Zinc, bis(1-hydroxy-2(1H)-pyridinethionato-O,S)-, (T-4)-: Human health tier II assessment

13 February 2015

CAS Number: 13463-41-7

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

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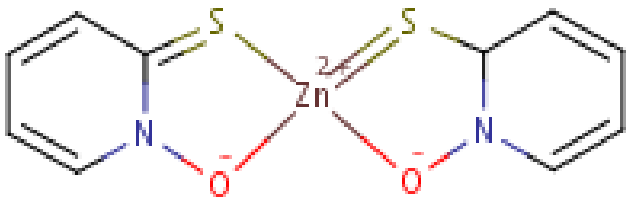
Acronyms & Abbreviations

Chemical Identity

Synonyms	zinc pyrithione or zinc pyridinethione or zinc omadine zinc 2-pyridinethiol-1-oxide 2(1H)-pyridinethione, 1-hydroxy-, zinc complex 2-mercaptopyridine 1-oxide zinc salt bis(2-pyridinethiol-1-oxide)zinc
Structural Formula	
Molecular Formula	C10H8N2O2S2Zn
Molecular Weight (g/mol)	317.68
Appearance and Odour (where available)	White to light yellow or beige powder with mild odour
SMILES	C1(=S)C=CC=CN1O{-}.[Zn]{2+}.O{-}N1C(=S)C=CC=C1

Import, Manufacture and Use

Australian

The chemical has reported cosmetic use as an ingredient in anti-dandruff shampoos.

The chemical has reported non-industrial uses as an active ingredient in antibacterial and antifungal topical creams and sprays, and in anti-fouling paints (APVMA, 2001).

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients

(INCI) dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the Scientific Committee on Consumer Safety (SCCS) opinion on zinc pyrithione.

The chemical has reported cosmetic use:

- in shampoo and hair conditioning products (maximum concentration of 2.0 %);
- as a preservative in cosmetics (maximum concentration of 0.5 %); and
- as an ingredient in leave-on hair products (maximum concentration of 0.1 %).

The chemical has reported domestic use in:

- paints; and
- lacquers and varnishes.

The chemical has reported commercial use in:

- product synthesis and formulation; and
- fabrics.

The following non-industrial uses have been identified:

- in fungicides and bactericides for topical application;
- in marine antifouling paints; and
- as a biocidal active (e.g. in disinfectant, pest control).

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 2, 5 and 6 (SUSMP, 2014).

Schedule 6:

'Pyrithione Zinc except:

(a) when included in Schedule 2 or 5;

(b) for human use in preparations for the treatment of the scalp containing 2 per cent or less of pyrithione zinc when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(c) in semi-solid hair preparations for animal use;

(d) in shampoos for animal use containing 2 per cent or less of pyrithione zinc when labelled with the statements "Keep out of eyes" and "If in eyes rinse well with water";

(e) when immobilised in solid preparations containing 0.5 per cent or less of pyrithione zinc; or

(f) in paints, jointing materials or sealants containing 0.1 per cent or less of pyrithione zinc calculated on the non-volatile content'

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, 2014).

Schedule 5:

'Pyrithione zinc in paints containing 0.5 per cent or less of pyrithione zinc calculated on the non-volatile content of the paint except in paints containing 0.1 per cent or less of pyrithione zinc calculated on the non-volatile content of the paint'

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2014).

Schedule 2 (Pharmacy medicine):

'Pyrithione zinc for human therapeutic use, except in preparations for the treatment of the scalp containing 2 per cent or less of pyrithione zinc when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*' (SUSMP, 2014).

