Benzisothiazolinone and its salts: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,2-Benzisothiazol-3(2H)-one	2634-33-5
1,2-Benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine	38521-29-8
1,2-Benzisothiazol-3(2H)-one, sodium salt	58249-25-5

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

Grouping Rationale

The chemical, 1,2-benzisothiazol-3(2H)-one, sodium salt (CAS No. 58249-25-5), is a salt resulting from benzisothiazolinone (CAS No. 2634-33-5) reacting with 1 sodium ion. The toxicity of both chemicals is considered similar since the speciation of the chemicals in biological fluids will be dependent on pH but independent of the original form.

The chemical, 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine (CAS No. 38521-29-8), is a salt resulting from benzisothiazolinone (CAS No. 2634-33-5) reacting with 1,2-ethanediamine (CAS No. 107-15-3). Although 1,2-ethanediamine presents a different toxicological profile compared with benzisothiazolinone, the toxicity of 1,2-ethanediamine is not considered to be relevant compared with that of benzisothiazolinone, apart from adding to sensitisation potential. For further information on the toxicological profile of 1,2-ethanediamine (CAS No. 107-15-3), its Human Health Tier II IMAP assessment report is available at **www.nicnas.gov.au**.

Import, Manufacture and Use

Australian

Benzisothiazolinone (CAS No. 2634-33-5) has reported domestic use in automotive aftermarket products including car wash soaps, boat wash soaps, polishes, waxes, rubbing compounds and sealants. The chemical is also used as in-can preservative for architectural and automotive paints, and resins at 0.02–0.06 %.

No Australian use information is available for the 2 salts (CAS No. 38521-29-8; CAS No. 58249-25-5) in this group.

International

The following international uses have been identified through 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; the US Environmental Protection Agency (EPA) Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the International Fragrance Association (IFRA) Transparency List (IFRA, 2016); and various international assessments [European Commission (EC) Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP, 2004), US EPA Re-registration Eligibility Decision (RED) (US EPA, 2005), and EC Scientific Committee on Consumer Safety (SCCS, 2012)].

Benzisothiazolinone has reported cosmetic uses as an antimicrobial agent, a preservative, and in fragrance compounds. The chemical has been reported to be present in tattoo inks.

The chemical (CAS No. 2634-33-5) has reported domestic uses, including as preservatives in paints, lacquers and varnishes, and as ingredients in:

- adhesive and binding agents;
- air fresheners;
- fabric softeners;
- carpet cleaners;
- stain removers;
- multi-purpose cleaners;
- wood floor cleaners;
- glass surface cleaners;
- floor polishers;
- tile grout and tile sealer;
- laundry and dishwashing detergents;
- dish soaps;
- handwash products; and
- odour eliminators.

The chemical has reported commercial uses, including:

- in concrete glues;
- as a wood preservative;
- in ink cartridges; and
- in metal working fluids.

The chemical has reported site-limited uses, including as preservatives in latex.

The chemical has reported non-industrial uses, including:

- as a fungicide;
- as a microbicide;
- as an insecticide;
- as a slimicide;
- in disinfectants; and
- as an inert ingredient in pesticide products.

No international use information is available for the 2 salts (CAS No. 38521-29-8; CAS No. 58249-25-5) in this group.

Restrictions

Australian

No known restrictions have been identified for the chemicals.

International

No known restrictions have been identified for the chemicals.

Existing Worker Health and Safety Controls

Hazard Classification

Benzisothiazolinone is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – Category 4; H302 (Harmful if swallowed)
- Skin irritation – Category 2; H315 (Causes skin irritation)
- Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction)
- Eye damage – Category 1; H318 (Causes serious eye damage).

The salts (CAS No. 38521-29-8; CAS No. 58249-25-5) are not listed on the HCIS (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available for the chemicals.

International

No specific exposure standards are available for the chemicals.

Health Hazard Information

Toxicity data exist for benzisothiazolinone for most health endpoints. No information is available for the salts (CAS No. 38521-29-8; CAS No. 58249-25-5).

The information on health hazards is obtained from the following comprehensive reviews of benzisothiazolinone: SCCNFP (2004), US EPA (2005), and SCCS (2012). The review by the SCCS is an updated version of the previous review by the SCCNFP. Unless otherwise noted, references to individual studies below are taken from these reviews.

This report should be read in conjunction with the Human Health Tier II IMAP assessment report for 1,2-ethanediamine (CAS No. 107-15-3) (NICNAS).

