2-Imidazolidinethione: Human health tier II assessment

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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.

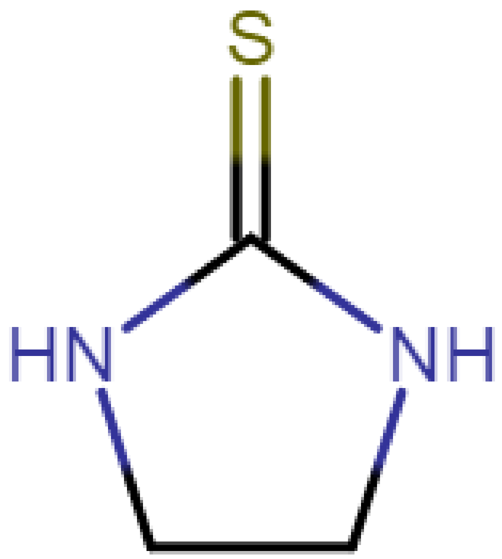
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-mercaptoimidazoline ethylene thiourea 4,5-dihydroimidazole-2(3H)-thione imidazolidine-2-thione 2-thiol-dihydroglyoxaline
Structural Formula	
Molecular Formula	C3H6N2S
Molecular Weight (g/mol)	102.16
Appearance and Odour (where available)	White to pale-green needle-like crystals, with a faint amine odour.
SMILES	C1(=S)NCCN1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (International Agency for Research on Cancer (IARC)).

The chemical has reported commercial use in electroplating baths.

The chemical has reported site-limited uses, including:

- as an accelerator for vulcanising polychloroprene (neoprene) and polyacrylate rubbers; and

- as an intermediate in the production of antioxidants, dyes and synthetic resins.

The chemical has reported non-industrial uses for manufacturing pesticides/fungicides and pharmaceuticals.

Restrictions

Australian

No known restrictions have been identified.

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; and
- The 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.

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; R22 (acute toxicity)
- Repr. Cat. 2 R61 (developmental toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standard is identified (Galleria Chemica):

- an exposure limit of 0.1 mg/m^3 time weighted average (TWA) in Poland.

Health Hazard Information

Toxicokinetics

Animal studies have shown that the chemical (ETU) can be absorbed orally and dermally, with accumulation observed in the thyroid, independent of the administration route and species.

Following oral administration in rats and mice, the chemical was readily absorbed from the gastrointestinal tract, and widely distributed. Accumulation was observed specifically in the thyroid, in both species. The primary elimination route was via urine; mice eliminated the chemical more rapidly than rats. Mice showed increased hepatic cytochrome P450 (CYP450) and aniline hydroxylase activities, while these liver enzymes were markedly decreased in rats (NTP, 1992; IARC, 2001).

The chemical is metabolised via different pathways in rats and mice, and the rate of metabolism was reported to be higher in mice compared with rats. In mice, the chemical is rapidly metabolised preferentially via the flavin-dependent mono-oxygenase (FMO) system. FMO-mediated binding of the metabolites of the chemical to mouse liver proteins is associated with chronic hepatotoxicity effects in this species. In mice, the major metabolite identified in vivo (following oral exposure) or in vitro (with mouse liver microsomes), was 2-imidazolin-2-yl sulfenate (NTP, 1992; IARC, 2001).

In male Sprague Dawley (SD) rats, the major metabolites identified in the urine at 24 hours following an oral dose of the chemical at 4 mg/kg bw were imidazoline, ethylene urea, and 4-imidazoline-2-one (imidazolone). In cats (at the same dose), the metabolites ethylene urea and S-methyl ethylenethiourea were identified in the urine at 24 hours (NTP, 1992; IARC, 2001).

The chemical was readily absorbed in pregnant Wistar rats, treated orally with the chemical at single doses of 100–240 mg/kg bw on gestation day (GD) 12, and was distributed throughout the maternal system and into the embryo. Peak concentrations were observed in the maternal plasma and amniotic fluid at two hours, and in the embryo at 30 minutes; no detectable levels of the chemical were observed after 48 hours. Around 70 % of the chemical was excreted unchanged in the urine by 24 hours following administration, and indicated minimal metabolism of the parent compound. Wistar rats and Swiss mice administered a single dose of 240 mg/kg bw of radiolabelled chemical on GD 15 had similar maternal and foetal concentrations in tissues at three hours. The half-life (elimination from maternal blood) was 5.5 and 9.4 hours in mice and rats, respectively (IARC, 2001; REACH).