International

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

- EU Regulation (EC) No 1223/2009 Annex III—List of Substances which cosmetic products must not contain except subject to the restrictions laid down (Annex V—List of preservatives allowed in cosmetic products)—maximum concentrations allowed are 1.0 % in rinse-off hair products and 0.5 % in other products. The chemical should not be used in oral products;
- Council of Europe Resolution ResAP (2008) 1 on requirements and criteria for the safety of tattoos and permanent make-up—Table 3—Maximum allowed concentrations of impurities in products for tattoos and PMU;
- Canada Cosmetic Ingredient Hotlist—List of Ingredients that are prohibited for use in cosmetic products;
- ASEAN Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down (Annex VI—Part 1—List of preservatives allowed for use in cosmetic products);
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down (Schedule 7: Preservatives cosmetic products may contain with restrictions—Table 1: List of preservatives allowed);
- Phillipines restricted ingredients for use in cosmetics—List of preservatives which cosmetic products may contain subject to restrictions and conditions laid down; and
- Thailand Cosmetic Act—Controlled substances.

The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) recommended that the chemical should not be used in oral hygiene products (SCCNFP, 2002).

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):

- T+; R26; Xn; R22 (acute toxicity);
- Xi; R41 (irritation).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific international exposure standards are available.

Health Hazard Information

Toxicokinetics

The chemical is extensively absorbed via oral exposure in animals (Sprague Dawley (SD) rats (88–105 %), New Zealand White rabbits, rhesus monkeys and beagle dogs), but not readily absorbed via dermal exposure on intact or abraded sites (<1 % in vitro in human skin and <6 % in animals) (HSDB; REACH).

The chemical is widely distributed throughout the body following oral exposure in animals, but only small amounts (<1 %) were found in the liver (highest amount), blood cells, intestines and kidneys (REACH).

Following oral administration, the chemical is predominately metabolised in animals via glucuronic acid conjugation of the thiol group, followed by rapid excretion of metabolites via the urine (75–98 %) or faeces (2.6–20 %) (HSDB; REACH). In Yorkshire pigs dermally exposed to the chemical either as a single dose or after repeated exposure for five days, urinary excretion accounted for 3 % of the administered dose, as the majority of the chemical remained at the site of application due to low absorption (HSDB).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS (Safe Work Australia). The available data support this classification.

The median lethal dose (LD50) in rats was reported to be 269–774 mg/kg bw (US EPA, 2008; REACH). Reported signs of toxicity were ptosis (droopy eyelids), diarrhoea, lethargy, piloerection, chromodacryorrhoea and chromorhinorrhoea (red secretions from the eyes and nose), emaciation, alopecia, ataxia, bloated abdomen, ocular abnormalities, hunched posture, decreased respiratory rate, soiled body surfaces, and wet and brown-stained anogenital area (US EPA, 2008; REACH).

The oral LD50 was >1000 mg/kg bw in male cynomolgus monkeys. Sublethal clinical effects included vomiting, decreased spontaneous activity and decreased appetite (REACH).

Dermal

The chemical has low acute dermal toxicity based on the results of animal tests.

The dermal LD50 was >2000 mg/kg bw in SD rats. There were no clinical signs of systemic toxicity or local irritation (REACH).

The dermal LD50 was >2000 mg/kg bw in New Zealand White rabbits. Observed sublethal effects included diarrhoea and reduced hind limb mobility (US EPA, 2008).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Very toxic by inhalation' (T+; R26) in the HSIS (Safe Work Australia). The available data for the median lethal concentration (LC50), equals 0.14 mg/L in SD rats, which supports this classification.

In a study conducted similar to the Organisation for Economic Cooperation and Development Test Guideline (OECD TG) 102, the LC50 was reported to be 0.14 mg/L in SD rats exposed (whole body) to the chemical contained in an aerosol of aqueous suspension. Reported sublethal signs of toxicity included prostration, gasping, laboured breathing, rales, trembling and hunched posture (REACH).

Other studies indicated LC50 values of 1.03 mg/L and 5.08 mg/mL in SD rats exposed (nose-only) to dust or aerosol containing the chemical (SCCS, 2014; REACH).

Observation in humans

A probable fatal dose was reported to be 50–500 mg/kg bw (equivalent to between one teaspoon and approximately 28 g for a 70 kg person), which was not solely related to the zinc content of this chemical (details not available) (HSDB).

