg/kg bw/day from GD 3–20. Reduced body weight and food consumption were reported in the high dose female group. Clinical signs of toxicity including pale skin, pale eyes and irregular respiration were reported in the high dose female group. The pups from the high dose group had reduced body weight gain. In high dose pups, differences in the pre-pulse inhibition of the auditory startle response in males and impaired performance in females in the Morris water maze test on day 61/62 were observed. Based on the results of the study the NOAEL for maternal toxicity and functional developmental neurotoxicity was reported as 3.8–9.2 mg/kg bw/day and the NOAEL for morphological developmental neurotoxicity was reported as 6.6–18 mg/kg bw/day (KEMI, 2015).

In an in vitro study in neuronal-like PC12 (rat pheochromocytoma) cells, the chemical induced dose and time dependent cell death. With 1 µM of the chemical, the type of cell death showed 'typical apoptotic features like DNA fragmentation and an increase of subdiploid nuclei' (KEMI, 2015).

Endocrine Disruption

According to KEMI (2015), 'In 2002, after evaluation at the expert meeting thiram was placed in Category 16 for human health relevant endocrine disruption based on Stoker et al. (1993) as the key-study.' Three rat studies were published by Stoker et al. in 1993. In these studies, the chemical was administered as a single i.p. dose (6, 12, 25, 50, or 100 mg/kg bw/d in the first study and 12, 25, or 50 mg/kg bw/d in second and third studies) to investigate acute effects of the chemical on 'hormonal control of ovulation in rats'.

'In the first experiment, thiram caused complete suppression of estradiol-induced luteinizing hormone surge in a dose-dependent manner in the ovariectomised estrogen-primed rats. In the second experiment, thiram blocked the ovulation in intact proestrous rats and in the third experiment, it caused complete suppression of luteinizing hormone surge also in intact animals' (KEMI, 2015).

Following evaluation of the studies available for the chemical, KEMI (2015) concluded, 'In the light of general systemic toxicity, the available data set does not allow concluding that thiram alters function of the endocrine system and consequently causes adverse health effects.'

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (eye and skin irritation and skin sensitisation).

The chemical may have some genotoxic potential and can also cause harmful effects following acute inhalation exposure and harmful effects including neurotoxicity, following acute and repeated oral exposure.

Public Risk Characterisation

Although domestic industrial use in Australia is not known, the chemical is reported to be used as a preservative in paints overseas.

The chemical is listed in Schedule 6 of the *Poisons Standard*, with an exemption for paint containing up to 0.5 % of the chemical (SUSMP, 2016).

The critical health effects identified above are not expected to occur from use of the chemical as a preservative in paint, at up to 0.5 % concentration. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)*	May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

Galleria Chemica. Accessed October 2016 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Hazardous Substances Data Bank (HSDB) Accessed June 2016 at https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm

Hazardous Substances Information System (HSIS). Safe Work Australia. Available: http://hsis.safeworkaustralia.gov.au/HazardousSubstance

International Agency for Research on Cancer (IARC) 1991. Thiram. IARC Monographs Volume 53. Accessed November 2016 at https://monographs.iarc.fr/ENG/Monographs/vol53/mono53-16.pdf

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Thiram CAS No. 137-26-8. Accessed October 2016 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Swedish Chemicals Agency (KEMI) 2015. Substance Evaluation Conclusion Document, Evaluation report for Thiram. EC No 205-286-2, 18 March 2015.

The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), 2016. The Poisons Standard. Commonwealth of Australia. Accessed at https://www.tga.gov.au/publication/poisons-standard-susmp

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