3(2H)-Isothiazolone, 4,5-dichloro-2-octyl-: Human health tier II assessment

26 October 2018

CAS Number: 64359-81-5

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.

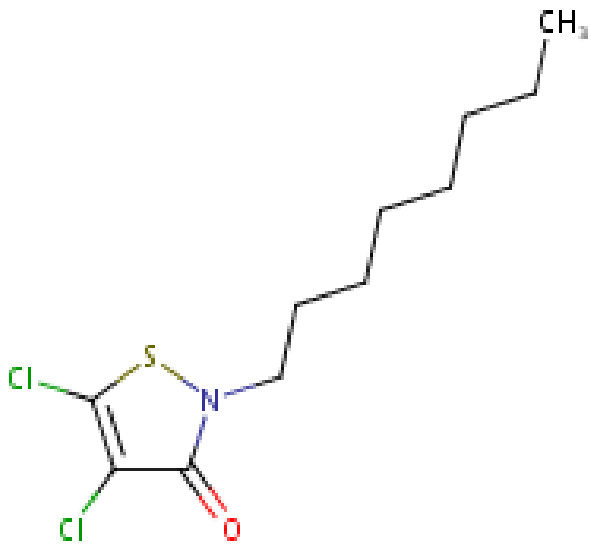
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	dichloro-2-n-octyl-4-isothiazolin-3-one DCOIT 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one
Structural Formula	
Molecular Formula	C11H17Cl2NOS
Molecular Weight (g/mol)	282.2
Appearance and Odour (where available)	off-white solid with a moderately sweet, pungent odour
SMILES	C1(=O)C(Cl)=C(Cl)SN1CCCCCCCC

Import, Manufacture and Use

Australian

The following Australian industrial use was reported under previous mandatory and/or voluntary calls for information.

The chemical has reported commercial use as an ingredient in marine paint.

International

The following international uses have been identified through Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US EPA Human Health Benchmarks for Pesticides (EPA HHBP); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); Norway's active substance evaluation to the European Union (EU) for DCOIT in antifouling products (EU, 2014); the European Chemicals Agency (ECHA) Harmonised Classification and Labelling (CLH) Report (ECHA, 2018); and the Dow Product Safety Assessment (2012).

The chemical has reported commercial uses including:

- as a broad-spectrum biocide for paints;
- as a preservative for masonry and other construction products;
- in metalworking cutting fluids; and
- formulated into silicone sealants.

The chemical may also be used in paints used in the domestic setting. However, North American databases do not indicate widespread use of the chemical in domestic products.

The chemical has reported site-limited uses, including:

- in food processing water systems; and
- formulation into plastics.

The chemical has reported non-industrial uses, including as fungicide, bactericide, marine antifouling products, wood preservative and algaecide.

Restrictions

Australian

The chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6 (SUSMP, 2018).

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, 2018).

International

No known restrictions have been identified for the chemical.

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

No specific exposure standards are available.

Health Hazard Information

The chemical is referred to as 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one (DCOIT) in this assessment. Where available, data for two commercial antifouling products C-9211 HQ (32.6 % of DCOIT in xylene) and Acticide® DCOIT (97.1% purity) are used for some health end-points.

The information on health hazards is primarily obtained from the comprehensive reviews from the Norwegian Environment Agency as part of its ECHA CLH proposal (ECHA, 2018) and an EU (Norway) DCOIT evaluation for the use of DCOIT as a biocide in antifouling products (EU, 2014). Unless otherwise noted, references to individual studies below are taken from these reviews.

Toxicokinetics

The chemical, DCOIT is moderately absorbed through skin and moderately absorbed via oral route. It is then extensively distributed to tissues (liver, kidney, stomach and intestine) and metabolised following oral administration.

In a study conducted in rats, 81–93 % of orally administered ^{14}C-DCOIT was excreted primarily in the faeces within a 2-day period. Plasma elimination half-life of ^{14}C-DCOIT was 16.1–19.4 hours for males and 20.5–25.0 hours for females. The highest concentration of ^{14}C-DCOIT was found in liver, stomach, intestine and kidney. More than 80 % of the administered dose was eliminated via faeces, 11–18 % was eliminated via urine and less than 2 % of the dose was eliminated through exhaled air. DCOIT metabolised to form six metabolites in the faeces and eight metabolites in the urine. Degradation of DCOIT involves cleavage of the ring and subsequent oxidation of 7–18 % of the administrated dose to N-(n-octyl) malonamic acid (NNOMA, major metabolite), N-(n-octyl)acetamide, N-(n-octyl)oxamic acid and N-(n-octyl)-β-acetyl propionamide. The chemical undergoes subsequent biotransformation involving hydroxylation, dealkylation and acetylation (EU, 2014; ECHA, 2018).