Toxicokinetics

Benzisothiazolinone is absorbed via the gastrointestinal tract and the skin. No distribution, metabolism, or excretion studies are available.

In a dermal absorption study, maximum dermal absorption of 40.6 % was measured at 72 hours in rats following the application of benzisothiazolinone to the skin for durations of 4–72 hrs (US EPA, 2005). No other details were provided.

In a skin absorption study conducted in accordance with the Organisation of Economic Co-operation and Development (OECD) Test Guideline (TG) 428 (Skin absorption: in vitro method), 0.01 % w/v aqueous benzisothiazolinone was applied to human dermatomed skin. The absorbed dose of the chemical was 25.63 % and the total dislodgeable dose was 42.05 % of the applied dose. The SCCS (2012) concluded that the applicable dermal absorption was 61.9 % of the applied dose (1.29 µg/cm²) when an aqueous solution of 0.01 % benzisothiazolinone was applied.

The SCCS (2012) assumed 50 % oral absorption but did not provide details of how this value was estimated.

Metabolic simulations based on the software Meteor Nexus v.3.1.0, Nexus v.2.2.1 and OASIS-TIMES (Optimized Approach based on Structural Indices Set–TIssue MEtabolism Simulator) v.2.28.16 indicated potential biotransformation pathways which include hydroxylation of the benzene ring, sulfonation of aromatic alcohols, glutathione conjugation, amide hydrolysis, and glucuronidation of aromatic alcohols.

Acute Toxicity

Oral

Benzisothiazolinone is classified as hazardous with the hazard category ‘Acute Toxicity Category 4’ and the hazard statement ‘Harmful if swallowed’ (H302) in HCIS (Safe Work Australia). The available data for the chemical (median lethal dose (LD50) in rats <2000 mg/kg bw) support this classification. The salts also warrant classification (see **Recommendation** section).

Sprague Dawley rats were administered 82.3 % benzisothiazolinone by gavage at doses of 823, 1646, or 4115 mg/kg bw. This study was conducted according to the US EPA Office of Pesticide Programs (EPA OPP) 81–1 method. The effects observed at any of the doses were not specified. The reported oral LD50, calculated using Probit analysis, was 2100 mg/kg bw for males. The reported acute oral LD50 for females, estimated graphically, was 1050 mg/kg bw (SCCNFP, 2004; SCCS, 2012).

The following acute oral LD50 values were reported for benzisothiazolinone, but no study details are available:

- 670 mg/kg bw in males and 784 mg/kg bw in females in unspecified animal species and strain (US EPA, 2005);
- 1020 mg/kg bw in rats (strain not specified) (HSDB; RTECS); and
- 1150 mg/kg bw in mice (strain not specified) (HSDB; RTECS).

Dermal

Benzisothiazolinone has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rats is >2000 mg/kg bw for benzisothiazolinone.

Topical application of a single dose of 4115 mg/kg bw of 82.3 % benzisothiazolinone to Sprague Dawley rats resulted in no gross toxicity, adverse effects, or abnormal behaviour (details not provided). This study was conducted in accordance with EPA OPP 81–2. The acute dermal LD50 was >4115 mg/kg bw (SCCNFP, 2004; SCCS, 2012).

An acute dermal LD50 value of >2000 mg/kg bw (unspecified animal species and strain) was reported for benzisothiazolinone but no study details are available (US EPA, 2005).

Inhalation

No data are available for the chemicals.

Corrosion / Irritation

Skin Irritation

Benzisothiazolinone is classified as hazardous with the hazard category ‘Skin Irritation Category 2’ and the hazard statement ‘Causes skin irritation’ (H315) in HCIS (Safe Work Australia). The available data for the chemical support this classification.

In a skin irritation test in New Zealand albino rabbits conducted in accordance with EPA Office of Pesticide Programs (OPP) 81–5, 82.3 % benzisothiazolinone was applied semi-occlusively. Well-defined moderate erythema and oedema were observed at all treated sites 1 hour after patch removal. The chemical was concluded to be a skin irritant based on the conditions of the test (SCCNFP, 2004; SCCS, 2012).

1,2-Ethanediamine (CAS No. 107-15-3) is corrosive to the skin and eyes (NICNAS). When 1,2-ethanediamine (CAS No. 107-15-3) is reacted with benzisothiazolinone (CAS No. 2634-33-5) to produce 1,2-benzisothiazol-3(2H)-one compound with 1,2-ethanediamine (CAS No. 38521-29-8), the resultant conjugate acid of 1,2-ethanediamine is expected to be less corrosive than 1,2-ethanediamine.