Corrosion / Irritation

Respiratory Irritation

Based on the effects reported in acute and repeated dose inhalation toxicity studies (see **Acute toxicity: Inhalation** and **Repeat dose toxicity: Inhalation**), the chemical is considered to be a severe respiratory (mucous membrane) irritant, warranting hazard classification (see **Recommendation** section).

Skin Irritation

The chemical is considered to cause only slight skin irritation.

In a skin irritation study in New Zealand White rabbits, very slight erythema and slight oedema (scores not available) were observed in half of the rabbits treated with the chemical. The effects were reversible after 48 hours (US EPA, 2008).

The chemical produced no skin irritation in New Zealand White rabbits in studies that were performed in accordance with OECD TG 404 (REACH).

In studies that were performed in accordance with the US Environmental Protection Agency Office of Pesticide Program (EPA OPP) 81-5, the chemical was applied to the intact skin of New Zealand White rabbits. Slight erythema (irritation score 0.5–1) was observed after a 30-minute exposure, but there was no erythema observed 24, 48 or 72 hours after dosing. The chemical produced slight to well-defined oedema after 30 minutes (irritation score 0.67–2), but the effects were reversible as they were minimal to slight 24 hours after exposure (irritation score 0.33–1) and absent 48 and 72 hours after exposure (REACH).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS (Safe Work Australia). The available data support this classification.

In an eye irritation study (OECD TG 405) with one New Zealand White rabbit, the chemical severely irritated the eye, with conjunctivitis and dense corneal opacity observed 24 hours post application. The animal was euthanised after the 24-hour observation period due to the severity of the effects, and further animals were not tested (REACH).

Severe irritation (corneal opacity, sluggish and unresponsive iris, conjuctivitis, chemosis and eye discharge) was reported both in the washed and unwashed eyes of rabbits following exposure to the chemical (study was conducted according to EPA OPP 81-4). The effects were not reversible in the unwashed eyes by the seventh day after exposure, and only 1 of 3 animals showed signs of reversibility in the washed eye by day 14 (US EPA, 2008; REACH).

Sensitisation

Skin Sensitisation

The chemical is not considered to be a skin sensitiser.

Dunkin-Hartley guinea pigs were induced by intradermal injection of Freund's Complete Adjuvant followed by topical application of the chemical at a 25 % concentration on the injection site. A second topical induction was followed by a challenge, two weeks after the last induction, using a topical (occlusive) application of the chemical at a 10 % concentration. The chemical was not found to induce dermal sensitisation in guinea pigs (REACH).

In a Buehler test (according to EPA OTS 798.4100), no dermal sensitisation was observed in male Hartley guinea pigs exposed to 0.4 g of the chemical in the induction phase (three six-hour exposures, each one week apart) and challenged (two weeks after the last induction) for six hours using a topical (occlusive) application of 0.4 g of the chemical (US EPA, 2008; REACH).

Observation in humans

A patch test was performed in 100 male and female volunteers using 16 occlusive applications of the chemical at a 1 % concentration for induction. The subjects were challenged two weeks after the last induction, using a topical (occlusive) application of the chemical at a 0.5 % concentration. No skin sensitising effects were observed (REACH).

A modified Draize test with the chemical (3 % suspension in petrolatum or 1 % solution in dimethyl sulphoxide (DMSO) for induction and 3 % suspension in petrolatum or a 0.5 % solution in DMSO for the challenge) showed no evidence of skin sensitisation in 10 volunteers (SCCS, 2014).

Repeated Dose Toxicity

Oral

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

Hind limb paralysis in rats was reported to be the most consistent finding in repeated dose oral studies conducted with the chemical and also with sodium pyrithione. A 90-day rat study with sodium pyrithione showed hind limb paralysis at a dose of 8 mg/kg bw/day, with a dose-dependent increase in the severity of hind limb muscle atrophy from 2 mg/kg bw/day. No hind limb muscle atrophy was observed at 0.5 mg/kg bw/day in rats (HSE, 2003).