Male rats (n=not specified, Crl:CD® BR) were dermally exposed to the chemical at a dose of 3 % or 0.045 % ^{14}C-DCOIT in acetone for 10 and 24 hours. The dermal absorption of the chemical ranged from 31–51 % (EU, 2014; ECHA, 2018).

In an in vivo dermal absorption study, two groups of Sprague Dawley (SD) rats were treated with 0.25% ^{14}C-DCOIT in DPGME (DOW1) for 24 hours. Around 27 % of the administered dose was excreted in faeces in the first 11 days. Urinary excretion was more than the faecal excretion in the first three days and around half (13 %) during the 30 day period. Excretion in the carcass was 5.5 % (at 24 hr post exposure), 4 % (7 days observation) and less than 1 % (after 14 days). Radioactivity in skin was 40 % (at 24 hr), 18 % (at 7 days) and 3 % (after 14 days). The dermal delivery value of 51 % and absorption value of 49 % over a period of 30 days was reported. Radiographic examination showed that the radioactivity penetrated the stratum corneum and was present in the epidermis and underlying musculature at 14 and 30 days post exposure. Hair follicles were the major portals for entry for the chemical (EU, 2014; ECHA, 2018).

In an in vitro study, split-thickness human skin was treated with 0.25 % ^{14}C-DCOIT in DPGME for 24 hours. A dermal delivery value of 17 % and absorption value of 1 % over a period of 24 hours indicate a significantly lower dermal delivery of the chemical through human skin than rat skin (EU, 2014; ECHA, 2018).

In an dermal absorption study, conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 427, six groups of male Wistar rats (n=4/group) were treated with 0.4 mg/mL (0.04 %) or 4.0 mg/mL (0.4 %) of radio-labelled chemical in propylene glycol (THOR) on shaved skin for 10 hours, occlusively. Dermal absorption of the chemical was 46 % and 39 % for both the doses, respectively. The chemical was metabolised rapidly via oxidation, dechlorination, decarboxylation and truncation (EU, 2014; ECHA, 2018).

Acute Toxicity

Oral

The chemical has moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) values in rats and in mice are 1636 and 567 mg/kg bw, respectively. Observed sub-lethal effects included lethargy, abdominal breathing, gasping, nostril discharge, piloerection, salivation, diarrhoea and toe walking. There is sufficient evidence to warrant hazard classification (see **Recommendation** section).

In an oral acute toxicity study according to OECD TG 423, Wistar rats (n=3 animals/sex/group) were administered DCOIT (THOR) in peanut oil at 200, 500 or 2000 mg/kg bw. All animals in the 2000 mg/kg bw dose group died within 24 hours of the treatment. Clinical signs included lethargy, abdominal breathing, nostril discharge, toe walking, piloerection salivation, diarrhoea and unusual locomotion. Pathological changes in lung, liver, kidney and spleen were observed in the autopsy of the deceased animals. The reported LD50 was between 500 and 2000 mg/kg bw (EU, 2014; ECHA, 2018).

A number of Crl:CD® BR rats (n=6 animals/sex/dose) were administered DCOIT (DOW1) in corn oil at 500, 750, 1000, 1500 or 2000 mg/kg bw by oral gavage in a study according to OECD TG 401. Dose-dependent mortality was recorded. Males from the 750 mg/kg bw dose group and greater showed treatment-related decrease in body weight gain. Clinical signs included irritation around the anal-genital area, passiveness, scant faeces and/or tan-stained muzzle. Observations from pathological examinations included: high incidence of viscous material in the caecum, intestines and stomach; black material adhered to stomach mucosa; reddened stomach and intestinal mucosa; and mottled liver. Thickened stomach walls were seen in all surviving treated animals. The reported LD50 was 1636 mg/kg bw (CPA, 2010; EU, 2014; ECHA, 2018).

