1H-Isoindole-1,3(2H)-dione, 3a,4,7,7a-tetrahydro-2-[(trichloromethyl)thio]-: Human health tier II assessment

21 April 2016

CAS Number: 133-06-2

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.

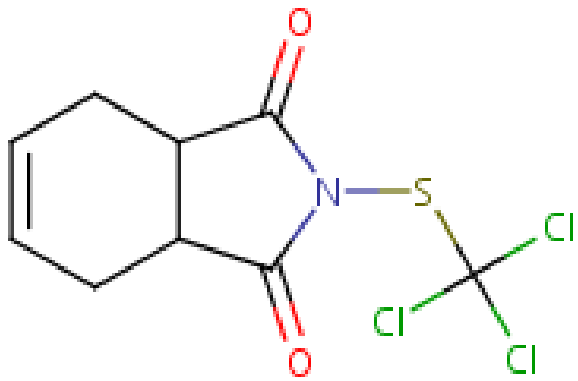
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	3a,4,7,7a-tetrahydro-2-((trichloromethyl)thio)-1H-isoindole-1,3(2H)-dione captan N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide 1,2,3,6-tetrahydro-N-(trichloromethylthio)phthalimide
Structural Formula	
Molecular Formula	C9H8Cl3NO2S
Molecular Weight (g/mol)	300.59
Appearance and Odour (where available)	White solid and odourless. The technical grade is an amorphous powder which is colorless to beige with a pungent odour.

SMILES	C1(=O)C2C(C(=O)N1SC(Cl)(Cl)Cl)CC=CC2

Import, Manufacture and Use

Australian

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

The chemical has non-industrial use as a fungicide for agricultural application (APVMA).

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers;
- the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary;
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and
- various other sources (IARC, 1983; IPCS, 1990a; Haz-map; US EPA, 1990).

The chemical has reported cosmetic use as a biocide/ preservative in underarm deodorants, foot powders and sprays, skin care preparations, tonics, dressings and hair grooming aids.

The chemical has reported domestic use as a biocide in paints and polishes, adhesives, binders, sealants, filters, lacquers, wallpaper pastes, textiles (vinyl coated fabrics), and in polyethylene used for garbage bags.

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

- vinyl resins;
- rubber stabilisers;
- papers;
- construction materials;
- electrical or electronic products; and
- leather tanning.

The chemical has non-industrial uses as a fungicide in the cultivation of both food and non-food crops, food packaging as an agent in cotton-seed treatment, and as a therapeutic agent to treat fungal infections of the skin.

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 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):

- 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;
- Bahrain Resolution No. 7 of 2002 on the control of the importation and use of prohibited and severely restricted chemical substances - Prohibited Chemical Substances;
- Canada Cosmetic Ingredient Hotlist —List of Ingredients that are prohibited for use in cosmetic products;
- Chile List of substances which must not form part of the composition of cosmetic products;
- China List of Banned substances for use in cosmetics;
- EU Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the Composition of Cosmetic Products;
- Korea (South) Toxic Chemicals Control Act—Prohibited/Restricted Chemicals; and
- New Zealand Cosmetic Products Group Standard — Schedule 4: Components cosmetic products must not contain - Table 1.

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):

- Carc. Cat. 3; R40 (carcinogenicity);
- T; R23 (acute toxicity);
- Xi; R41 (eye damage); and
- Xi; R43 (skin sensitisation).

Exposure Standards

Australian

The chemical has an exposure standard of 0.5 mg/m^3 time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 4-5 mg/m^3 time weighted average (TWA) and 10-15 mg/m^3 short-term exposure limit (STEL) has been set in different countries such as Canada, Chile, Denmark, Estonia, France, Greece, Iceland, Indonesia, Ireland, Malaysia, Mexico, Norway, Poland, Singapore, South Africa, Spain, Switzerland, and United Kingdom.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a TLV of 5 mg/m^3 for a normal 8-hour work day and a 40-hour work week.

Health Hazard Information

Toxicokinetics

The toxicokinetics of the chemical (captan) have been studied in laboratory animals.