Eye Irritation

Benzisothiazolinone is classified as hazardous with the hazard category ‘Eye Damage Category 1’ and the hazard statement ‘Causes serious eye damage’ (H318) in HCIS (Safe Work Australia). The available data for the chemical support this classification. The hazard properties for irritation cannot be read across to the salts and there are no data available for these salts.

In an eye irritation test in New Zealand albino rabbits conducted in accordance with EPA OPP 81–4, 82.3 % benzisothiazolinone was instilled undiluted in the eyes. All of the treated eyes showed severe to maximal irritation with corneal opacity, iritis and conjunctivitis from 1 to 48 hours with the severity of irritation increasing with time. The chemical was found to be severely irritating to the rabbit eye (SCCNFP, 2004; SCCS, 2012).

An in vitro assessment of the eye irritancy potential of benzisothiazolinone using the bovine corneal opacity and permeability assay is available. Bovine eyes were exposed up to 7500 ppm aqueous solution of the chemical and corneal opacity and permeability were determined to give an in vitro score. The chemical was considered to be non-irritating to the eyes at all dose levels under the conditions of the test (SCCNFP, 2004; SCCS, 2012). The SCCS (2012) noted that the method used in this test was not validated at the time the study was submitted.

Observation in humans

A randomised double-blind open epicutaneous application study, aimed to compare the effects of a cream with and without a preservative (containing 2.5 % benzisothiazolinone and 2.5 % methylisothiazolinone (CAS No. 2682-20-4)), was conducted. Subjects with determined sensitivity to isothiazolinones were excluded from the study. The treatment regime included twice daily application of 1.5 mL of test cream and control for 4 weeks, assessing the skin reactions at 2 and 4 weeks after application. Irritant effects such as redness or itching, tingling or stinging sensation were reported on application, but disappeared after product absorption. Under the conditions of the test, the cream was tolerated by the individuals treated (SCCNFP, 2004; SCCS, 2012).

Fifty-six individuals were subjected to irritancy patch tests containing benzisothiazolinone at concentrations of 0.002 and 0.05 % in aqueous propylene glycol and 0.1 % in petrolatum. Positive results were observed in 10 individuals at 4 days with the chemical in petrolatum (HSDB).

Sensitisation

Respiratory Sensitisation

1,2-Ethanediamine is a respiratory sensitiser (NICNAS). It has a high vapour pressure and is a volatile chemical which produces vapour at room temperature and in atmospheric conditions, which facilitates inhalational exposure in humans. When 1,2-ethanediamine is present as a salt in 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine (CAS No. 38521-29-8), the potential for inhalational exposure and subsequent respiratory sensitisation is absent in products that are not applied by spraying.

Skin Sensitisation

Benzisothiazolinone is classified as hazardous with the hazard category ‘Skin Sensitisation Category 1’ and the hazard statement ‘May cause an allergic skin reaction’ (H317) in HCIS (Safe Work Australia). The available data for the chemical (EC3 > 2 %) support applying a sub-classification for this classification. The salts (CAS No. 38521-29-8; CAS No. 58249-25-5) warrant classification based on read across information for benzisothiazolinone (see **Recommendation** section); however the sensitisation potency for 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine needs further evaluation.

1,2-Ethanediamine is a skin sensitiser (NICNAS). 1,2-Benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine (CAS No. 38521-29-8) is also expected to be a skin sensitiser. Elicitation of reactions in individuals sensitised to 1,2-ethanediamine could occur.

The following study results are available for benzisothiazolinone based on information submitted to the SCCNFP (2004) and SCCS (2012):

- an EC3 (the effective concentration required to produce a 3-fold increase in stimulation index) of 2.3 % identified from a local lymph node assay (LLNA) dataset review; however, the experimental details were not provided;
- moderate contact sensitiser at 79.8 % in a guinea pig maximisation test (GPMT) (OECD TG 406); and
- not a sensitiser at 82.3 % under the conditions of a Buehler test in accordance with EPA OPP 81–6 in Hartley albino guinea pigs.

Additionally, benzisothiazolinone was reported as a moderate dermal sensitiser, but no study details are available (US EPA, 2005).

