2-Pyridinethiol, 1-oxide, sodium salt: 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.

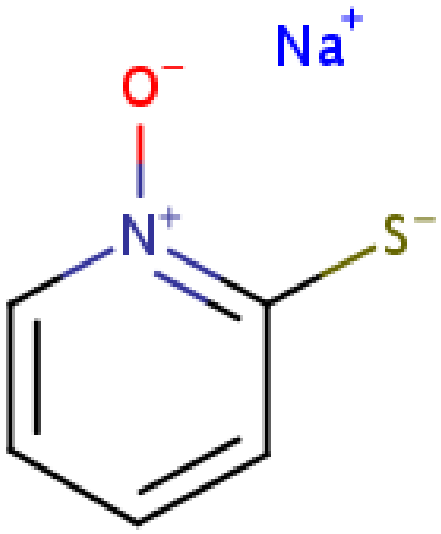
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	sodium pyrithione or pyridinethione 2-mercaptopyridine-N-oxide sodium salt sodium omadine sodium 1-oxidopyridine-2-thione 1-hydroxypyridine-2-thione sodium
Structural Formula	
Molecular Formula	C5H5NOS.Na
Molecular Weight (g/mol)	149.15
Appearance and Odour (where available)	off-white powder with mild odour
SMILES	c1(S{-}.[Na]{+})ccccn1=O

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 Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and various international assessments (US EPA, 1984; Bingham, Cohrssen and Powell, 2001; MAK, 2012; Health Canada, 2016).

The chemical has reported domestic uses, including in:

- cleaning and washing agents; and
- paints, lacquers and varnishes.

The chemical has reported commercial uses, including:

- as a preserving agent for gypsum wallboards; latex emulsions (in adhesives, caulks, sealants, paints, grouts); fibre, leather, rubber and polymerised materials; products during storage; and working or cutting fluids; and
- in commercial laundry preparations.

The chemical has reported site-limited use as an intermediate in the manufacture of other chemicals.

The chemical has reported non-industrial use as a disinfectant or algaecide not intended for direct application to humans or animals.

Historically, the chemical has reported cosmetic use as a preservative.

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;
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II—List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 1 mg/m^3 time weighted average (TWA) and 2 mg/m^3 short-term exposure limit (STEL)/MAK/occupational exposure limit (OEL) in different countries such as Denmark, Germany and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed following oral exposure, but has much lower absorption following dermal exposure. It has broad tissue distribution, with liver being the main site of detection. It is metabolised predominately by glucuronic acid conjugation and excreted primarily in the urine.

In a toxicokinetic study (according to EPA OPP 85-1), Sprague-Dawley (SD) rats (n = 10/sex/dose) were exposed to the radiolabelled chemical once at 0.5 or 25 mg/kg by oral gavage; or exposed to the chemical at 0.5 mg/kg bw/day for 14 days by oral gavage followed by a single dose of radiolabelled chemical at 0.5 mg/kg bw/day, either by oral or intravenous (i.v.) administration. The oral absorption of the chemical was calculated to be 88–105 %. It was distributed to many tissues, with the highest proportion found in the liver with no evidence of bioaccumulation. The chemical was metabolised mainly by glucuronic acid conjugation of the thiol group, forming S-linked conjugates, and twelve metabolites were identified. Urinary excretion accounted for 74–86 % of the dose, and faecal excretion for 3–12 % of the dose (US EPA, 1995; REACH).

In a toxicokinetic study in female Yorkshire pigs (n = 2/dose), radiolabelled chemical was administered i.v. at 0 or 50 mg/kg bw for 96 hours. Within 96 hours, 95 % of the chemical was recovered in urine, and the major urinary metabolite identified was omadine disulfide. The initial plasma half-life was approximately 2.8 hours, and the secondary plasma half-life approximately 27 hours (Bingham, Cohrssen and Powell, 2001; MAK, 2012; REACH).

In an in vivo dermal absorption study (according to the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 427), male SD rats (n = 5/dose) were dermally exposed (open patch) to radiolabelled chemical at 1 or 25 mg/kg for six hours and samples taken for up to 48 hours. At 48 hours, percutaneous absorption was 8 % and 2 % for the low and high dose animals, respectively. Distribution of the chemical was highest to the gastrointestinal (GI) tract, followed by the liver. Presence of the chemical in the GI tract was reported to be related to grooming. Urinary excretion accounted for 87 % of the chemical over the 48 hour study period at the low dose, and decreased with increased dose (REACH).