In a guideline study (OECD TG 401), Crl:CD® BR mice (n=6 animals/sex/dose) were administered DCOIT in corn oil by gavage at doses of 100, 250, 500, 1000 or 2000 mg/kg bw. A dose-dependent increase in mortality for dose groups of 500 mg/kg bw and above was reported. Observed effects in females at the 3 highest dose groups and in males at the 2 highest dose groups included soft or scant faeces, passiveness, tremors and ataxia. The reported combined LD50 was 567 mg/kg bw (EU, 2014; ECHA, 2018).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 values in rabbits and rats are >652 and >2000 mg/kg bw, respectively. Observed effects included skin lesions including cutaneous thickening, alopecia and erythema.

In an acute dermal toxicity study (OECD TG 402), a single dose of 2000 mg/kg bw of an antifouling agent, C-9211 HQ (containing 32.6 % DCOIT in xylene), was applied on the skin of New Zealand White (NZW) rabbits (6 animals/sex/group) for 24 hours. No mortality was observed. Clinical signs included ataxia, reduced body weights, decreased feed consumption, scant faeces and passiveness with fluid-filled thoracic and abdominal cavity observed at necropsy. Skin irritation effects included erythema, oedema, pocketing oedema, eschar and blanching. The reported LD50 for the DCOIT equivalence was >652 mg/kg bw (CPA, 2010; EU, 2014; ECHA, 2018).

In another study (OECD TG 402), topical application of a single dose of 2000 mg/kg bw of DCOIT to Wistar rats resulted in no mortality. Varying degree of skin lesions comprising cutaneous thickening, alopecia, and erythema were observed in all treated animals. The reported LD50 was >2000 mg/kg bw (CPA, 2010; EU, 2014; ECHA, 2018).

Inhalation

The chemical has high acute inhalation toxicity in animal tests following inhalation exposure. The median lethal concentration (LC50) for DCOIT is 0.164–0.26 mg/L air. There is sufficient evidence to warrant hazard classification (see **Recommendation** section).

Wistar rats (n=5 animals/sex/group) were exposed to DCOIT aerosols dissolved in dimethylsulfoxide (DMSO) at 0.143, 0.221 or 0.289 mg/L air by nose only inhalation exposure for 4-hours. Mortality was observed at 0.143 mg/L (40 %), 0.221 mg/L (70 %) and 0.289 mg/L (90 %). Clinical signs of toxicity included lethargy, tremors, abdominal breathing, gasping and nasal irritation. Vascular/inflammatory changes and redness in lobes of the lungs were observed on histopathological examination. The reported LC50 was 0.164 mg/L (EU, 2014; ECHA, 2018).

In another study (OECD TG 403) conducted on Crl:CD® BR rats (n=6 animals/sex/group), the chemical was administered via single nose-only inhalation for 4 hours at doses of 0.23, 0.12, 0.46 or 0.20 mg/L. The rats were observed for 14 days. Mortality was observed in all dose groups but dose-dependency was not established. Signs of toxicity included unkempt appearance, red stained eyes and muzzle, scant faeces and yellow stained anogenital area. Gas-filled stomachs and scattered incidences of red pinpoint foci on the lungs were observed. These effects were considered to be consistent with the clinical signs of respiratory irritation and were attributed to the corrosive properties of the chemical. The LC50 for males was 0.21 mg/L and for females was 0.34 mg/L. A combined LC50 of 0.26 mg/L was reported (CPA, 2010; EU, 2014; ECHA, 2018).

Corrosion / Irritation

Corrosivity

The chemical and formulations containing the chemical applied to intact rabbit skin produced severe erythema, oedema and scar formation. The exposed areas had effects that were not reversible. Data indicates corrosive effects in the respiratory tract. While no data are available for effects in the eyes, the chemical is deemed to capable of causing severe damage. There is sufficient evidence to warrant hazard classification (see **Recommendation** section).

Skin effects

In a skin irritation study (OECD TG 404), New Zealand White (NZW) rabbits (n=6 animals) were treated on intact skin with 0.5 mL C-9211 HQ reformulation (C-9211 HQ; 32.6 % DCOIT in xylene) for 4 hours and observed for up to 14 days. The chemical formulation was reported as corrosive with a mean erythema score of 4.0 and oedema score of 3.9. Scar formation was observed in 5 of 6 animals at 14 days post-application. The effects were not reversible in 5 of 6 animals within 14 days (CPA, 2010; EU, 2014; ECHA, 2018).