A dermal absorption factor of 26 % of the chemical (dose level not stated) was reported in rats, following dermal exposure for 10 hours. In tissues, the chemical was found at the highest concentration in the thyroid (HSDB).

Five non-smoking male volunteers were administered a diet containing 8.8 µg/L of the chemical in wine for 8 days (this was reported to be the only detectable level of the chemical in the diet). The subjects were not occupationally exposed to the chemical. Urine was collected for every 24-hour period. Approximately 48 % of the chemical (on average) was observed to be excreted unchanged in the urine during the 8-day study period (REACH).

The chemical is an environmental degradation product or metabolite of ethylenebisdithiocarbamate (EBDC) fungicides. Human case studies have indicated measurable concentrations of the chemical in the urine following exposure to EBDCs. In a surveillance study in Mexico, elevated urinary concentrations of the chemical was reported in agricultural workers who were repeatedly exposed to EBDCs. The chemical was not detected in an unexposed control group (NTP, 2014; REACH). A 22-day biomonitoring study in potato farm workers applying EBDCs reported a urinary half-life of ETU of approximately 100 hours (Kurttio et al., 1990).

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). Athough the oral median lethal dose (LD50) for mice of >2000 mg/kg bw is above the classification cut-off, the available data for the preferred species (rat) —LD50 values of 545–1832 mg/kg bw— support this classification (HSDB).

The chemical affected microsomal enzymes in the livers of male rats, including inhibition of aminopyrine-n-demethylase and aniline hydroxylase activities. Cytochrome P450 content was observed to decrease in rats but increase in mice. A dose-dependent increase in microsomal aniline hydroxylase was observed in mice within 24 hours following acute oral exposure of 50–600 mg/kg bw (HSDB). Mice displayed hypoactivity and tonic convulsion, but only at a very high dose (>4000 mg/kg bw) (REACH).

Dermal

Based on the available information, the chemical is considered to have low acute dermal toxicity.

In an acute dermal study conducted according to the OECD Test Guideline (TG) 402, the chemical (2000 mg/kg bw) was applied to the shaved intact dorsal skin of SD rats for 24 hours, with observation up to 14 days. No mortality, clinical signs of toxicity, or skin reactions were observed (REACH). The dermal LD50 is considered to be >2000 mg/kg bw.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not a skin irritant.

In a skin irritation study (OECD TG 404), the chemical (500 mg) was applied to the shaved intact dorsal skin of Himalayan rabbits (n = 3) (occlusively) for four hours, with observation up to 72 hours. No reactions (erythema and oedema) were observed. The animals did not display any systemic intolerance reactions (REACH).

Eye Irritation

Based on the available data, the chemical is considered to be a mild eye irritant. The effects do not warrant hazard classification.

In an eye irritation study (OECD TG 405), the chemical (0.1 mL) was instilled in the conjunctival sac of the left eye of female Japanese white rabbits (n = 3), with observation for up to 21 days. The animals were scored according to the Draize test (range: 0–110). The chemical was reported to induce mild to no effects (scores: 0–7), which were reversible within 24 hours (REACH).

Sensitisation

Skin Sensitisation

Based on the limited available data, the chemical is not considered a skin sensitiser

In a mouse ear swelling test (non-guideline), female B6C3F1 mice (n = 8/dose) were epicutaneously administered the chemical at concentrations of 1.0, 3.0 or 10.0 % in ethylene glycol on a dorsal surface site for five consecutive days. At seven days after the last application, the animals were challenged (epicutaneously) with 10 % of the chemical on the dorsal and ventral sites on the left ear, then evaluated at 24 and 48 hours. No signs of skin irritation (erythema and oedema), and no statistically significant or dose-related hypersensitivity response was observed in the animals at concentrations up to 10 % of the chemical (REACH).

Observation in humans

There are a few reported cases of contact dermatitis in humans. However, there is no definitive conclusion for the sensitisation potential of the chemical in humans.

In one case, 11 patients developed contact dermatitis within 11 days after using rubber (Vulkan) heat retainers. Subsequent patch testing was conducted with the chemical, with positive reactions observed in 6/7 patients tested. The authors stated that the relevance of contact allergy to the chemical, in relation to use of the heat retainers, was hard to determine (REACH).