The chemical is rapidly absorbed, metabolised and eliminated after oral and dermal exposure in rats. Results from a radiolabelling study of [^{14}C]-captan in Simonsen albino rats showed the following distribution of radioactivity four days after oral exposure: 51.8 % in the urine; 22.8 % expired air; 15.9 % in the faeces; and 0.6 % in the tissues. Approximately 50 % of administered dose was excreted by all routes within nine hours of oral exposure. No organ-specific accumulation of captan was observed (DeBaun et al., 1974).

In another radiolabelling study, >90 % of [^{35}S]-captan, was excreted in the urine and faeces within 24 hours and 100 % was eliminated within three days. Approximately 0.01- 0.05 % of radioactivity was detected in organs or incorporated in proteins and nucleic acids (IARC, 1983). The rapid systemic clearance of captan in rats occurred mostly via the kidneys. The kidneys and the blood contained negligible levels of radiolabelled captan 96 hours after dosing (HSDB).

The urinary metabolites identified in Sprague Dawley (SD) rats fed with radiolabelled captan included: thiazolidine-2-thione-4-carboxylic acid (TTCA), a salt of dithiobis(methanesulphonic acid), and the disulphide monoxide derivative of dithiobis(methanesulphonic acid) (DeBaun et al., 1974). In another oral study in rats, the metabolites found in the urine and the faeces included 1,2,3,6-tetrahydrophthalimide (THPI); 6-carbamoyl-3-cyclohexene-1-carboxylic acid (THPAM); 3-hydroxy-1,2,3,6-tetrahydrophthalimide (3-OH-THPI); and 5-hydroxy-6-carbamoyl-3-cyclohexene-1-carboxylic acid (FAO). Captan also produced a highly reactive metabolite, thiophosgene, which was further metabolised to trichloro isocyanuric acid (TCCA) (IARC, 1983).

The chemical is rapidly degraded in the gastrointestinal tract of SD rats. This process appeared to play a major role in the metabolism of captan. The N-S bond of captan (see **Structural Formula**) is rapidly cleaved in the blood and gastrointestinal tract of rats (IPCS, 1990b). In mice, a greater proportion of the administered dose reaches the small intestine compared with rats (IPCS, 1990a).

In humans, two known captan metabolites (TCCA and THPI) were detected in the urine (12-24 h) after oral and dermal exposure to captan, although these metabolites represented only small percentages (1-9 %) of the orally administered doses. In five human volunteers, the reported mean elimination half-life of THPI was 13.4 hours following oral administration and 21.3 hours following dermal administration (HSDB).

The dermal absorption of captan has been investigated in vivo in rats, mice and humans. The dermal absorption rates reported in these studies were: 11 % in SD rats after eight hours exposure and ~9 % in Fischer 344 rats after 72 hours. In mice, the dermal absorption rates were 3.6, 3.8, and 7.8 % for one, six, and 24 hours exposure, respectively (Fisher et al., 1992; CEPA, 1999). In a human dermal absorption test in vivo, a rate of 0.3 % for 24 hours was reported. Approximately 2 % dermal absorption of captan was reported in a biological monitoring study on strawberry harvesters (CEPA, 1999).

Acute Toxicity

Oral

The chemical has low acute toxicity following oral exposure in rodents. The median lethal dose (LD50) in rats and mice is in the range of 7500-12500 mg/kg bw (IARC, 1983; IPCS, 1990a). The low toxicity is attributed to the rapid degradation of the chemical in the gastrointestinal tract (see **Toxicokinetics** section) (HSDB).

Results from a study predating good laboratory practice (GLP) indicated that protein deprivation increased the acute oral toxicity of captan in rats (IARC, 1983). In this study, oral exposure of protein-deprived rats to high doses of captan (doses and strain not specified) resulted in the following effects: hypothermia; irritability; listlessness; anorexia; weakening of reflexes (hyporeflexia); abnormally small amount of urine (oliguria); higher than normal glucose content in the urine (glycosuria); presence of blood in the urine (haematuria) and eventually death due to cardiac or respiratory failure (HSDB). Captan has been reported to cause deaths in sheep at 250 mg/kg bw (Extoxnet). However, no further details were provided.

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The median lethal dose (LD50) in rabbits is >2000 mg/kg bw (REACH). No reports of sub-lethal effects were reported.

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). The available data support the hazard classification.