In a skin irritation study (OECD TG 404), a formulation containing 20 % DCOIT in phenoxypropanol (propylene glycol phenyl ether) was applied to intact skin of one NZW rabbit for 4 hours with observation up to 14 days. The chemical was reported as corrosive with mean erythema and oedema scores of 4.0 and 3.3, respectively. Concave eschar was observed by 48 hours. Oedema was reversed by day 14 (CPA, 2010; EU, 2014; ECHA, 2018).

Topical application of DCOIT formulation (97.1 % purity) to three male NZW rabbits conducted in accordance with OECD TG 404 caused mild to severe erythema and oedema. The effects increased in severity and were not reversible within 14 days.

Mean erythema and oedema scores of 2.3 and 2.2 were reported (EU, 2014; ECHA, 2018).

Respiratory effects

In the inhalation acute toxicity study (see **Acute toxicity: Inhalation** section), lung damage was reported with vascular/inflammatory changes in the lungs and clinical signs including gasping and nasal irritation suggesting a corrosive effect.

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive results seen in several guinea pig maximisation tests (GPMT), a local lymph node assay (LLNA) (EC3 is 0.03%) and effects in humans (see **Skin sensitisation: Observations in humans** section). There is sufficient evidence to warrant hazard classification (see **Recommendation** section).

In a LLNA study conducted according to OECD TG 429, mice (n=4/group) were treated topically with 25 µL of DCOIT in acetone:olive oil, 4:1(v/v) at 0, 0.005, 0.01, 0.1, 0.25 or 0.5 % w/v (equivalent to 0, 2.5, 5, 50, 125 or 250 µg/cm^3, respectively) onto the dorsum of one ear lobe for three consecutive days. DCOIT caused positive results at concentrations of 0.1, 0.25 and 0.5 %; with stimulation indices of 11.6, 25.7 and 27.0, respectively. An EC3 value (estimated concentration value for a stimulation index of 3) of 0.03% (w/v) (15 µg/cm^3) was reported (EU, 2014; ECHA, 2018).

In a GPMT conducted according to OECD TG 406, guinea pigs (n=10/sex) were treated with 5 % DCOIT in propylene glycol formulation with or without Freund's Complete Adjuvant intradermally and 0.2 mL of 25 % DCOIT in propylene glycol in 80 % alcohol formulation epicutaneously in the induction phase. For the challenge, the animals were treated with 0.2 mL of 5 % DCOIT in propylene glycol. Observations were made at 24 and 48 hours. Around 60 % (12/20) animals were positive at 24 hours and 45 % (9/20) at 48 hours µg/cm^3 (CPA, 2010; EU, 2014; ECHA, 2018).

In another GPMT conducted using DCOIT technical in mineral oil formulation, animals (number not specified) were exposed to 0.01, 0.02 or 0.03 % of the chemical (equivalent to 4.4, 8.8 and 12.12 µg/cm^2) via intradermal injection for induction phase. Two weeks later, the same concentrations were applied at a naïve site via topical application. Observations were made at 24 and 48 hours. In the lowest dose group, 75 % (15/20) of animals were positive at 24 hours and 55 % (11/20) at 48 hours after the challenge. Positive response was observed for 95 % animals at 0.02 % and 100 % at 0.03 % (EU, 2014; ECHA, 2018).

Various paint formulations (n=15) dosed with two dry film paint preservatives, ROZONE^{TM} 2000 and BIOBAN^{TM} 200 (containing 20 % DCOIT) were investigated for their skin sensitisation potential using the following assays: LLNA (OECD TG 429); and the in vitro ARE-Nrf2 Luciferase (KeratinoSens^{TM}) assay (OECD TG 442D). The concentrations of DCOIT in the paint formulations (acrylic- and vinyl acrylic-based) dosed with the paint preservatives ranged from 0.0925-0.2179 %. The LLNA and KeratinoSens^{TM} assay results for the paint formulations showed 86.7 % correlation in the samples tested. The formulations were reported as sensitising at DCOIT concentrations of >0.1 % for both the acrylic and vinyl acrylic paint types (Unpublished report (a) provided by Dow DuPont Specialty Products Division, 2018).