Observation in humans

Volunteers with identified sensitivity to isothiazolinones were included in a randomised double blind open epicutaneous application study aimed to compare the effects of a cream with and without a preservative. The cream with preservative

contained 0.15 % w/w benzisothiazolinone. A flare of eczema was noticed in some of the individuals who were withdrawn from the study. SCCS (2012) noted that limited conclusions can be drawn from this study.

Occupational dermatitis has been reported when water-based solutions containing benzisothiazolinone were used in cutting fluids, paint and varnish manufacture, pottery mould-makers, acrylic emulsions manufacture, printer, metal and paper makers (HSDB; SCCNFP, 2004; SCCS, 2012).

Benzisothiazolinone has been used as a slimicide in disposable powder-free polyvinyl chloride (PVC) glove manufacture. Allergic contact dermatitis was reported in individuals wearing such gloves with a concentration of 20 ppm benzisothiazolinone causing sensitisation (Aalto-Korte et al., 2007).

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

Repeated Dose Toxicity

Oral

Based on the available data for benzisothiazolinone, the chemicals are not considered to cause serious damage to health from repeated oral exposure. Although repeated oral exposure to benzisothiazolinone in rats was consistently associated with increased incidence of histopathological lesions on the non-glandular portion of the stomach, these effects are attributed to the local irritant effects of the chemical.

In a study conducted in accordance with OECD TG 407 (Repeated dose 28-day study), benzisothiazolinone at 84.29 % was administered by gavage to Wistar rats for 28 days at doses of 12.63, 37.89, or 113.67 mg/kg bw/day. There were no adverse effects observed at the lowest dose. Histopathological lesions were observed in the non-glandular portion of the stomach only at the 37.89 mg/kg bw/day dose. At the highest dose, significant decrease in bodyweight gain in males (no details reported) and slight salivation, in all males and 2 females, were observed. Based on the histopathological lesions found in the non-glandular portion of the stomach, the no observed adverse effect level (NOAEL) for this study was determined to be 12.63 mg/kg bw/day. The SCCS (2012) concluded that the adverse effects reported in this study were most likely due to the irritant property of the chemical.

In a study conducted in accordance with OECD TG 408 (Repeated dose 90-day study), Wistar rats were administered 84.9 % benzisothiazolinone by gavage at doses of 8.42, 25.26, or 63.15 mg/kg bw/day for 90 days. There were no treatment-related clinical signs, neurological effects or adverse effects on growth reported in any dose group. At the 25.26 mg/kg bw/day dose, treatment-related effects observed included macroscopic and histological changes in the non-glandular stomach region, such as increased incidence of lesions (hyperkeratosis, epithelial hyperplasia, and ulceration) in males and females. The effects were reversible in the recovery group and were likely to be due to the irritant property of the chemical. At the 63.15 mg/kg bw/day dose, treatment-related salivation was seen in both sexes. Bodyweight gain was significantly reduced in males. In both sexes, increased incidence of histopathological lesions in the non-glandular portion of the stomach (hyperkeratosis, epithelial hyperplasia, ulceration, and keratin cysts) were observed. This study confirms the SCCS (2012) findings that the histopathological lesions reported at the mid-dose were due to the irritant properties of the chemical and the NOAEL for systemic effects is 25.26 mg/kg bw/day.

1,2-Ethanediamine (CAS No. 107-15-3) did not produce serious damage to health in animals from repeated dermal or inhalational exposure (NICNAS). The adverse effects observed from repeated oral exposure to 1,2-ethanediamine appear to be driven by the irritative/corrosive effects of the chemical. Based on the overall information, 1,2-benzisothiazol-3(2H)-one compound with 1,2-ethanediamine (CAS No. 38521-29-8) is likely to not produce serious health damage from repeated oral, dermal or inhalational exposure.

Dermal

No data are available for the chemicals.

Inhalation

No data are available for the chemicals.

Genotoxicity

Based on the available in vitro and in vivo genotoxicity studies for benzisothiazolinone, the chemicals are not considered to be genotoxic.

The following in vitro results are available for benzisothiazolinone (SCCNFP, 2004; SCCS, 2012):

- negative in a mammalian cell gene mutation test (OECD TG 476) up to 5.2 µg/mL, with and without metabolic activation; and
- not clastogenic in a mammalian chromosome aberration test (OECD TG 473) in Chinese hamster ovary (CHO) cells at levels up to 6.4 µg/mL, with and without metabolic activation.