In an acute inhalation toxicity study, male and female SD rats (n=10/dose) were exposed to 93 % pure captan dust administered in air (nose only) for four hours. This study was conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 403. In this study, three nominal concentrations of captan were tested: 0.4; 1.8; and 12.6 mg/L. The actual doses received were approximately 0.23, 0.94 and 4.81 mg/L of captan during the four hours' exposure. The treated animals exhibited the following effects: wet fur; decreased respiratory rate; hunched posture; lethargy; piloerection; uncoordinated movements (ataxia); drooping of the upper eyelid (ptosis); gasping; laboured/noisy respiration; red/brown stains around the snout; pallor of the extremities; dehydration; and frequent sneezing. Post-mortem examination revealed haemorrhaged and swollen lungs that also contained fluid, haemorrhaged/reddened or congested small intestines, dark coloured liver, and the presence of fluid in the nasal/oral tract. The median lethal concentration (LC50) values reported in this study were 0.90 mg/L and 0.67 mg/L in males and females, respectively. The combined LC50 was 0.78 mg/L (REACH).

In resting mice, the LC50 determined over two to four hours' exposure ranged between 4 and 5 mg/L (ChemIDPlus; HSDB). Administration of mechanically milled technical grade captan resulted in LC50 values of 1.7 mg/L for male mice and 3.7 (2.8-4.8) mg/L for female mice for an exposure duration of two hours (IARC, 1983).

Observation in humans

Few reports of acute toxicity of captan in humans are available (HSDB). Death of one individual was reported following oral exposure to 1071 mg/kg bw of captan (NIOSH, 1995). No further details were supplied.

After attempted suicide by ingestion of 7.5 g of captan, a 17-year old woman developed headache, nausea, weakness, numbness of upper limbs, and substernal pain. Similar symptoms were presented by a 22-year old woman following suicide by ingestion of 5 g of captan. Changes in the electrocardiogram (ECG) were observed in both cases (HSDB).

A systematic toxicological post-mortem analysis was conducted on a 40-year old woman (47 kg) who died after ingesting a mixture of prescription tablets (lacosamid and citalopram), and an unknown amount of captan. The total amount of the captan metabolite THPI in the gastric contents was 1.5 mg; THPI was detected: heart blood (0.35 µg/mL), bile (0.30 µg/mL), liver (0.24 µg/mL), femoral blood (0.22 µg/mL), kidney (0.14 µg/mL) and cerebrum (0.06 µg/mL). The cause of death was non-specific. A slight overdose of two prescription drugs was not sufficient to explain the fatality. The authors concluded that the combination of captan, citalopram, and lacosamid in high concentrations was fatal (Gottzein et al., 2011).

Corrosion / Irritation

Corrosivity

There are no available studies indicating that the chemical is corrosive. However, some of the decomposition products of the chemical are reported to be corrosive (HSDB). No further details are available.

Skin Irritation

The chemical is reported to slightly irritate the skin of New Zealand White (NZW) rabbits (REACH). In this guideline-compliant study, a single dose of 0.5 g of captan was applied to the skin of rabbits (n=3), under a semi-occlusive condition for four hours. Effects were evaluated at 1, 24, 48 and 72 hours after patch removal using the Draize scoring method. The chemical induced slight erythema in all treated skin sites at 24 hours and in one site at 48 hours. These effects were reversible by 72 hours (REACH). The chemical was also reported to be a slight skin irritant at 900 mg/kg (HSDB). However, no further details were provided.

Overall, available data are not sufficient to recommend a hazard classification.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Results from an irritation study in a female NZW rabbit indicated irreversible eye irritation following a single exposure to captan. This study was conducted in accordance with the OECD TG 405. In this study, the right lower eyelid of the rabbit was exposed to 82 mg of captan (in 0.1 mL solution) for five hours. The effects were scored within one hour or five hours of exposure to captan using the Draize method. This level of exposure resulted in corneal changes (dulling of the normal lustre of the corneal surface) after one hour exposure. Areas of diffuse corneal opacity were noted after five hours. In both studies, inflammation and severe conjunctival irritation were observed. Haemorrhage of the nictating and conjuctival membranes was also reported after five hours. The maximum overall scores were: 4 for chemosis; 3 for conjunctival redness; 1 for iritis; 1 for corneal opacity; and 4 for area of corneal opacity (REACH). Under the conditions of study, captan is considered a severe eye irritant.