In another study (OECD TG 442D), the in vitro skin sensitisation (KeratinoSens^{TM} assay) was investigated using paint formulations dosed with two “polymer shielded technology (PST)” dry film paint preservatives – BIOBAN^{TM} 200 PST (containing 14.6 % DCOIT), and BIOBAN^{TM} PST 350 (containing 13.5 % DCOIT and 6.5 % IPBC – iodopropynyl butylcarbamate). Three different paint types, acrylic, styrene acrylic and vinyl acrylic, were tested. DCOIT was reported as skin sensitiser at >0.2 % DCOIT in acrylic paints dosed with BIOBAN^{TM} 200 PST, at >0.14 % DCOIT in acrylic paints dosed with BIOBAN^{TM} 350 PST, and at >0.09 % DCOIT in styrene acrylic paints dosed with BIOBAN^{TM} 350 PST. The chemical IPBC, the other active ingredient in BIOBAN^{TM} 350 PST, is a skin sensitiser and may have contributed to the skin sensitisation potential of this preservative formulation (Unpublished report (b) provided by Dow DuPont Specialty Products Division, 2018).

Observation in humans

The positive data in animal studies are supported by the human case reports detailed below.

Open patch tests (OPT) were performed on 6 dermatology patients with a textile finishing agent containing 0.2 % biocide (equivalent to 0.06 % or 600 ppm of DCOIT). The formulation was applied directly to a 2 cm^2 skin area on the upper arm. Strong positive reactions were observed in 5 of the 6 patients (EU, 2014; ECHA, 2018).

In a human repeat insult patch test (HRIPT), 34 volunteers per dose were exposed to 0.2 mL of 0.025 % or 0.035 % DCOIT in ethanol in the induction phase and 0.01, 0.025 or 0.035 % DCOIT in ethanol for the challenge phase. Positive responses were reported in 4/34 (12 %) subjects at 0.025 % DCOIT and 14/34 (41 %) subjects at 0.035 % (EU, 2014; ECHA, 2018).

In the follow-up HRIPT, 8 of the 34 subjects that showed positive responses (0.035 % DCOIT in ethanol dose group) in the induction and challenge phases were re-challenged in a 24-hour occlusive patch test (OPT) with 0 or 0.025 % DCOIT in ethanol. Three of the eight subjects responded positively (EU, 2014; ECHA, 2018).

In another OPT, 10 human volunteers were exposed to 0.1 mL of DCOIT in ethanol at 0.035 %, 0.05 %, 0.075 % or 0.1 % concentrations. Observations were made at 24 and 48 hours. No significant differences in irritation response were observed between the four concentrations; however, two subjects (20 %) gave positive responses to all the doses tested (EU, 2014; ECHA, 2018).

Airborne allergic contact dermatitis following non-occupational exposures to isothiazolinones in water-based paints has been reported (Lundov et al., 2014; Aerts et al., 2017; Amsler et al., 2017).

Repeated Dose Toxicity

Oral

Based on the available data, DCOIT is not likely to cause serious damage to health from repeated oral exposure. The adverse effects observed including histopathological changes in the forestomach and small intestine are attributed to the local irritant effects of the chemical.

In a 4-week study, SD (Crj:CD) rats (n=10/sex/group) were administered 97.5 % pure DCOIT diluted in olive oil at 0, 20, 100 or 500 mg/kg bw/day by gavage. Three of ten females at 500 mg/kg bw/day died on day 4 of treatment.

Treatment-related effects at 500 mg/kg bw/day included mucosal hyperplasia in the gastrointestinal tract, increased granulocytes in the spleen and changes in the neutrophil counts and enlarged adrenals. Additional effects observed included thickening of the non-glandular mucosa and intestines, reduced spontaneous movement, diarrhoea, salivation and abdominal distension. Males at 500 mg/kg bw/day showed effects on body weight gain and food consumption and changes in absolute and relative organ weights and urine analysis. Significant although slight decrease in relative liver weight was observed in males at 100 mg/kg bw/day. Clinical chemistry and haematology parameters showed significant changes at 100 and 500 mg/kg bw/day. Thickening of the non-glandular mucosa and intestines was noted at 500 mg/kg bw/day. Atrophy of the liver was observed in five male animals at 500 mg/kg bw/day. A lowest observed adverse effect level (LOAEL) of 100 mg/kg bw/day and a no observed adverse effect level (NOAEL) of 20 mg/kg bw/day were reported (CPA, 2010; EU, 2014; ECHA, 2018).