Similar results for dermal absorption were also observed in other species. In juvenile monkeys exposed to the radiolabelled chemical on shaved abdominal skin for 60 min, up to 13.5 % of the dose was retained on the skin and 1–2 % was recovered in

urine over 72 hours. In rabbits exposed to radiolabelled chemical at 110 mg/kg bw for four hours, 1.2 % of the dose was absorbed through intact skin and 16.4 % was absorbed through abraded skin (Bingham, Cohrssen and Powell, 2001). In rhesus monkeys exposed to the chemical via their finger or toe nails, <10 % was systemically available (MAK, 2012).

In humans, dermal absorption of the chemical is vehicle-dependent. In volunteers dermally exposed to 14 µg of the chemical in acetone, 5.5 % of the dose was recovered in urine over seven days, compared with 38 % recovered in urine using 10 µg of the chemical in a water-based cream (MAK, 2012; FoBiG, 2013).

Acute Toxicity

Oral

Based on the available data, the chemical is considered to have moderate acute oral toxicity, warranting hazard classification (see **Recommendation** section).

The following oral median lethal dose (LD50) values were available (US EPA, 1984; US EPA, 1995; Bingham, Cohrssen and Powell, 2001; MAK, 2012; REACH):

- 660–900 mg/kg bw in albino rats;
- 980–1120 in CD rats;
- 1208 mg/kg bw in female SD rats;
- 1500 mg/kg bw in Wistar rats; and
- 1000 mg/kg bw in mice.

Observed sub-lethal effects included ataxia, hunching, lethargy, tremors, salivation, lacrimation (tearing), diarrhoea, altered muscle tone, piloerection and laboured breathing.

Dermal

Based on the available data in rabbits, the chemical is considered to have moderate acute dermal toxicity, warranting hazard classification (see **Recommendation** section).

The following dermal LD50 values were available (US EPA, 1995; Bingham, Cohrssen and Powell, 2001; MAK, 2012; REACH):

- 1800 mg/kg bw in New Zealand White (NZW) rabbits;
- >2000 mg/kg bw in SD rats; and
- 2500 mg/kg bw in rats.

Observed sub-lethal effects included lethargy, nasal discharge, bloating and diarrhoea, ptosis (drooping eyelids), pupil dilation and weight loss.

Inhalation

Based on the available data, the chemical is considered to have moderate acute inhalation toxicity, warranting hazard classification (see **Recommendation** section).

The reported median lethal concentration (LC50) was 1.08 mg/L in SD rats (US EPA, 1995; MAK, 2012; REACH).

Observed sub-lethal effects included salivation; staining of the face, abdomen and genital areas; hindlimb impairment; and prostration.

Corrosion / Irritation

Skin Irritation

Based on the available data in animals and humans (see **Observation in humans** below), the chemical is considered to be slightly irritating to skin.

In an acute dermal irritation study (OECD TG 404), NZW rabbits (n = 3) were exposed (semi-occlusive) to 0.5 g of the chemical (92.5 % purity) on shaved skin for four hours and observed for up to 14 days. The average erythema score for the 24, 48 and 72 hour measurements was 1.9. Erythema was observed in two animals from one hour and persisted for 10 days. Eschar formation was noted from 48 hours and normal skin was visible at 14 days. The average oedema score for the 24, 48 and 72 hour measurements was 1.7. Oedema was observed in all animals from one hour and was reversed by 10 days (REACH).

In an acute dermal irritation study (according to EPA OPP 81-5), NZW rabbits (n = 6) were exposed (semi-occlusive) to 0.5 g of the chemical (43.7 % purity) on shaved skin for four hours and observed for 72 hours. The average erythema score was 0.8 and the average oedema score was 0.17, with effects completely reversible (REACH).

Transient erythema was also reported in albino rabbits exposed to the chemical at up to 100 mg/kg bw in an acute dermal toxicity study (US EPA, 1984).

It was reported that irritation was not observed in guinea pigs exposed to aqueous solutions of the chemical at 10–40 %. Irradiation with UVA light did not cause phototoxicty reactions (MAK, 2012).