The chemical suspended in 1 % gum tragacanth was administered (oral gavage) to rhesus monkeys at 0, 0.5, 2 or 8 mg/kg bw/day for 90 days (non-guideline study). No significant treatment-related effects were reported in haematological and histopathological examinations, clinical chemistry or urinalysis. A no observed adverse effect level (NOAEL) of 0.5 mg/kg bw/day was derived based on a dose-related reduction in the relative uterus

weight (associated with immature uteri) at 2 and 8 mg/kg bw/day (SCCS, 2014). No evidence of hind limb paralysis was observed in cynomolgus monkeys up to oral doses of 22 mg/kg bw/day (HSE, 2003).

In a 90-day oral gavage study (conducted according to EPA OTS 798.2650) in SD rats (n = 10/sex/dose), the animals were exposed to the chemical at doses of 0, 0.2, 1.0 or 5.0 mg/kg bw/day. The NOAEL was established as 0.2 mg/kg bw/day, based on the effects seen at 1 mg/kg bw/day (increased salivation from day 37 onwards and isolated red to brown staining around the mouth in males and females; and significantly increased neutrophil counts on day 30 and signficantly decreased plasma urea on day 90 in females only). Following day six, animals in the 5 mg/kg bw/day group displayed increased salivation at dosing, noisy respiration, hunched posture, fur wetting and red to brown staining of the body surfaces. Females in the 5 mg/kg bw/day group also showed hindlimb paralysis, lethargy, piloerection, emaciation, altered gait, loss of righting reflex and vocalisation from day 12 onwards. There was one female death at this dose, and two further female deaths after the dose was reduced (new dose details not available). Death was associated with darkened kidneys, thickened and inflamed gastric epithelium, and raised white patches on the forestomach. Females also had reduced plasma urea and plasma creatinine levels, and increased neutrophil and eosiniphil counts when measured on days 30 and 90 (REACH).

Rats fed with the chemical in the diet at 0, 5, 25 or 125 ppm for 90 days, first showed clinical signs on week two at 125 ppm (reduced respiratory rate and onset of progressively restricted movement of the hind limbs). Most of the animals in the 125 ppm dose group died from dehydration and/or starvation, due to paralysis. The no observed effect level (NOEL) was reported to be 5 ppm (0.35 mg/kg bw/day for males and 0.39 mg/kg bw/day for females), based on reduced body weights observed at 25 ppm (APVMA, 2001).

In a three-month feeding study in rats, a NOAEL of 0.75 mg/kg bw/day was established based on effects observed at 3.75 mg/kg bw/day (increased liver, kidney and testes weights; decreased survival; and hind limb weakness) (US EPA, 2008).

The UK Health and Safety Executive report (2003) on the chemical stated that 'Specific neurotoxicity studies indicate that the observed loss of hind limb function is mediated by peripheral axonopathy. Therefore, muscle atrophy is considered to be a secondary event due to underlying nerve damage. Although there is an apparent species difference regarding loss of hind limb function, on the basis of the available information, the results obtained in the rat must be considered of relevance to human health' (HSE, 2003).

Dermal

Based on the treatment-related effects reported, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a 90-day dermal study (according to EPA OPP 82-3) in CrlCD BR rats (n = 15/sex/dose), a NOEL of 100 mg/kg bw/day was established based on decreased body weight gain and food intake at 1000 mg/kg bw/day in females (US EPA, 2008; REACH).