Air fresheners containing mixtures of citral and either benzisothiazolinone or triclosan were examined for cytotoxicity in human A549 lung epithelial cells. Observed effects of the mixtures include: significant decrease in the viability of the lung epithelial cells; dose-dependent cell growth inhibition; and increased reactive oxygen species (ROS) generation. However, the mixtures did not increase DNA damage by comet analysis (Kwon et al., 2013).

The following in vivo results are available for benzisothiazolinone (SCCNFP, 2004; SCCS, 2012):

- not clastogenic in Swiss albino mice in an in vivo mammalian erythrocyte micronucleus test (OECD TG 474) at doses up to 210.5 mg/kg bw/day; and
- negative in Wistar rat hepatocytes at concentrations up to 750 mg/kg bw/day in an unscheduled DNA synthesis (UDS) test (OECD TG 486).

1,2-Ethanediamine (CAS No. 107-15-3) is not considered to be genotoxic based on the weight of evidence from the available in vitro and in vivo genotoxicity studies (NICNAS). Therefore, 1,2-benzisothiazol-3(2H)-one compound with 1,2-ethanediamine (CAS No. 38521-29-8) is expected to be also not genotoxic.

Carcinogenicity

No animal data are available for the chemicals. Based on the information available for benzisothiazolinone from the genotoxicity (see **Genotoxicity** section) and Quantitative Structure Activity Relationship (QSAR) modelling, the chemicals are not expected to be carcinogenic.

Benzisothiazolinone has a structural alert for binding to DNA based on the mechanistic profilers of the OECD QSAR Toolbox v.4.2. The alert relates to the carboxamide side chain in the chemicals' structure that may affect DNA intercalation. However, this postulation is applicable for chemicals that are positive in both in vitro bacterial mutation and chromosome aberration assays (Snyder et al., 2006; Ferguson & Denny, 2007). Benzisothiazolinone is negative in a chromosome aberration and did not damage the DNA in a comet analysis.

1,2-Ethanediamine (CAS No. 107-15-3) is not considered to be carcinogenic (NICNAS). Therefore, 1,2-benzisothiazol-3(2H)-one compound with 1,2-ethanediamine (CAS No. 38521-29-8) is expected to be not carcinogenic.

Reproductive and Developmental Toxicity

Based on the available data for benzisothiazolinone, the chemicals are not expected to cause reproductive or developmental toxicity. 1,2-Ethanediamine (CAS No. 107-15-3) produced developmental effects only secondary to maternal toxicity (NICNAS). 1,2-Benzisothiazol-3(2H)-one compound with 1,2-ethanediamine (CAS No. 38521-29-8) is not expected to cause reproductive and developmental effects.

In a 2-generation reproductive toxicity study (EPA OPPTS 870.3800), Crl:W1 rats were fed benzisothiazolinone in the diet at concentrations of 250, 500, or 1000 ppm (24, 50, 100 mg/kg bw/day). The same doses were administered to the parent (P) and first filial (F1) generation. The P generation received the chemical for 10 weeks before being paired for up to 2 weeks. Dosing continued during the pairing period, and throughout the resulting pregnancies. The treatment of the F1 generation was continued during maturation, mating, and weaning of the second (F2) generation offspring. For the P generation, there were no treatment-related effects observed on bodyweight, clinical chemistry, and fertility in any dose group. At 1000 ppm, the effects observed were increased mean liver weight in males, decreased mean testes weight, and presence of limiting ridge hyperplasia in the stomach. No details of the changes were provided. Pup weights in the high dose group were slightly low up to 2 weeks post-partum but returned to normal later. In the F1 generation, effects observed at the 1000 ppm group were slightly lower (magnitude not specified) F2 pup survival and F2 mean pup weight gain. In the 500 and 1000 ppm groups, limiting ridge hyperplasia in the stomach was reported, more prominently for the females at the high dose group with squamous cell hyperplasia, forestomach gastritis, hyperkeratosis, and erosion/ulcer. There were no adverse effects at the lowest dose of benzisothiazolinone tested. The NOAEL for the parental local effect is 50 mg/kg bw/day. No fertility or developmental effects have been observed in the absence of parental toxicity.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation for benzisothiazolinone and its salts include systemic acute effects (acute toxicity from oral exposure) and local effects (skin sensitisation). The parent base can also cause skin and eye irritation.

The possibility of 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine (CAS No. 38521-29-8) to induce or elicit respiratory sensitisation cannot be ruled out if it is present in paint intended for spray use. However, no data are available to indicate this use occurs.