Eye Irritation

Based on the available data, the chemical is considered to be a mild eye irritant. However, the serious health effects (death) following ocular administration warrant hazard classification (see **Recommendation** section).

In an acute eye irritation study (according to EPA OPP 81-4), NZW rabbits (n = 3/sex) were exposed to 0.1 mL (84 mg) of the chemical (>92 % purity) in the conjunctival sac of one eye and observed for up to seven days. Four rabbits (two males and two females) died within one day. Clinical observations included lethargy; reduced muscle tone and prostration; convulsions; tachypnoea (rapid breathing); and ocular, nasal and oral discharge. At necropsy, observations included changes in the lung (red areas), liver (pale and patchy areas), GI tract (pale areas) and eyes (clear discharge). Corneal opacity was not observed in any of the rabbits at one hour or for the duration of the study in the surviving rats. Iritis was observed in 4/6 rabbits at one hour (score = 1) but was reversed in the one surviving rabbit that was affected by 24 hours. In the surviving rabbits, conjunctival lesions were observed in the male for up to 72 hours (average 24, 48 and 72 hour score = 1.67 each for redness and chemosis) and in the female for up to 24 hours (average 24, 48 and 72 hour score = 1 each for redness and chemosis). There were no ocular effects observed on study day seven in the surviving rabbits (Olin Corporation, 1995; Bingham, Cohrssen and Powell, 2001; MAK, 2012).

In two separate acute eye irritation studies (according to OECD TG 405 or EPA OPP 81-4), NZW rabbits (n = 6/study) were exposed to 10 or 100 µL of the chemical (40 % purity) and observed for 72 hours or 14 days, respectively. On day two of each study, two and three rabbits died after exposure to 10 µL and 100 µL of the chemical, respectively. Clinical observations included lethargy and prostration; ataxia and convulsions; rapid or shallow breathing; and nasal and oral discharge. At necropsy, changes were seen in the lungs, peritoneal cavity and GI tract. In the study where 10 µL of the chemical was administered, ocular lesions included reversible corneal opacity in one rabbit, reversible iritis in two rabbits and reversible conjunctival irritation in all six rabbits. In the study where 100 µL of the chemical was administered, ocular lesions included reversible iritis and reversible conjunctival irritation in all six animals (REACH).

In several other eye irritation studies in albino rabbits exposed to commercial preparations (aqueous solution or powder) containing the chemical at 2–40 %, reversible redness, eye discharge and corneal opacity were reported (US EPA, 1984).

These studies were deemed unacceptable in a subsequent registration application, due to experimental insufficiencies related to short study duration (US EPA, 1995).

In an acute eye irritation study (EPA OPP 81-4) in cynomologous monkeys (n = 2 males and 1 female), 0.1 mL of the chemical (40 % purity) was administered and monkeys observed for up to seven days. Conjunctival irritation was reported in the two males and was reversed by seven days (REACH).

Observation in humans

In studies in humans, the chemical did not generally cause skin irritation, but instances of mild skin irritation were reported.

In separate studies in healthy volunteers, exposure (occlusive) to the chemical on the upper arm once at 1 % in an aqueous solution for 24 hours did not cause irritation; whereas exposure to the chemical on cheek, neck or back of hand skin using one drop of an aqueous solution at 1–2 % produced reversible reactions (burning sensation or erythema) in 10–60 % of subjects (MAK, 2012).

In repeated dose toxicity studies, it was reported that dermal exposure (occlusive) to the chemical resulted in mild skin irritation effects in a small proportion of people (see **Repeated dose toxicity: Observation in humans** section).

Sensitisation

Skin Sensitisation

Based on the available data in guinea pigs and humans (see **Observation in humans** below), the chemical is not considered to be a skin sensitiser.

In a guinea pig maximisation test (GPMT) (OECD TG 406) in male Hartley guinea pigs (n = 10/dose), the chemical (43.7 % purity) was administered for induction intradermally at approximately 2 % on day zero and epicutaneously at approximately 4 % on day seven. Guinea pigs were challenged on day 21 using the chemical at approximately 2 %. Erythema scores were reported to be mild to severe during the induction phase. Positive reactions (mild erythema) were noted in 2/10 and 3/10 animals at 24 and 48 hours, respectively, after the challenge dose (MAK, 2012; REACH).