In a sub-chronic study conducted in accordance with OECD TG 408, DCOIT (98.8% purity) was administered in diet to Crl:CD® BR rats (n=10/sex/group) at 0, 100, 500, 1000 or 4000 ppm (equivalent to 6.2–7.2, 32.5–36.7, 60.7–74.7 and 248.2–278.4 mg/kg bw/day) for 90 days. There were no mortalities observed at any dose level tested. Significant reduction in body weight gain (in females at 1000 ppm and both sexes at 4000 ppm); feed consumption (in females at 1000 ppm) and feed and water consumption (about 53 % in females and 41 % in males) were observed mainly during the early weeks of treatment. There were no adverse effects on organ weights or on gross pathology observed. Histopathological changes including dose-dependent irritation, ranging from minimal hyperkeratosis and slight epithelial hyperplasia to erosion/ulceration with associated inflammation and oedema of the submucosa were observed in the forestomach at 1000 ppm (one male and one female) and at 4000 ppm (all treated animals). At the highest dose, mean cell volume and mean cell haemoglobin were significantly reduced with accompanying significantly increased red blood cell and platelet count in male animals. No treatment-related changes in any

clinical chemistry parameters were observed in doses up to 1000 ppm in males and 500 ppm in females. Serum triglyceride, total protein and globulin levels were significantly reduced and potassium and albumin/globulin ratio were significant higher in all treated animals at 4000 ppm. Other observed effects included significantly increased serum glutamic, oxalacetic transaminase (GOT) activity in males and significantly elevated blood urea nitrogen levels in females. A NOAEL of 500 ppm (equivalent to 32.5 mg/kg bw/day in males and 36.7 mg/kg bw/day in females) and a LOAEL of 1000 ppm (equivalent to 60.7 mg/kg bw/day for males and 74.7 mg/kg bw/day in females) were determined based in the effects on forestomach, reduced body weight gain and reduced serum triglyceride levels (CPA, 2010; EU, 2014; ECHA, 2018).

In a 90-day study conducted according to OECD TG 409 in beagle dogs (n=4/sex/group), DCOIT (98.42 % purity) was administered in diet at 100, 300 or 1500 ppm. There were no mortalities, effects on organ weights or gross histopathological changes observed. Significantly reduced body weight and food consumption (23 % as compared to control values) was reported in females at 1500 ppm. All treated animals except one, showed body weight loss with no significant systemic toxicity during week 13 of the treatment. Haematological changes at 1500 ppm including decreased haemoglobin, haematocrit, red blood cell counts and reticulocytes and increased platelet counts in males were considered to be secondary to decreased in body weight at 1500 ppm. Females at 1500 ppm were reported to have increased incidence and severity of thymic atrophy, which was considered to be secondary to decreased body weight and food consumption. A NOAEL of 300 ppm (10.2 mg/kg bw/day for males and 10.1 mg/kg bw/day for females) and A LOAEL of 1500 ppm (47.5 mg/kg bw/day for males and 45.9 mg/kg bw/day for females) were reported (CPA, 2010; EU, 2014; ECHA, 2018).

Dermal

In a 21-day dermal study conducted in NZW rabbits (n=6/sex/group), 1 mL of DCOIT formulation C-9211M (35 % DCOIT in mixed xylene diluted at 1 % in acetone) was dermally administered at 0, 1 or 5 mg/kg bw/day, 5 days/week for 21 days. There were no mortalities and no treatment-related adverse effects. Slight skin irritation at 1 mg/kg bw/day and moderate to severe skin irritation at 5 mg/kg bw/day were observed. Skin lesions included hyperplasia, hyperkeratosis or parakeratosis of the epidermis, increased inflammatory cell infiltration in the dermis and focal dermal haemorrhage. A systemic NOAEL of 1.75 mg/kg bw/day and a LOAEL of 0.35 mg/kg bw/day (equivalent to 0.035 % of DCOIT) were derived (EU, 2014; ECHA, 2018).

In 28-day study (OECD TG 410) conducted in Wistar rats (n=20 animals/sex/dose), DCOIT (96.47 % purity) in corn oil at 0, 3, 15 and 60 (later reduced to 30) mg/kg bw/day was applied occlusively on an exposed area for 6 hours/day over 28 days. Severe, dose-dependent local skin reactions due to the corrosive nature of the test substance were observed. Skin reactions such as erythema, oedema, wounds and necrosis were observed. All these effects were considered to be secondary to immunological responses and stress due to the large inflamed area of the skin. A NOAEL of 3 mg/kg bw/day and a LOAEL of 15 mg/kg bw/day were reported (EU, 2014; ECHA, 2018).