In another study in Poland, patch tests were performed on 200 patients with contact dermatitis. The chemical was applied at a concentration of 2 % in yellow soft paraffin. Only one person exhibited a positive reaction (REACH).

In two contact dermatitis studies with limited documentation, patch testing with the chemical at 1 % for 72 hours caused 2/31 positive reactions in one study, and 1/5 positive reactions in another study (concentration and duration not stated) (REACH). A 53-year old female, who had a 13-year occupational history in a synthetic and natural rubber product industry, reported allergic contact dermatitis at a concentration of 0.01 % ETU. The patient also showed positive reactions to nickel and cobalt (REACH).

Repeated Dose Toxicity

Oral

Based on the available data from studies in rats, the chemical is considered to cause effects, specifically in the thyroid, following repeated oral exposure to doses >8 mg/kg bw/day (90-day). Similar effects are also reported in rodent carcinogenicity studies (see **Carcinogenicity**). Worker studies did not show marked thyroid effects in humans (see **Observations in Humans**).

The main adverse effects observed in rats and mice were in the thyroid and liver. Rats showed a greater sensitivity to thyroid lesions (~8 mg/kg bw/day), whereas mice were more susceptible to liver lesions (~100 mg/kg bw/day). The difference in observations is partially attributed to the different metabolism rates and pathways of the chemical in these species (see **Toxicokinetics**).

In a repeat dose toxicity study (OECD TG 408), SD rats were administered the chemical in the diet at doses of 0, 1, 5, 25, 125 or 625 ppm (~0, 0.07, 0.3, 1.7, 8.0 or 42 mg/kg bw/day), daily for up to 90 days. Thyroid hormone levels (triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH)) were observed at 30-day intervals. At the highest dose, mortality occurred in 14 out of 40 rats between days 40 and 60. Clinical signs of toxicity including excessive salivation, hair loss and failure to replace it, rough coat and scaly skin texture were observed before day 8. At doses ≥125 ppm, thyroid hormone effects (decreased serum T3 and T4 concentrations, increased TSH concentrations), decreased iodine uptake, and moderate thyroid hyperplasia were observed. The no observed adverse effect level (NOAEL) was determined as 25 ppm (~1.7 mg/kg bw/day) based on thyroid effects at 125 ppm (~8 mg/kg bw/day) (REACH).

In a 28-day repeat dose toxicity study (OECD TG 407), SD rats (n = 5/sex/dose) were administered the chemical at 0, 1, 6 or 30 mg/kg bw/day, for 28 days. Prominent effects were mainly observed at the highest dose, and included abnormal fur conditions, decreased body weights and food consumption. Clinical chemistry effects at 30 mg/kg bw/day included raised total cholesterol levels, low alkaline phosphatase (ALP) and inorganic phosphorus in males, and high chlorine levels in both sexes. Effects on organ weights at 30 mg/kg bw/day included increased relative liver weights in females, absolute and relative thyroid weights in both sexes. Decreased absolute and relative thymus weights were seen in females at ≥6 mg/kg bw/day. Hypertrophy of the basophilic cells in the pituitary and sebaceous glands and atrophy of the skin in both sexes were observed at 30 mg/kg bw/day. At 6 mg/kg bw/day, decreased colloid and diffuse follicular cell hypertrophy in the thyroid were observed in males, and were considered to be severe. Based on these effects, the NOAEL was determined as 1 mg/kg bw/day (REACH).

In repeat dose toxicity dietary studies in rats conducted for 90–120 days, thyroid effects were observed from 100 ppm (~10 mg/kg bw/day), and included serum hormone changes, increased weights, ultrastructural changes and decreased iodine uptake (REACH). Rats administered 1–500 mg/L of the chemical in drinking water showed alterations in hepatic cell morphology, increased smooth endoplasmic reticulum, and decreased rough endoplasmic reticulum at the highest dose at four months. The authors considered these effects to be 'a response to the sustained ingestion of high concentrations of highly toxic materials' and are most likely not directly representative of the toxic effects of the chemical (REACH).