In a photosensitisation study, Hartley guinea pigs (n = 12) were exposed 10 times to the chemical at 40 %, followed by irradiation with UVA and UVB light, for induction. The guinea pigs were challenged with the chemical at 4 %, 8 % or 40 %, followed by UVA irradiation, 14 days after the last induction dose. Positive reactions (minimal erythema) were reported in one animal at each dose, 24 and 48 hour after the challenge dose (MAK, 2012).

Deaths were reported (4/20) following exposure to the chemical after the induction phase of a GPMT in female Dunkin-Hartley guinea pigs. The reliability of this study is unclear, based on mortality that was not observed in other reported studies using similar exposure regimens, and the lower than expected response in positive controls (1/10) exposed to alpha-hexylcinammic aldehyde (REACH).

Observation in humans

In studies in humans, the chemical did not cause skin sensitisation reactions.

In several studies in healthy volunteers, induction using the chemical on skin (at up to 2 % or concentration not specified) by repeated exposure (occlusive patch), with or without irradiation, followed by challenge using the chemical once or with repeated exposure (at 0.5 % or concentration not specified) did not elicit significant reactions indicative of sensitisation (MAK, 2012).

In several patch test studies in workers with previous exposure to metal-working fluids that contained the chemical, and who were currently suffering from dermatitis, dermal reactions to the chemical did not occur consistently (MAK, 2012).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is considered to cause serious health effects following repeated oral exposure, warranting hazard classification (see **Recommendation** section).

In a repeated dose oral toxicity study (according to EPA OTS 798.2650), SD rats (n = 20/sex/dose) were exposed to the chemical (41.2 % purity) by oral gavage at 0, 0.5, 2 or 8 mg/kg bw/day, once daily for 90 days. Compared with controls, food intake was reduced by 9–10 % for the duration of the study in rats exposed at 8 mg/kg bw/day, and body weight gain in this group was significantly reduced from the second week of the study. In a neurological test battery performed during week five and 13 of the study, hindlimb grip strength and foot spread on landing were significantly reduced in rats exposed at 8 mg/kg bw/day. In addition, in this dose group, signs of toxicity (emaciation, hunched posture, bloating) were reported in 8/20 males and 11/20 females. Hindlimb ataxia progressing to paralysis was also reported in 4/20 males and 11/20 females. As a consequence, 10 females exposed at 8 mg/kg bw/day were euthanised moribund. In the high dose group, absolute heart weight was significantly increased in males, and there was atrophy of upper hindlimb muscles in 19/20 males and all females. Atrophy was also reported in 5/20 males and 6/20 females exposed at 2 mg/kg bw/day, with a dose dependent increase in the severity from 2 mg/kg bw/day. No hind limb muscle atrophy was observed at 0.5 mg/kg bw/day. The no observed adverse effect level (NOAEL) is determined to be 0.5 mg/kg bw/day, based on muscle atrophy that was reported at 2 mg/kg bw/day (the lowest observed adverse effect level (LOAEL)) (US EPA, 1995; HSE, 2003; MAK, 2012; REACH). The muscle atrophy has been described as 'evidence of neurotoxicity' (US EPA, 1995).

In a repeated dose oral toxicity study (according to EPA OTS 798.2650), SD rats (n = 10/sex/dose) were exposed to the chemical (40 % purity) by oral gavage at 0, 0.1, 0.5 or 2.5 mg/kg bw/day, once daily for 90 days. There were no deaths, and body weight and food intake were not affected. In rats exposed at 2.5 mg/kg bw/day, liver and adrenal weights were increased in females, and heart weight was increased in males; liver cell hypertrophy was reported for the group; and there was mononuclear cell infiltrates in liver of female rats. An NOAEL of 0.5 mg/kg bw/day is determined based on the effects seen at the highest dose (REACH).

In two combined repeated dose oral toxicity and carcinogenicity studies (OECD TG 453) in SD rats exposed to the chemical by oral gavage at up to 5 mg/kg bw/day for 104 weeks (see **Carcinogenicity** section), an NOAEL of 0.5 mg/kg bw/day (LOAEL of 1.5 mg/kg bw/day) was determined for the first study, and an LOAEL of 0.5 mg/kg bw/day was determined for the second study (MAK, 2012; REACH).