Inhalation

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

In a 13-week repeated dose inhalation toxicity study (according to EPA OPP 82-4), SD rats (n = 15/sex/dose) were exposed (whole-body) to the chemical as an aerosol at concentrations of 0, 0.0005, 0.0025 or 0.01 mg/L/day. The no observed adverse effect concentration (NOAEC) was reported to be 0.0005 mg/L/day (0.5 mg/m^3), based on mortalities of one male and one female rat at 0.0025 mg/L/day (2.5 mg/m^3). Three males and four females died at 0.01 mg/L/day (10 mg/m^3). The deaths of two female rats at 0.01 mg/L/day were attributed to severe chronic inflammation of the tracheal mucosa, which resulted in reduced lung capacity. Other signs of toxicity reported in the animals that died during the study include laboured breathing; rales; increased salivation; decreased activity; dry red to brown staining around the nose; and increased lung weight (by 20–22 % in males, and by 13–25 % in females). The necropsy findings were confined to the lungs and associated vasculature. Body weight was significantly decreased (23 % less compared with the control group) in females at 0.01 mg/L/day (US EPA, 2008; HSDB; REACH). The HSE (2003) stated the lungs as the principal target organ, with a dose dependent increase in lung weight observed from the chemical administered at 2.5 mg/kg bw/day, 'with supportive histopathological findings of inflammation of the interstitium and medial hypertrophy of pulmonary arteries. Information from these repeated dose studies indicates that the criteria for classification with “danger of serious damage to health by prolonged exposure” were satisfied by the inhalation and oral routes of exposure' (HSE, 2003).

In a 21-day repeated dose inhalation toxicity study (according to EPA OPPTS 870.3465), SD rats (n = 20/sex/dose) were exposed (nose only) to the chemical as a dust at 0, 2, 6 and 13.5 mg/m^3 for six hours/day, five days/week. The NOAEC was 2 mg/m^3 based on effects observed at 6 mg/m^3 (one female mortality, swelling around the eyes, wet fur around the nose and mouth, gasping, respiratory gurgles, and increased lung weight). Significant weight loss compared with controls was reported in the 13.5 mg/m^3 dose females, as well as the 6 and 13.5 mg/m^3 dose males. Lung weights were significantly increased in male and female rats at the 6 and 13.5 mg/m^3 doses compared with controls, and this corresponded with histopathological signs of irritation and inflammation (e.g. increased alveolar macrophages, squamous metaplasia of the nasal mucosa, larynx and trachea; alveolar duct smooth muscle hypertrophy and hyperplasia). There were also four deaths in the 13.5 mg/m^3 dose group. Information on the cause of these deaths was not available, although stress from not acclimatising the animals to the restraining tubes might have contributed to the deaths (SCCS, 2014; REACH).

In a 28-day repeated dose inhalation toxicity study (similar to EPA OPPTS 870.3465), Crl:CD SD rats (n = 15/sex/dose) were exposed (nose only) to the chemical dust at 0, 0.5, 1.5 and 5 mg/m^3 for six hours/day, five days/week. A NOAEC of 1.5 mg/m^3 was established based on systemic toxicity

observed at 5 mg/m^3. These effects (one female death, decreased body weight in males, decreased food intake in females, increased lung weight, decreased thymus weight, broncho-interstitial pneumonitis and smooth muscle hypertrophy in the lungs) were described as test-substance related and adverse, but data on the statistical significance were not available. Local inflammatory effects were observed in all treated groups (SCCS, 2014).

Genotoxicity

The chemical is not considered to be genotoxic.

Several in vitro assays gave negative results for gene mutation and clastogenicity (SCCNFP, 2002; US EPA, 2008; SCCS, 2014; REACH):

- two bacterial reverse mutation assays (according to OECD TG 471 or EPA OPP 84-2) with *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100;
- a bacterial reverse mutation assay using *Escherichia coli* strain WP2 uvrA;
- two in vitro mammalian cell gene mutation assays, in Chinese hamster lung fibroblasts (V79) (OECD TG 476) or Chinese hamster ovary (CHO) cells (EPA OPP 84-2);
- a gene mutation assay (OECD TG 476) in CHO cells and human renal proximal tubular (HRPT) cells;
- a chromosome aberration assay (Japanese guideline) using human peripheral lymphocytes; and
- an unscheduled DNA synthesis test in cultured human fibroblasts (WI-38 cells).