Public Risk Characterisation

The chemical, benzisothiazolinone, has reported domestic use in automotive aftermarket products and as a preservative in paints and resins (See **Import, Manufacture and Use: Australian** section). Although use in cosmetics is not known in Australia, the chemical is reported to be used in cosmetic products overseas. Currently, there are no restrictions in Australia on using the chemicals in cosmetics or domestic products.

Considering the range of domestic, cosmetic and personal care products that may contain the chemicals, 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.

Direct exposure to paint formulations containing benzisothiazolinone and several other isothiazolinones have resulted in allergies (see **Skin sensitisation: Observation in humans**).

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.

Further characterisation of the risks from the use of benzisothiazolinone in cosmetic and domestic products is required. Additionally, the risks from the use of the chemical and other isothiazolinones, as a preservative in water-based paint formulations, should be examined. Quantitative risk assessment of products containing 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine needs to take into account the sensitising potential of both constituents of the salt.

Occupational Risk Characterisation

During product formulation, dermal, oral, 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 chemicals at lower concentrations could also occur while using formulated products

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

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate for benzisothiazolinone, although a sub-classification for this classification could apply. An amendment to the hazard classification in the HCIS for the sodium salt is recommended (see **Recommendation** section). The classification for 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine will be evaluated as part of the Tier III IMAP assessment.

NICNAS Recommendation

The chemicals are recommended for Tier III IMAP assessment to further characterise the risks from the use of the chemicals in cosmetic and domestic products.

The Tier III IMAP assessment would additionally 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. This assessment will further clarify the extent of use of 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine (CAS No. 38521-29-8) in paint in Australia.

Regulatory Control

Public Health

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

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. The acute toxicity classification applies to all chemicals in the group. The skin and eye irritation classifications only apply to benzisothiazolinone (CAS No. 2634-33-5). The skin sensitisation classification applies to benzisothiazolinone and the sodium salt (CAS No. 58249-25-5). The classification for 1,2-benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine (CAS No. 38521-29-8) will be evaluated as part of the Tier III IMAP assessment. 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)*
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318)* Causes skin irritation - Cat. 2 (H315)*

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (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 chemicals 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 or inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and

- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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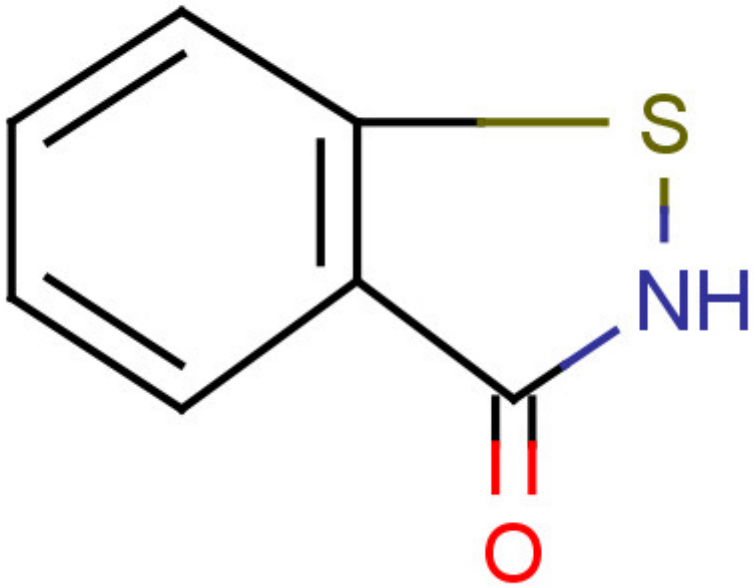
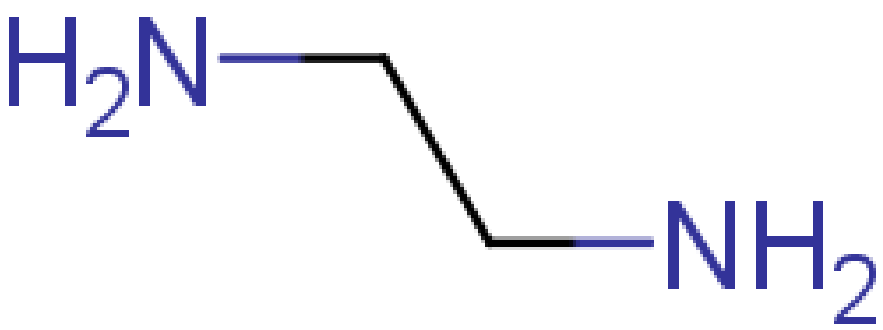
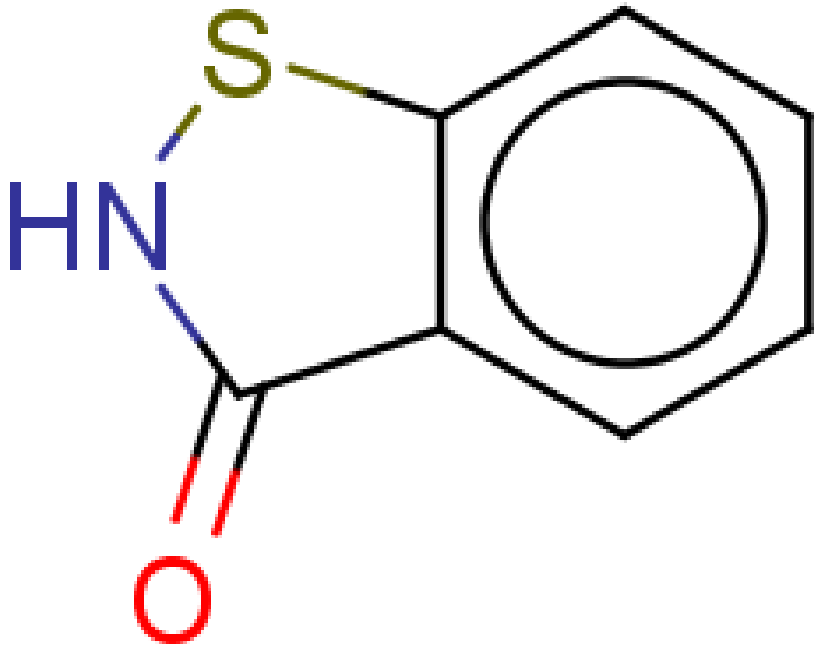
Last Update 12 December 2019