In the first study, no effects were reported for animals exposed at the lowest dose (0.5 mg/kg bw/day). There was increased mortality in rats exposed at ≥1.5 mg/kg bw/day, but effects were not dose-dependent. Terminal body weight was significantly reduced in females exposed at the highest dose (5 mg/kg bw/day for the first 12 weeks, reduced to 3.5 mg/kg bw/day thereafter). Hindlimb muscle wastage was reported in females exposed at the highest dose, and in males exposed at the intermediate (1.5 mg/kg bw/day) and highest doses. Red blood cell count, haemoglobin concentrations and packed cell volumes were significantly reduced in females exposed at the intermediate and highest doses, when measured on weeks 27 and 53. Relative lung weights were increased in males at the intermediate and highest doses; relative liver weights were increased in males at the highest dose. Skeletal muscle, sciatic nerve and retinal atrophy were reported in rats exposed at the highest dose; and spinal cord degeneration was reported in females exposed at the highest dose (MAK, 2012; REACH).

In the second study, mortality was increased in exposed rats compared with controls. Body weight was significantly reduced in females exposed at ≥1.4 mg/kg bw/day and in males exposed at the highest dose (4 mg/kg bw/day for the first 7 weeks, reduced to 2.8 mg/kg bw/day thereafter). Food intake was significantly reduced in rats exposed at ≥1.4 mg/kg bw/day. Ataxia, reduced muscle tone, generalised weakness and reduced landing foot splay were reported in rats exposed at ≥1.4 mg/kg bw/day. Kidney and spleen weights were significantly reduced in females exposed at ≥1.4 mg/kg bw/day and heart weights were significantly reduced in females exposed at the highest dose. Dose dependent muscle wastage (necrosis and atrophy) was reported in rats exposed at ≥1.4 mg/kg bw/day. Sciatic nerve degeneration, with fibrous tissue replacement and macrophage infiltration was seen in all exposed groups (MAK, 2012; REACH).

Dermal

Based on the available data, the chemical is considered to cause serious health effects following repeated dermal exposure, warranting hazard classification (see **Recommendation** section).

In a repeated dose dermal toxicity study (according to EPA OPP 82-3), SD rats (n = 20/sex/dose) were exposed (occluded) to the chemical (41.2 % purity) at 0, 5, 15 or 50 mg/kg bw/day for six hours per day, for 90 days. There were no treatment related deaths, but body weight gain and terminal body weights were significantly reduced in rats exposed at the highest dose. Gross muscle wastage was reported in 3/20 females exposed at 15 mg/kg bw/day, and in 19/20 females and 2/20 males exposed at 50 mg/kg bw/day. By microscopic examination, upper hindlimb muscle and subcutaneous panniculus muscle atrophy was noted in 17/20 males and 20/20 females exposed at the highest dose, and to a lesser extent in animals exposed at 15 mg/kg bw/day. In 10/20 females exposed at the highest dose, sciatic nerve degeneration of individual fibres within the nerve trunk was reported. An NOAEL of 5 mg/kg bw/day was reported, based on muscle atrophy observed at higher doses (US EPA, 1995; MAK, 2012; REACH).

Inhalation

Based on the available data, the chemical is considered to cause serious health effects following repeated inhalation exposure, warranting hazard classification (see **Recommendation** section).

In a repeated dose inhalation toxicity study (according to EPA OPP 82-4), SD rats (n = 15/sex/dose) were exposed (whole body) to the chemical (40 % purity) as an aerosol at 0, 0.46, 1.1 or 3.8 mg/m^3 (equivalent to 0.0005, 0.001 and 0.004 mg/L) for six hours per day, five days per week, for 90 days. The highest concentration was increased to 8.1 mg/m^3 (or 0.008 mg/L) after six weeks. There were no treatment-related mortalities. No adverse effects were reported in males exposed to the chemical. In females exposed at the highest concentration, body weight gain was significantly reduced from week 10 of the study; haemoglobin concentration was reduced (but within the normal range) when measured in week six of the study; and impaired hindlimb function and muscle degeneration were reported. In females, the NOAEL is determined to be 0.001 mg/L, based on hindlimb muscle effects at 0.008 mg/L (US EPA, 1995; MAK, 2012; REACH).