In 13-week range-finding studies (conducted by the National Toxicology Program), rats exhibited dose-dependent hyperplasia of the thyroid follicular epithelium at ≥60 ppm (calculated as ~5.4 mg/kg bw/day), and liver centrilobular cytomegaly (hypertrophy) at ≥750 ppm (~67.5 mg/kg bw/day). In comparison, mice showed both increased thyroid follicular hyperplasia and hepatocellular cytomegaly at ≥500 ppm (calculated as ~100 mg/kg bw/day). An increase in hepatic cytochrome P450 in mice was also observed (NTP, 1992)

Short-term studies in rats (28 days) reported similar effects in the thyroid, at the lowest administered dose of 100 mL (~10.6 mg/kg bw/day) in drinking water. Renal toxicity (alterations in renal proximal tubule epithelial cells) was observed at 300 mg/L (~23.4 mg/kg bw/day), but prolonged administration had only minor effects on renal function (IARC, 2001; REACH). Similar thyroid effects were reported in chronic studies (104 weeks) in rats administered 125 ppm (calculated as ~6.25 mg/kg bw/day) in the diet (REACH).

Dermal

No data are available.

Inhalation

Based on the available study in rats, the chemical causes thyroid effects following repeated inhalation exposure to concentrations ≥0.04 mg/L.

In a repeat dose toxicity study (OECD TG 412), Wistar rats (n = 5/sex/dose) were exposed to the vapour of the chemical at 0, 0.01, 0.04 or 0.20 mg/L, five days/week, six hours/day for 28 days. Primary clinical toxicity signs observed at the highest dose (0.2 mg/L or 200 mg/m^3) were alopecia (hair loss) from week two, and hunched posture from week three. Other effects observed at this dose were severely reduced mean body weights, changes in haematological parameters (decreased reticulocyte count) and mean serum T4 levels, and histological changes in the pituitary and mandibular salivary glands. Thyroid effects observed at ≥0.04 mg/L (40 mg/m^3) consisted of increased follicular epithelial height, colloid depletion and agglomeration, diffuse hyperplasia, and increased vascularity. The no observed adverse effect concentration (NOAEC) was determined as 0.01 mg/L (10 mg/m^3) based on thyroid effects at 0.04 mg/L (REACH).

Observation in humans

The chemical is a metabolite, degradation product or contaminant in ethylenebisdithiocarbamate (EBDC) fungicides and serves as a biomarker for changes to thyroid hormone levels. Available studies show changes in TSH and T4 levels following occupational exposure to EBDCs (as measured by detectable levels of ETU). However, it is unclear whether these changes were caused by the chemical alone, or due to combined exposure to the parent chemical or other substances in EBDCs.

An epidemiology study was conducted to correlate blood levels of the chemical (blood ETU) with the incidence of thyroid disorders among randomly selected banana plantation workers (n = 88) in the Philippines. The workers were exposed to EBDCs either directly or indirectly for three years. The controls were 43 workers from an organic farm. The exposed group showed higher mean TSH levels compared with the controls, although these values were within the normal range. Around 9/88 workers showed abnormal thyroid ultrasound findings (mainly solitary nodules). Significantly different blood ETU levels were observed between the exposed and control groups, but there was minimal difference in the urine ETU levels. A direct correlation between blood ETU levels and thyroid nodule sizes was established and, therefore, blood ETU was stated to be a reliable biomarker to detect thyroid disorders in humans (HSDB; REACH).

In another study, elevated TSH levels were reported in 49 Mexican pesticide applicators consistently exposed to EBDC fungicides without using personal protective equipment. However, these levels were considered as within the normal range. There were no changes in T4 levels or in thyroid function. Significantly increased sister chromatid exchanges and chromosome aberrations in the form of total translocations in peripheral lymphocytes were also observed but it was uncertain whether these effects were due to combined exposure to other chemicals in the fungicide (IARC, 2001; REACH).

In a human cohort study in England, the employment records of workers (n = 1929) at rubber manufacturing firms (where the chemical was used), and at firms producing the chemical were investigated within the period 1957–1971. None of the workers were reported to have developed thyroid cancer (IARC, 2001).

In another epidemiology study, male factory workers (ages 26–62) exposed to dust of the chemical over three years were evaluated. Concentrations of the chemical were measured as around 120–160 mg/m^3 . Serum T4 levels were lower (by 20 %) in exposed workers compared with controls. Levels of TSH were within normal limits, except for one worker who showed extremely high levels but was found to have premyxoedema (subclinical hypothyroidism). There was no evidence that thyroid function was affected by exposure to the chemical at these levels and no clinical toxicity effects were observed (IARC, 2001; REACH).

Genotoxicity

Based on the weight of evidence, the chemical is not genotoxic.