Chemical Identities

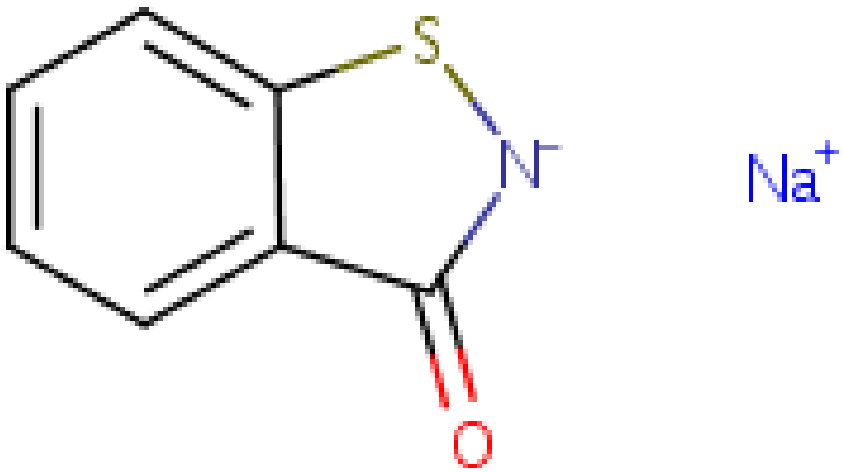
Chemical Name in the Inventory and Synonyms	**1,2-Benzisothiazol-3(2H)-one** 1,2-benzisothiazolin-3-one benzisothiazolinone BIT
CAS Number	2634-33-5
Structural Formula	

	
Molecular Formula	C7H5NOS
Molecular Weight	151.19

Chemical Name in the Inventory and Synonyms	**1,2-Benzisothiazol-3(2H)-one, compound with 1,2-ethanediamine** 1,2-benzisothiazol-3(2H)-one, compd. with 1,2-ethanediamine
CAS Number	38521-29-8
Structural Formula	

	 
Molecular Formula	C7H5NOS.xC2H8N2
Molecular Weight	211.28 (for 1:1)

Chemical Name in the Inventory and Synonyms	**1,2-Benzisothiazol-3(2H)-one, sodium salt** sodium benzisothiazolinone
CAS Number	58249-25-5
Structural Formula	

	
Molecular Formula	C7H5NOS.Na
Molecular Weight	173.17

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