Observation in humans

In workers (n = 9 males) involved in the production of the chemical for 2–13 years, no signs of toxicity were reported (MAK, 2012).

In a repeated dose study in healthy volunteers (n = 100), it was reported that exposure (occlusive) to the chemical at 1 % on upper arm skin for 24 hours, every second day for 30 days, caused marked erythema and oedema in one subject on day 10 and one subject on day 14. In another study in healthy volunteers (n = 11 males and 34 females), exposure (occlusive) to 0.2 mL of the chemical (no details available) for 24 hours, 12 times over three weeks, mild erythema was reported in 14 subjects and oedema in 'isolated cases' (MAK, 2012).

In patients treated for fungal skin infections with preparations containing the chemical at 1 %, no reactions were reported when using a 'lotion' vehicle (n = 25) for up to six weeks and two reactions (erythema and blisters, 30 hours after the first application) were reported when using a 50 % alcohol or ointment base (n = 103) for up to four weeks (MAK, 2012).

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

Most in vitro tests using the chemical gave negative results (US EPA, 1995; Bingham, Cohrssen and Powell, 2001; MAK, 2012; REACH):

- negative in two bacterial reverse mutation assays in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, TA 100 exposed to the chemical at up to 100 µg/plate, with and without metabolic activation;

- negative in a mammalian cell gene mutation assay in Chinese hamster lung fibroblasts (V79) exposed to the chemical at up to 1875 µg/mL, with and without metabolic activation;
- negative in a mammalian cell gene mutation assay in Chinese hamster ovary (CHO) cells exposed to the chemical at up to 100 µg/mL, with and without metabolic activation;
- positive in a chromosome aberration assay in Chinese hamster lung fibroblasts (V79) exposed to the chemical at up to 80 µg/mL, with and without metabolic activation; and
- negative in an unscheduled DNA synthesis assay using primary rat hepatocytes exposed to the chemical at up to 220 ng/mL.

It has been reported that due to cytotoxicity, sodium pyrithione is used in low concentrations in vitro, which may limit the value of these assays (MAK, 2012).

All in vivo tests using the chemical gave negative results (US EPA, 1995; MAK, 2012; REACH):

- negative in a micronucleus assay using bone marrow from NMRI mice exposed to the chemical once by oral gavage at up to 580 mg/kg bw; and
- negative in a micronucleus assay using bone marrow from CD-1 mice exposed to the chemical once by intraperitoneal (i.p.) injection at 238 mg/kg bw.

Carcinogenicity

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

In a combined repeated dose oral toxicity and carcinogenicity study (according to US EPA 83-2), SD rats (n = 50/sex/dose) were exposed to the chemical (41.2 % purity) by oral gavage at 0, 0.5, 1.5 or 5.0 mg/kg bw/day, once daily for 104 weeks. After 12 weeks, the highest dose was reduced to 3.5 mg/kg bw/day due to effects on body weight gain. Systemic toxicity (including skeletal muscle wastage; sciatic nerve and retinal atrophy; and spinal cord degeneration) was reported in rats exposed at ≥1.5 mg/kg bw/day (see **Repeated dose toxicity: Oral** section), but there were no treatment related neoplastic changes (US EPA, 1995; REACH).

In a combined repeated dose oral toxicity and carcinogenicity study (according to OECD TG 453), SD rats (n = 56/sex/dose) were exposed to the chemical (40.8 % purity) by oral gavage at 0, 0.5, 1.4 or 4 mg/kg bw/day once daily for 104 weeks. Due to severe toxicity, the highest dose was reduced to 2.8 mg/kg bw/day from week seven in all rats, and reduced again to 2.1 mg/kg bw/day from nine months for female rats only. Systemic toxicity (including skeletal muscle and nerve degeneration) was reported in rats exposed at ≥1.4 mg/kg bw/day (see **Repeated dose toxicity: Oral** section), but there were no treatment related neoplastic changes (MAK, 2012; REACH).