The majority of in vitro and in vivo genotoxicity results are negative. The DNA damage was observed in rats and mice in in vivo comet assays at high concentrations, but point mutation (Ames) tests were predominantly negative.

The chemical showed primarily negative results in the in vitro assays listed below (NTP, 1992; IARC, 2001):

- predominantly negative results in bacterial reverse mutation assays with several strains of *Salmonella typhimurium* and *Escherichia coli*, with or without metabolic activation;
- induced λ phage in *E. coli* in a DNA damage and/or repair test at 10000 µg/mL, with metabolic activation;
- negative in DNA damage assays: SOS repair chromotest in *E.coli*, and SOS repair Vitotox test in *S. typhimurium;*
- induced mitotic gene conversion (in one study at 50 µg/mL but not in studies up to 2 mg/mL), aneuploidy, intrachromosomal recombination and DNA damage in the yeast *Saccharomyces cerevisiae*;
- no induction of chromosomal aberrations or sister chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells, up to 10000 µg/mL;
- no induction of chromosomal aberrations or SCEs in Chinese hamster DON cells, rat liver R1 cells;
- no induction of micronuclei in Syrian hamster embryo cells; and
- positive results in one mouse lymphoma assay in L5178Y cells at 1800 µg/mL with metabolic activation, but negative in another study at 3000 µg/mL.

The chemical showed negative results in the following in vivo studies (IARC, 2001):

- no induction of chromosomal aberrations in the bone marrow of rats, administered the chemical twice orally at 400 mg/kg bw/day;
- no induction of micronuclei or SCE in the bone marrow of mice, administered the chemical intraperitoneally (i.p.) up to 2500 mg/kg bw/day, or orally up to 6000 mg/kg bw/day;
- negative in sex-linked recessive lethal mutation assays in *Drosophila melanogaster*; and
- no induction of dominant lethal mutations (up to an oral dose of 3500 mg/kg bw/day), sperm abnormalities in male mice (up to an i.p. dose of 2655 mg/kg bw/day), or inhibition of DNA synthesis of the mouse testes at an i.p. dose of 100 mg/kg bw/day.

The chemical showed positive in vivo results in the following DNA damage/comet assays in rats and mice.

In an in vivo single cell gel/comet assay, rat thyroid cells were examined for DNA damage. Rats were administered a single oral dose of the chemical at 916 mg/kg bw and evaluated for DNA fragmentation after 16 hours. A statistically significant increase in DNA fragmentation was observed in thyroid cells, also in the kidney (REACH).

In another in vivo comet assay, DNA damage was observed in the liver, kidney, lung and spleen, but not in the bone marrow of male mice administered (i.p.) a single dose of 2000 mg/kg bw/day, with observation up to 24 hours. The effect was greatest in the liver (REACH).

The International Agency for Research on Cancer (IARC) stated that the chemical is not genotoxic, on the basis of the 'lack of activity in appropriate tests in bacterial, mammalian cells in vitro and mice and rats treated in vivo' (IARC, 2001).

Carcinogenicity

A number of carcinogenicity studies have been conducted in rats and mice. Only thyroid tumours were observed in rats, whereas tumours in the liver, thyroid and pituitary gland were observed in mice. The relevance of thyroid tumours in rodents to humans is questionable, and alteration of thyroid hormone homeostasis has been observed to span doses that induce thyroid tumours in rodents (IARC, 2001). Although tumours were also observed in the liver and pituitary gland in mice, these were poorly characterised and, therefore, insufficient to allow for hazard classification.

The IARC has classified the chemical as 'not classifiable as to its carcinogenicity to humans (Group 3)', based on inadequate evidence for carcinogenicity in humans but sufficient evidence in experimental animals. The chemical was reported to be a hepatocarcinogen in mice, produced via a non-genotoxic mechanism. IARC further stated that the chemical produces thyroid tumours via a non-genotoxic mechanism, which is based on interference with the enzyme thyroid peroxidase resulting in thyroid hormone changes that will be much more pronounced in rodents than in humans. The chemical is thus not expected to cause thyroid tumours in humans at concentrations that do not alter thyroid hormone homeostasis (IARC, 2001).

The effects of DNA damage observed in the thyroid of rats and liver of mice, exposed to high concentrations of the chemical (see **Genotoxicity** section), were considered to be consistent with the carcinogenicity effects observed in the respective organs of these rodent species (REACH).