Inhalation

Limited information is available.

In an inhalation study, the DCOIT formulation, C-9211M HQ (32.6 % DCOIT in o-xylene) was administered to Crl:CD® BR rats (n= 32/sex/group) by nose-only inhalation at concentrations of 0, 0.02, 0.63 or 6.72 mg/m^3 for 6 hours/day, 5 days a week for 13 weeks. Included in the study were 6 months and 1 year recovery groups. Mortalities recorded were four males and 15 females out of which, 12 of these deaths occurred in the control and vehicle groups, and 2–6 animals/group died during recovery phase. There was a dose-dependent increase in incidence and severity in rales, gasping and dyspnoea throughout the treatment. At 6.72 mg/m^3, statistically significant decreases in body weights in both sexes were observed. No changes in body weight or other clinical signs of respiratory distress were observed during the recovery period. Females in the 6.72 mg/m^3 group had statistically significant increases in absolute lung weight. Histopathological findings at the two highest doses included dose-dependent and treatment-related chronic inflammation, epithelial hyperplasia, brightly staining eosinophilic material in the olfactory epithelium of the nose and larynx, squamous metaplasia in epiglottis and goblet cell hyperplasia in the lungs were observed. No signs of histopathological lesions or systemic toxicity were observed at the 6-month necropsy. The no observed adverse effect concentration (NOAEC) was calculated to be 0.21 mg/m^3 and a lowest observed adverse effect concentration (LOAEC) of 0.63 mg/m^3 was reported (CPA, 2010; EU, 2014; ECHA, 2018).

Genotoxicity

Based on the available *in vitro* and *in vivo* genotoxicity studies, the chemical is not considered to be genotoxic.

In vitro studies

In a bacterial gene mutation test, DCOIT was tested in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 up to a maximum concentration of 300 µg/plate with negative responses in all strains with and without metabolic activation (EU, 2014; ECHA, 2018).

In two mammalian chromosomal aberration assays in Chinese hamster ovary (CHO) cells, DCOIT was tested at concentrations of up to 0.7 µg/mL without metabolic activation and up to 8.0 µg/mL with metabolic activation. The chemical, DCOIT caused a negative response, with and without metabolic activation (EU, 2014; ECHA, 2018).

In a cytogenetic test conducted in accordance to OECD TG 473 in human primary lymphocytes with DCOIT at concentrations up to 1.5 µg/mL, negative responses were reported both in the presence and absence of metabolic activation (ECHA, 2018; EU, 2010).

DCOIT was negative for genotoxicity in two gene mutation studies conducted according to OECD TG 473 in Chinese hamster V79 cells and CHO cells, respectively at concentrations up to 25 µg/mL (EU, 2014; ECHA, 2018).

In another bacterial gene mutation test, N-(n-octyl) malonamic acid (NNOMA, major metabolite of DCOIT) was negative in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia Coli* WP2 *uvrA* at concentrations up to 5000 µg/plate in the presence and absence of metabolic activation (EU, 2014; ECHA, 2018).

In vivo studies

In two micronucleus assays, DCOIT was tested in CD-1 mice (5-9 mice/sex/dose) at doses up to 325 mg/kg bw/day by gavage. No genotoxicity was reported in both studies (EU, 2014; ECHA, 2018).

In a chromosomal aberration assay, Swiss albino mice (5 animals/sex/dose) were administered DCOIT at 0, 100, 200 or 400 mg/kg bw/day in peanut oil by gavage. Chromosome preparations were made from the bone marrow (femur) of the mice. No increase in chromosome aberrations in bone marrow cells were reported (EU, 2014; ECHA, 2018).

In an unscheduled DNA synthesis study in rat hepatocytes according to OECD TG 486, DCOIT was negative for genotoxicity in Wistar rats (n=4 males/group) at doses of 0, 1000 or 2000 mg/kg bw/day in corn oil (EU, 2014; ECHA, 2018).

Carcinogenicity

No data are available for the chemical. However, based on the available genotoxicity and repeat dose toxicity data and comparison with structurally related isothiazolinones, the chemical is not considered to be carcinogenic.