Observation in humans

The chemical is reported to be irritating to the eyes and skin in humans. However, no further details were supplied (IPCS, 1990a).

Sensitisation

Respiratory Sensitisation

The chemical was reported to cause respiratory sensitisation in animal studies (IPCS, 1990a). However, no further details were supplied. The available information is insufficient to recommend hazard classification.

Skin Sensitisation

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

A guinea pig maximisation test (GMPT) (OECD TG 406 compliant) was conducted in female Dunkin-Hartley guinea pigs (n=20 treated; n=10 control). The intradermal induction used 0.1 mL solution containing 0.1 % captan suspended in arachis oil or in

Freund's Complete Adjuvant (FCA) in distilled water. The topical induction used 50 % captan in arachis oil applied to the skin of animals under occlusive conditions for 48 hours. Effects were monitored at one hour and 24 hours. The animals were challenged at day 21 by applying 0.1-0.2 mL of solution containing 10 % captan in arachis oil to the skin of animals for 24 hours under an occlusive condition. The effects were evaluated 24 and 48 hours after exposure. Positive skin reactions were reported in 16/20 treated animals 24 hours after challenge exposure and 14/20 after 48 hours. Clinical observations after one hour included bleeding and scattered mild and diffuse redness. At 24 hours, the treated skin showed the following effects: bleeding; hardened light brown scab; small superficial scattered scabs; peeling; and oedema. No skin reactions were observed in the control group. Under the conditions of this study, the chemical is considered as a sensitiser in guinea pigs (REACH).

Observation in humans

Several available reports indicated that captan causes skin sensitisation in humans.

In one report, 30 fruit and vegetable farmers who had dermatitis in the face, neck, hands, and feet were patch tested with various pesticides. Captan was the most common sensitiser, with positive results in five patients (HSDB).

A patch test was conducted in 122 fruit farmers who regularly prepared and sprayed pesticides and 63 printing press workers with no known exposure to pesticides. Skin sensitisation was observed in 9 % of farmers and 8 % of press workers following a patch test with 0.5% captan. Positive patch tests results were strongly associated with hand dermatitis in farmers (Guo et al., 1996).

Captan was implicated in skin reactions presented by a 73-year old retired fruit grower. These include persistent erythema, itching, and skin peeling (desquamation) of the face and back of hands (HSDB).

Occupational exposure to captan has been reported to cause skin reactions in hairdressers. In one report, intense pruritis on hands and forearms, with swelling of eyelids, were reported in a hairdresser in Spain. These skin reactions progressed into pruriginous erythematous papules (itchy red lesions) in the hands, forearms, face, and neck during an 8-month period. Treatment with antihistamines and topical corticoids ameliorated these conditions but the dermatitis recurred within three days of returning to work (HSDB). In another report, 6/98 hairdressers had positive reaction to 0.5 % captan in a patch test. The majority of the hairdressers had occupational dermatosis (non-inflammatory skin disorder) (Guo et al., 1994).

Repeated Dose Toxicity

Oral

Studies in mice and dogs were conducted to evaluate the repeat dose oral toxicity of captan. Based on the treatment-related effects reported in these studies, repeated oral exposure to the chemical is not considered to cause serious damage to health. A recommendation for hazard classification is not warranted.

In a 28-day oral study, abnormalities in the duodenum of mice were reported following exposure to captan. In this study, CD-1 mice (25 males/group), were given diet containing 3000 ppm (equivalent to approximately 440 mg/kg bw/day) of captan (purity, 89.4%) for the first two days and the dose was increased to 700 mg/kg bw/day from day seven to 28. The effects were examined at 1, 3, 7, 14 and 28 days. No changes were observed at day one; however, the following abnomalities in the duodenum were observed at day three: crypt cell hyperplasia; shortening of the villi; and disorganised villus enterocytes. From day seven onwards, immature cells at the tips of the villi and gastritis in the glandular portion of the stomach were noted. On day 28, horny growth on the skin (focal parakeratosis) was observed in one mouse (FAO/WHO, 2004).