The US NTP, more recently, has stated that the chemical is 'reasonably anticipated to be a human carcinogen', based on sufficient evidence from animal studies (NTP, 2014).

In a chronic carcinogenicity study (OECD TG 453), SD rats (n = 68/sex/dose) were administered the chemical in diet at concentrations of 0, 5, 25, 125, 250 or 500 ppm (0, 0.25, 1.25, 6.25, 12.5 or 25 mg/kg bw/day), ad libitum for 12–24 months. A dose-dependent increase in the incidence of thyroid hyperplasia was observed from 5 ppm. Significantly increased incidences of thyroid carcinomas and adenocarcinomas were observed in males at ≥250 ppm, and in females at 500 ppm. Combined, incidences of thyroid tumours (adenomas and adenocarcinomas) were 4/72 (controls), 37/69 (250 ppm), and 65/70 (500 ppm) (IARC, 2001; REACH).

A carcinogenicity study was conducted by the NTP in F344/N rats and B6C3F1 mice to determine the carcinogenic potential of the chemical administered during and after the perinatal period, in addition to adult exposure of the offspring. Perinatal exposure included one week prior to breeding, throughout gestation and lactation until postnatal (PND) day 28. The offspring (F1 generation) were exposed to perinatal concentrations up to eight weeks of age, then exposed to adult concentrations for two years. Parental (F0) rats were administered the chemical in the diet at concentrations of 0, 9, 30 or 90 ppm during the perinatal period, and the F1 generation were administered 0, 25, 83 or 250 ppm as adults for two years. Mice were administered perinatal concentrations at 0, 33, 110 or 330 ppm, and the F1 generation were administered 0, 330 or 1000 ppm as adults. At the nine-month interim evaluation, the thyroid in rats and mice, and the liver in mice were identified as the target organs. Perinatal exposure alone had no carcinogenic effect in the animals. In rats, significantly increased incidences of thyroid follicular cell neoplasms (adenomas and carcinomas) were observed in males at ≥83 ppm and in females at 250 ppm (with or without perinatal exposure). Marginally increased Zymbal gland tumours were observed at the two highest combined perinatal and adult exposures of 90:250 ppm. In mice, significantly increased incidences of liver tumours were observed at 330 ppm (with or without perinatal exposure), significantly increased thyroid follicular cell neoplasms in females at 330 ppm (with perinatal exposure) and in both sexes at 1000 ppm (with or without perinatal exposure), and increased pituitary (pars distalis) adenomas at 1000 ppm (NTP, 1992; HSDB).

In 13-week range-finding studies (see **Repeat Dose Toxicity**), thyroid follicular cell adenomas were observed in rats, but not in mice. These observations were considered to be autonomous, due to prolonged elevated serum TSH levels (NTP, 1992).

The chemical was tested in two strains of mice (B6C3F1 and B6AKF1) in a 'screening' study. The mice were administered the chemical in 0.5 % gelatin in water by gavage at doses of 0 or 215 mg/kg bw/day for three weeks. The chemical was then mixed into the diet (calculated as 646 ppm, based on an approximate maximum tolerated dose) and administered to the 4-week old mice. This concentration was maintained throughout the study, from 4 weeks to 18 months. Statistically, a significantly increased incidence of hepatoma was observed in both strains (REACH).

No carcinogenic effects were observed in groups of hamsters (strain not stated) administered the chemical in diet at 0, 5, 17, 60 or 200 mg/kg bw for 20 months (IARC, 2001).

Observation in humans

Epidemiological studies are available regarding exposure to the chemical and cancer in humans, especially workers in the rubber industry and manufacturing facilities for the chemical. Overall, no incidences of thyroid cancer were reported. Available data are considered inadequate and insufficient for establishing a causal relationship due to shortcomings in these studies (IARC, 2001; HSDB).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 2 substance toxic to reproduction—with the risk phrase 'May cause harm to the unborn child' (T; R61) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). The available data support this classification.

Many developmental toxicity studies were conducted in animals and the chemical was found to be teratogenic in rats, but not in other tested species including mice, guinea pigs and hamsters. Most studies showed that teratogenicity was observed at doses that did not cause apparent maternal toxicity. Rats also showed sensitivity to effects on the brain and central nervous system, which are also considered developmental toxicity effects. Altered thyroid function was not found to play a role in teratogenicity.