However, one in vitro chromosome aberration assay (OECD TG 473) in Chinese hamster lung V79 cells showed chromosomal aberrations (SCCS, 2014; REACH).

Several in vivo tests gave negative results for genotoxicity (SCCNFP, 2002; US EPA, 2008; SCCS, 2014; REACH):

- a mammalian erythrocyte micronucleus assay (OECD TG 474) in bone marrow cells of Crl:NMRIBR mice that received one dose of the chemical by oral gavage at 800, 1000 or 1300 mg/kg bw (80, 100 or 130 mg/mL);
- a chromosome aberration assay in bone marrow cells of SD rats that received one dose of the chemical by intraperitoneal injection at 11, 22 or 44 mg/kg bw (EPA OPP 84-2); and
- a chromosome aberration assay in peripheral lymphocytes of cynomolgus monkeys receiving the chemical orally at 5.5, 11 or 22 mg/kg bw/day for 28 days (equivalent to OECD TG 473).

Carcinogenicity

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

No data are available for the chemical. Two 104-week studies are available for sodium pyrithione. Since the metal ion is hydrolysed from the chemical following uptake, and metabolised differently from the pyrithione moiety, studies on sodium pyrithione were considered appropriate as read-across for zinc pyrithione to provide supportive data for assessing carcinogenicity (SCCNFP, 2002).

Sodium pyrithione was not carcinogenic when administered once daily via oral gavage in two separate 104-week studies. The Crl:CD-1 (ICR) BR (VAF Plus) rats (OECD TG 453) were administered the chemical at doses of 0, 0.5, 1.5 or 5 (reduced to 3.5) mg/kg bw/day (n = 56/sex/dose); and SD rats (EPA OPP 83-2) were administered the chemical at doses of 0, 0.5, 1.5 or 4.0 (reduced to 2.8 or 2.1 in males and females, respectively) mg/kg bw/day (n = 70/sex/dose). There were many mortalities in Crl:CD-1 (ICR) BR (VAF Plus) rats (121 males and 90 females died or were euthanised during the study), but the deaths were reported as unrelated to treatment. There were no treatment-related tumour effects in either study. Non-neoplastic treatment-related effects at the highest doses in both studies included skeletal muscle and sciatic nerve degeneration. Based on these observations, a NOAEL of 0.5 mg/kg bw/day was established in both studies (SCCS, 2014).

Sodium pyrithione was applied once daily to shaved dorsal skin of Crl:CD-1 (ICR) BR (VAF Plus) mice (n = 50/sex/dose) at doses of 0, 5, 15 or 40 mg/kg bw/day for 80 weeks (EPA OPP 83-2). Several animals died or were euthanised (28 males, 44 females) during the study, but the deaths were reported as unrelated to the chemical. Treatment did not result in tumour formation. There was significant epidermal hyperplasia at the dosing site in the highest dose group and increased incidences in the mid dose (15 mg/kg bw/day) group. A NOEL of 5 mg/kg bw/day was derived based on these local effects (SCCS, 2014).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to cause reproductive and developmental toxicity. Reproductive organs were not significantly affected in any study, and since the reported malformations in offspring occurred at doses that were maternally toxic, the chemical is not considered to be a teratogen.

New Zealand White rabbits (n = 20/dose) were exposed to the chemical by oral gavage at doses of 0, 0.5, 1.5 or 3.0 mg/kg bw/day on gestation days (GD) 6–18 (according to EPA OPP 83-3). The maternal-developmental NOAEL was 0.5 mg/kg bw/day, based on dose-related post-implantation loss or early resorption and decreased foetus viability at 1.5 mg/kg bw/day. There was increased incidence of malformations in two litters when administered 3 mg/kg bw/day, but this was not statistically significant (US EPA, 2008; REACH).