In another 28-day oral study, the chemical was administered to beagle dogs in gelatin capsules containing captan at doses 0, 30, 100, 300, 600 or 1000 mg/kg bw/day. The results showed the following dose-related effects observed in all treated groups; vomiting (emesis); and reduction of bodyweight gain. At 600 and 1000 mg/kg bw/day, slight changes in clinical and biochemical parameters were reported. These changes were not statistically significant and were attributed to vomiting and changes in bodyweight and food consumption. However, it is noted in the report that the toxicological significance of these observations is unclear (FAO/WHO, 2004).

A no observed effect level (NOEL) of 300 mg/kg bw/day was reported in a one-year oral study in beagle dogs, which was conducted in accordance with the US Environmental Protection Authority (EPA) Guideline 83-1. In this study, male and female dogs (n=5/sex/dose) were given gelatin capsules containing 0, 5, 60, and 300 mg/kg bw/day of the chemical once daily for one year. No treatment related changes were observed in any of the treated groups (REACH).

In a two-year carcinogenicity study in Charles River CD rats (see **Carcinogenicity** section), a NOAEL of 25 mg/kg bw/day for systemic effects and a lowest observed adverse effect level (LOAEL) of 100 mg/kg bw/day were reported. The effects observed at 100 mg/kg bw/day included hepatocyte hypertrophy, increased relative organ weight for kidneys and reduced bodyweight in both sexes (US EPA, 1990).

Dermal

Considering the limited available information for the chemical, a recommendation for hazard classification is not warranted.

Changes in the skin were observed following a 21-day dermal study in rabbits. In this US EPA Guideline 83-1 compliant study, rabbits were exposed to 0 (control), 12.5, 110 and 1000 mg/kg bw/day of captan, six hours' exposure per day for 21 days. At 1000 mg/kg bw/day, a significant decrease in bodyweight gain was observed in males and females. In this group, the treated skin also showed desquamation (peeling), erythema, oedema, discolouration (acanthosis), and abnormal thickening (hyperkeratosis). On day four, some animals at 1000 mg/kg bw/day showed slight erythema, oedema and desquamation. At 110 mg/kg bw/day, one female rabbit died on day nine of the treatment. On day 21, the following effects were reported: a slight desquamation in one female at 12.5 mg/kg bw/day; and slight erythema in two females at 110 mg/kg bw. The reported NOELs were 110 mg/kg bw/day for systemic toxicity and less than 12.5 mg/kg bw/day for the local effects (REACH).

Inhalation

In a 13-week repeated dose inhalation toxicity study in male and female rats (Alpk:APfSD), the no observed adverse effect concentration (NOAEC) for captan was reported to be 0.6 µg/L (REACH). Based on the available information, hazard classification for repeated dose inhalation toxicity is not recommended.

In a guideline compliant study (US EPA 82-4), rats were exposed to captan 'nose only' for six hours a day, five days a week at 0, 0.1 µg/L, 0.5 µg/L, 5.0 µg/L, and 15 µg/L. The measured concentrations based on the gas chromatography analysis, were 0; 0.13; 0.60; 5.06; and 12.98 µg/L. The study used 10 animals per group, except for controls and high dose groups (n=20/sex/dose) (REACH). The results showed statistically significant reductions in bodyweight of males from all treated groups in week one. In weeks five to 13, four males from the high dose group (12.98 µg/L) died. Bronchial/bronchiolar epithelium necrosis was implicated in the death of these animals. In this group, one male was sacrificed in extremis during week 11. One female from each of the 0.13 and 5.06 µg/L groups was sacrificed in extremis during week six and 10. Other treatment related effects in higher dose groups included rales and microscopic changes in the lung, larynx, nasal passages and trachea. After a four-week recovery period, the effects observed in the lung and the nasal passage were reversible (REACH). Under the conditions of the study, the chemical is not considered to cause serious damage in rats.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is considered to be genotoxic. The chemical is recommended for hazard classification (see **Recommendation** section).

In vitro, the chemical was positive in the following tests:

- bacterial reverse mutation assays in *Salmonella typhimurium* assay in strains TA 1535, TA 1537, TA 98 and TA 100 up to 10 µg/plate (with and without metabolic activation) and in *Escherichia coli* WP2 uvrA, WP2 and SDS4-73 (IARC, 1983; REACH);
- growth inhibition assays in DNA repair-deficient strains of *E. coli* (WP2 uvrA, WP2 uvrA exrA, pol A^-, pol A^+) and *Bacillus subtilis* H17 rec^+ and M45 rec^- (IARC, 1983);
- chromosomal aberration (CA) and sister chromatid exhange (SCE) in Chinese hamster V79 lung cells (IARC, 1983);

- unscheduled DNA synthesis (UDS) in SV-40 transformed human VA-4 cells (with or without metabolic activation) and in human lymphocytes (IARC, 1983); and
- DNA damage in cultured Chinese hamster V79 lung cells (IARC, 1983).