In a developmental toxicity study (OECD TG 414), SD rats (n = 20–23) were administered (oral gavage) the chemical at 0, 15, 25 or 35 mg/kg bw/day, on gestation days (GD) 6–20. Maternal toxicity was not observed up to the highest dose. At the highest dose, teratogenic effects included significantly reduced foetal body weights, and malformations such as cranial meningocoele and meningorrhoea, vertebral abnormalities, and short tails. At ≥25 mg/kg bw/day, higher incidences of dilated brain ventricles and dilated ureter were observed in the foetuses, compared to controls. The NOAELs for maternal and developmental toxicity were determined to be >35 mg/kg bw/day and 15 mg/kg bw/day, respectively (REACH).

The chemical was studied for perinatal toxicity in groups of SD rats (n = 12–39) and CD-1 mice (n = 31–33) on GDs 7–21 and 7–16, respectively. Rats were administered (oral gavage) doses of 0, 5, 10, 20, 30, 40 or 80 mg/kg bw/day, and mice were administered 0, 100 or 200 mg/kg bw/day. Further evaluation for postnatal toxicity in pups was conducted in a separate group of dams from GD 7 to PND 15, at doses of 20–30 mg/kg bw/day. In rats, maternal toxicity was observed at 80 mg/kg bw/day, and foetal toxicity including decreased body weights at ≥10mg/kg bw/day, hydrocephalus (abnormal enlargement of brain ventricles) at ≥20 mg/kg bw/day, and various malformations and limb defects at ≥30 mg/kg bw/day. Postnatal toxicity (hydrocephalus, pup mortality) was observed at 30 mg/kg bw/day; also increased defaecation in the open-field test. The maternal and developmental NOAEL for rats were 40 mg/kg bw/day and 10 mg/kg bw/day, respectively. In mice, the maternal NOAEL was <100 mg/kg bw/day based on increased relative liver weights, and the developmental NOAEL was 100 mg/kg bw/day based on increased incidence of supernumerary ribs at 200 mg/kg bw/day (IARC, 2001; HSDB; REACH).

The teratogenic potential of the chemical was also investigated in golden hamsters (n = 15–19) and Hartley guinea pigs (n = 3–5), administered on GD 5–10 to doses of 75–300 mg/kg bw/day, and on GD 7–25 to doses of 50–100 mg/kg bw/day, respectively. No significant maternal or foetal toxicity was observed in hamsters and guinea pigs (IARC, 2001; REACH).

Several in vitro studies were conducted to investigate the direct effect of the chemical on rodent embryo development. The chemical caused malformations in cultured rat embryos exposed for 48 hours at concentrations ≥30 ug/mL. When embryo-sensitivity of rats and mice was compared using a 48 hour exposure to the chemical, rats were found to have twice the sensitivity for excessive accumulation of fluid, particularly in the neural tube. The chemical inhibited the differentiation of midbrain cells in rats but not in mice at 200 mg/kg bw. This was considered a possible reason for teratogenicity effects in rats but not in mice (IARC, 2001; HSDB; REACH).

One human retrospective study is available on the pregnancy outcomes of women employed in manufacturing rubber containing the chemical. No exposure-related effects were reported (IARC, 2001).

Other Health Effects

Neurotoxicity

The chemical was reported to induce central nervous system (CNS) and brain defects in rat foetuses (see **Reproductive and Developmental Toxicity**). Any CNS malformations were reported to be phase sensitive, and included spinal raphism (malformations of the spinal cord), exencephaly (brain exposed due to defect in the skull), hydranencephaly (cyst or cavity in the brain’s cerebral hemispheres) and hydrocephaly at 120 mg/kg bw (IARC, 2001).

Deficiency of the nervous tissue was observed in rat foetuses at 80 mg/kg bw (HSDB).

Endocrine Disruption

The chemical is listed in the European Commission Endocrine Disruptors Priority List under Category I classification (i.e. evidence of endocrine disrupting activity in at least one species using intact animals) (EC, 2015); and the US EPA’s Universe of Chemicals list for potential endocrine disruptor screening and testing (US EPA, 2012). This is in relation to thyroid hormone activity in animals.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (developmental toxicity); and
- systemic acute effects (acute toxicity from oral exposure).

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal or inhalation 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 long-term and acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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.

Based on the available data, the hazard classification in the Hazardous Substances Information System (HSIS) (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

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 if swallowed - Cat. 4 (H302)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)*	May damage fertility or the unborn child - Cat. 1B (H360D)

[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 dermal and/or 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.

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