In a carcinogenicity study (according to EPA OPP 83-2) using a dermal route of exposure, CD-1 mice (n = 50/sex/dose) were exposed (non-occlusive) to the chemical (41.2 % purity) at 0, 5, 15 or 40 mg/kg bw/day once daily for 80 weeks. No systemic toxicity was reported. There was increased incidence in epidermal hyperplasia in rats exposed at the highest dose compared with controls. No neoplasms were reported (US EPA, 1995; MAK, 2012; REACH).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to cause specific reproductive or developmental toxicity. Some minor reproductive effects were reported, and developmental effects (if observed) only occurred secondary to maternal toxicity.

In a two-generation reproductive toxicity study (according to EPA OPPTS 870.3800), SD rats (n = 24/sex/dose) were exposed to the chemical (40.8 % purity) by oral gavage at 0, 0.7, 1.4 or 2.8 mg/kg bw/day for 10 weeks prior to mating and until one day prior to study termination. In the F0 and F1 generations, body weight and food intake were reduced in rats exposed at the highest dose; uterus weights were increased and kidney weights were reduced in females exposed at ≥1.4 mg/kg bw/day; and there were no effects on sperm parameters in males. In F1 rats exposed at the highest dose only, epididymis weight was

reduced in males and spleen weight was increased in females. In the F2 generation, pup weights were reduced and there were undescended testes in pups from the ≥1.4 mg/kg bw/day groups (REACH).

In another two-generation reproductive toxicity study (according to EPA OPP 83-4), SD rats (n = 25/sex/dose) were exposed to the chemical (41.2 % purity) by oral gavage at 0, 0.5, 1.5 or 4.5 mg/kg bw/day for 11 weeks prior to mating and up to 25 days post partum. The highest dose was reduced to 3.5 mg/kg bw/day from four weeks onwards. In the F0, F1 and F2 generations, no significant effects were reported in rats exposed at ≤1.5 mg/kg bw/day. In the F0 generation exposed at the highest dose, there was decreased body weight gain; hindlimb muscle atrophy; increased time to mating; and decreased number of mating and fertile rats. There were no changes in reproductive organs; non-significant decreases in the number of pups born; and non-significant delays in reaching developmental milestones in this group. In the F1 generation exposed at the highest dose, there was decreased body weight gain and hindlimb muscle atrophy. There were non-significant decreases in the number of pups born and non-significant delays in reaching developmental milestones in this group. In the F2 generation from the highest dose group, body weight was slightly (non-significant) decreased (US EPA, 1995; MAK, 2012; FoBiG, 2013; REACH).

In a developmental toxicity study (according to OECD TG 414), SD rats (n = 24/sex/dose) were exposed to the chemical (40.8 % purity) by oral gavage at 0, 1, 2 or 4 mg/kg bw/day on gestation day (GD) 6–19. Foetal effects (reduced body weight and higher incidences of incomplete sternebrae, metacarpal and metatarsal bone formation) were only reported in animals exposed at the highest dose, where there was concomitant maternal toxicity (reduced body weight, food intake, impaired mobility, emaciation and reduced uterine weights) (REACH).

In another developmental toxicity study (according to EPA OPP 83-3), NZW rabbits (n = 20/sex/dose) were dermally exposed to the chemical (43.8 % purity) at 0, 1, 2.5 or 5 mg.kg bw/day on GD 6–19. Maternal body weight was significantly reduced in rabbits exposed at the highest dose. There were no effects on implantation rates, foetal viability, foetal body weight, foetal sex distribution and litter size in exposed dams compared with controls. It was reported that there were no developmental effects (US EPA, 1995; MAK, 2012; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects following repeated oral, dermal and inhalation exposure, and systemic toxicity from ocular exposure.

The chemical can also cause harmful systemic effects following a single exposure through oral, dermal and inhalation exposure.

Public Risk Characterisation

Although use in domestic and commercial products in Australia is not known, the chemical is reported to be used in domestic and commercial products overseas. However, no evidence of the presence of the chemical in consumer products was found in available North American databases (Household Products Database), indicating that the chemical is not likely to be widely available for use. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, inhalation and ocular 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 HCIS (Safe Work Australia) (see **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

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Repeat Dose Toxicity	Not Applicable	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Other Health Effects	Not Applicable	Toxic by eye contact (AUH070)

[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, dermal, inhalation and ocular 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;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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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