Reproductive and Developmental Toxicity

The chemical does not cause specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a two-generation study conducted according to OECD TG 416, Crl:CD® BR rats (26 animals/sex/dose) were administered DCOIT (100 % purity) in diet at 0, 200, 400, 800 or 3200* ppm (*one generation only) (calculated as 0, 16–21, 30–41, 62–93 and 235–259 mg/kg bw/day). The exposure period was for 10 weeks before mating, through gestation and lactation until sacrifice. No mortality and treatment-related clinical signs were observed in the treated first parental animals (F0) generation at ≤800 ppm. At 3200 ppm, the effects observed were reduction in mean body weight gain in both sexes during premating (13–45 %), and in females during gestation (16–31 %) and lactation (8–18 % on post natal day (PND) 0, 4, 7 and 14. Additional observations at this dose groups included significant mortality in second generation of parental animals (F1) offspring with lactation index of 53.8 %, hyperplasia and hyperkeratosis of non-glandular mucosa and hypertrophy/vacuolisation of the adrenal cortex and decreased offspring viability. No effects on fertility, live litters, live pups/litter, sex ratio, oestrous cycle or sperm

parameters were observed. A dose-dependent statistically significant delay in vaginal opening and a statistically significantly delay in preputial separation in male pups of F1 generation were observed at ≥400 ppm. No treatment-related changes were observed in the anogenital distance evaluation, suggesting no oestrogenic or anti-androgenic effects on the pups. Pup weights in the 800 ppm dose group were lower on both F1 and F2 offspring at PND 14. Gross findings at this dose included thin and watery blood, enlarged heart, pale lungs, liver, kidney and/or intestines. A decrease in mean thymus weights in F1 offspring at 800 and 3200 ppm and F2 offspring at 400 and 800 ppm with decreased cellularity from 800 ppm was reported in both sexes on PND 21. In the F1 offspring at 400 ppm and above, lower mean spleen weights were observed in both sexes. The NOAEL for parental toxicity was 400 ppm (30–41 mg/kg bw/day) and the NOAEL for developmental toxicity was 200 ppm (16–21 mg/kg bw/day) (CPA, 2010; EU, 2014; ECHA, 2018).

In another 2-generation reproductive toxicity study (OECD TG 416), Wistar rats (n=24 animals/sex/dose) were administered DCOIT formulation Acticide® DCOIT (97.1 % purity) in the diet at concentrations of 0, 100, 350 or 1050 ppm (equivalent to 3–4, 14–16 and 57–71 mg/kg bw/day). The exposure period was for 10 weeks before mating, through gestation and lactation until sacrifice. No treatment-related effects were observed at 100 and 350 ppm in the F0 generation (CPA, 2010; EU, 2014; ECHA, 2018).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral and inhalation exposure) and local effects (corrosivity and skin sensitisation). The chemical is also corrosive to the respiratory tract.

Public Risk Characterisation

The chemical is used as a broad spectrum biocide for paints (see **Import, Manufacture & Use** section) that may have potential public exposures. The main route of public exposure is expected to be through the skin, inhalation from products applied as aerosols, and incidental oral exposure. Given the low concentrations expected for a preservative in these products, health effects apart from skin sensitisation are not expected.

The risks from the use of the chemical and other isothiazolinones as a preservative in water-based paint formulations should be examined. Direct exposure to paint formulations containing the chemical and several other isothiazolinones have resulted in allergies. In the absence of any regulatory controls, the characterised critical health effect of skin sensitisation has the potential to pose an unreasonable risk under the identified uses. Currently, there are no restrictions in Australia on using the chemical and several other isothiazolinones in paint formulations (see **Skin sensitisation: Observation in humans** section).

Occupational Risk Characterisation

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

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

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

In Europe a specific concentration limit (SCL) for the sensitisation classification is being proposed (ECHA, 2018). Further examination of the data is required to recommend a SCL.

NICNAS Recommendation

The chemical is recommended for Tier III assessment to further characterise the risks from the use of DCOIT in domestic products. The Tier III assessment would consider the risks and appropriate concentration limits to manage the risks from the use of the chemicals and other isothiazolinones as preservatives in paint formulations.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2018).

The need for further regulatory control for public health will be determined as part of the Tier III assessment.

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) Fatal if inhaled - Cat. 1 (H330)
Irritation / Corrosivity	Not Applicable	Corrosive to the respiratory tract (AUH071) Causes severe skin burns and eye damage - Cat. 1 (H314)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1A (H317)

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

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

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

Advice for consumers

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

Advice for industry

Control measures

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

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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;
- 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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Last update 26 October 2018

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