Incubation of the human embryonic lung cells L-132 with 10 µg/mL captan caused 50 % reduction in DNA synthesis and 40 % increase in chromosomal breaks (IARC, 1983).

The chemical gave negative results in vitro in CA and SCE assays in human fibroblast cells and UDS in human fibroblast cells and rat primary hepatocytes (IARC, 1983).

In vivo, captan induced micronuclei formation in the bone marrow and the testes of mice (strain not specified) (Feng and Lin, 1987). In this study, mice were fed captan at doses 0, 10, 50, 100, 400, and 800 mg/kg bw/day for two days. The results showed a dose-dependent increased incidence of micronuclei in the polychromatic eryththrocytes. Additionally, the chemical induced CA in bone marrow cells and spermatogonia at doses above 400 mg/kg bw/day. In other studies, the chemical was reported to be genotoxic in a comet assay in *Xenopus laevis* and *Pleurodeles waltl* at doses up to 62.5 µg/L (Mouchet et al., 2006).

In an OECD TG 474-compliant study, the chemical did not cause chromosomal damage following a micronucleus test in Charles River CD-1 mice (REACH). The chemical also gave negative results in the following in vivo assays: dominant lethal assays in mice (Swiss SC-1 and ICR/SIM); and sex linked recessive assay in *Drosophila melanogaste*r (IARC, 1983). However, the addition of of 2000 mg/L of captan (technical grade, unspecified purity) to the feeding solution caused a weak positive response in *D. melanogaste*r (IARC,1983).

Captan is reported to alkylate DNA producing 7-(trichloromethylsulphenyl)guanine (IARC, 1983).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). The available data support this classification.

Osborne-Mendel rats (n=50/sex/dose) were exposed to a diet containing 4000 mg/kg of captan for 21 days and 2000 mg/kg for the following 59 weeks (low dose) (equivalent to approximately to 200 and 100 mg/kg bw/day) or 8000 mg/kg captan for 41 weeks and 4000 mg/kg of captan for the following 39 weeks (high dose) (equivalent to approximately to 400 and 200 mg/kg bw/day). The results showed a dose-related increase in the incidence of C-cell adenomas of the thyroid (IARC, 1983).

Charles River CD rats were given 0 (control), 25, 100 or 250 mg/kg bw/day of captan in diet. At 100 mg/kg bw/day, treated rats displayed hepatocellular hypertrophy (males), increased relative organ weight (heart, brain, liver and thyroid/parathyroid) and reduced bodyweight in males and females. A significant increasing trend for the combined adenomas and carcinomas of the kidneys was observed in male rats (US EPA, 1990). In a 30-month feeding study, a slight but statistically significant increase in uterine sarcomas at 98 mg/kg bw/day was reported in Wistar rats (US EPA, 1990).

In another study, B6C3F1 mice (n=50/sex/dose) were administered a diet containing 8000 and 16000 mg/kg of the chemical (equivalent to approximately 900 and 2400 mg/kg bw/day) for 80 weeks. The results demonstrated a dose-related increase in the incidence of duodenal adenocarcinoma at 2400 mg/kg bw/day (IARC, 1983; US EPA, 1990). In another long term oral study (six months to one year) in male CD-1 mice, captan doses of 6000 ppm (equivalent to approximately to 900 mg/kg bw/day) produced adenomas and adenocarcinomas in the small intestine (IPCS, 1990b).

The mechanism of action underlying the carcinogenicity of captan is still not fully understood. However, thiophosgene, a toxic metabolite of captan, is implicated through the chronic irritation of the intestinal epithelium in long term mice dietary studies at high doses (US EPA, 1990).

Following a reclassification review of the carcinogenicity of captan, the US EPA noted that it is ‘not likely to be a human carcinogen at dose levels that do not cause cytotoxicity and regenerative cell hyperplasia’ and ‘likely to be carcinogenic to humans following prolonged, high-level exposures causing cytotoxicity and regenerative cell hyperplasia' (US EPA, 2004).