SD rats (n = 30/dose) were treated with the chemical by oral gavage doses of 0, 0.75, 3 or 15 mg/kg bw/day (according to EPA OPP 83-3) on GD 6–15. The maternal-developmental NOAEL was 0.75 mg/kg bw/day based on a dose-related post-implantation loss or early resorption when administered 3 mg/kg bw/day. There was a significant increase in foetal malformations (mainly rib and digit anomalies) at 15 mg/kg bw/day, but since this concentration was maternally toxic, the effects were not considered teratogenic (US EPA 2008; REACH).

The Crl:CD(SD)IGS BR VAF/Plus rats (n = 25/dose) were exposed to the chemical dermally at doses of 0, 10, 15, 30 or 60 mg/kg bw/day on GD 0–20 for six hours/day (according to EPA OPPTS 870.3700). The maternal NOAEL was 15 mg/kg bw/day based on a significant dose-related decrease in maternal body weight and body weight gain when administered at 30 mg/kg bw/day. The developmental NOAEL was 30 mg/kg bw/day based on significantly decreased foetal body weights and significantly increased foetal malformations in the ribs, sternum, caudal vertebrae and forelimb and hindlimb digits at 60 mg/kg bw/day. These were considered to be due to maternal stress or toxicity, and were within the historical control range of the testing facility (SCCS, 2014; REACH).

Two, two-generation reproductive toxicity studies on sodium pyrithione established a parental NOAEL of 1.5 mg/kg bw/day in SD or Crl:CD® (SD) BR rats based on hindlimb immobility, skeletal muscle atrophy and reduced mating at higher doses. A NOAEL of 3.5 mg/kg bw/day was established for fertility in SD rats based on no significant effects at the highest dose tested (SCCS, 2014).

Other Health Effects

Neurotoxicity

Data are available that indicate some neurotoxic effects in animals following repeated exposure to the chemical. However, these effects could be species specific. The hind limb paralysis observed in specific neurotoxicity studies was reported to be mediated by peripheral axonopathy (HSE, 2003) (see **Repeat dose toxicity: Oral**).

Following a 28-day dermal exposure to the chemical, NOAELs of 50 and 25 mg/kg bw/day were established in male and female rats, respectively, based on hindlimb effects (SCCS, 2014).

In repeated dose studies, rats were reported to show hindlimb weakness following oral exposure to the chemical. However, monkeys did not show hindlimb weakness during repeated oral exposure. The mode of action for potential neurotoxicity has been investigated in rats and monkeys, in vitro. Differing levels of calcium influx in motor neurons in rats and monkeys might have contributed to the differing sensitivities to hindlimb impairments. The relevance of this data to humans remains unclear (SCCS, 2014).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are local effects (serious eye and respiratory irritation), and systemic acute and repeated dose effects from oral and inhalation exposure.

Public Risk Characterisation

For cosmetic and/or domestic uses, the chemical is currently listed on Schedules 5 and 6 of the SUSMP. The chemical is on Schedule 6 of the SUSMP with exceptions for preparations to treat human scalps (up to a 2 % concentration); when immobilised in solid preparations (up to a 0.5 % concentration); and in paints, jointing materials or sealants (up to 0.1 % calculated on the non-volatile content). Any cosmetic or domestic product containing the chemical and not listed within the SUSMP exceptions allowed above should be labelled as a 'Poison' on the product label, except for paints containing 0.5 % or less of the chemical (which is on Schedule 5 of the SUMSP requiring a 'Caution' signal on the product label).

Given the uses of the chemical, public exposure by inhalation is very improbable. 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.

The Scientific Committee on Consumer Safety (SCCS) opinion (2014) states that 'zinc pyrithione, when used in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer' and that there should be 'thorough post-marketing surveillance of the product'.

Occupational Risk Characterisation

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

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (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

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2014).

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)* Very toxic by inhalation (T+; R26)*	Toxic if swallowed - Cat. 3 (H301) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)* Irritating to respiratory system (Xi; R37)	Causes serious eye damage - Cat. 1 (H318) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23) Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372) Causes damage to organs through prolonged or repeated exposure if swallowed - Cat. 1 (H372)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which 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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