Reproductive and Developmental Toxicity

Based on the available data, the chemical does not cause serious reproductive or developmental toxicity.

In an oral gavage study in HY/CR NZW rabbits, captan did not induce toxic effects in the foetuses. In this study, mated rabbits were treated with 0 (control), 10, 40, and 160 mg/kg bw/day of captan suspended in carboxymethycellulose, from gestational day (GD) seven to 19. The results indicated maternal effects including reduced food intake and decreased bodyweight gain at 160 mg/kg bw/day. Post implantation loss, one case of abortion, one case of foetal death and an increased frequency of minor skeletal variations were reported at 160 mg/kg bw/day. However, the publicly available summary for this study lacked details. No foetotoxicity was observed at 10 and 40 mg/kg bw/day (IPCS, 1990b).

In another developmental toxicity study in NZW rabbits (US EPA 83-3 guideline-compliant), the NOAEL and LOAEL values reported for maternal toxicity and developmental toxicity were 10 and 30 mg/kg bw/day, respectively. Female rabbits (n=20/dose) were exposed to captan by oral gavage in corn oil at doses of 0 (control), 10, 30 and 100 mg/kg bw/day once daily from GD seven to 19 (US EPA, 1990; REACH). The results showed that pregnancy was not affected by the treatment; however, significant reduction in maternal bodyweight gain was observed at 30 and 100 mg/kg bw/day. A significant increase in the incidence of early and late intra-uterine deaths (post-implantation loss) was seen at 100 mg/kg bw/day. Overall, the total implantation losses was not affected by exposure to the chemical. Similarly to the dams, the foetal bodyweights were significantly reduced at 100 mg/kg bw/day. Increased incidences of major and minor foetal body defects were observed at 30 and 100 mg/kg bw/day. These included head defects, unossified sixth and seventh lumbar transverse processes, asymmetric alignment of the pelvic girdle and skeletal defects as indicated by foetuses with 27 pre-sacral vertebrae (US EPA, 1990; REACH). According to the report, the diverse nature of major body defects in foetuses was not considered consistent evidence of a compound-related effect (REACH).

Results from a three-generation oral reproductive study in Crj: CD(SD) rats reported NOEL values of 25 mg/kg bw/day for maternal toxicity; 500 mg/kg bw/day for reproductive toxicity (fertility); and 100 mg/kg bw/day for foetal toxicity. In this study, the parental animals were given a diet containing captan at doses 0 (control), 25, 100, 250 and 500 mg/kg bw/day for 100 days. The parental bodyweights and food consumption were reduced in all generations in a dose-dependent manner. Significant decreases in the foetal bodyweight were noted at 500 mg/kg bw/day. Changes in the reproductive parameters included high incidences of perinatal pup losses in the first generation only, reduced pup survival up to lactation day four at 250 and 500 mg/kg bw/day, and reduced litter size from 250 mg/kg bw/day in all three generations. Compared with controls, no captan-induced teratogenic effects were reported (REACH).

In vitro, captan has been demonstrated to inhibit differentiation of the cultured cells from the midbrain and limb bud of somite rat embryos. The inhibition was more effective in the absence of metabolic activation (IPCS, 1990b).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (mutagenicity and carcinogenicity);
- systemic acute effects (acute toxicity from inhalation exposure); and
- local effects (skin sensitisation and eye irritation).

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic and domestic products overseas. The use of the chemical in wallpaper pastes and textiles could pose risk for accidental ingestion in children.

The chemical is currently listed on Schedule 6 of the SUSMP. A number of warning statements, first aid instructions and safety directions relating to the use of the chemical apply. The current controls are considered adequate to minimise the risk to public health posed by domestic and cosmetic products containing the chemical, therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, exposure may 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 systemic local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal exposure are implemented. Hence, 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	Toxic by inhalation (T; R23)*	Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)*	Causes serious eye damage - Cat. 1 (H318)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[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 industry

Control measures

Control measures to minimise the risk from oral, inhalation, dermal and ocular exposure to the chemicals 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 chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- air monitoring to ensure control measures in place are working effectively and continue to do so;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- 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 chemicals.

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 chemicals 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 this chemical has not been undertaken as part of this assessment.

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