Substituted Oxazolidines: Human health tier II assessment

26 October 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1H,3H,5H-Oxazolo[3,4-c]oxazole-7a(7H)-methanol	6542-37-6
1H,3H,5H-Oxazolo[3,4-c]oxazole, 7a-ethyldihydro-	7747-35-5

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 chemicals in this group are structurally related. Both chemicals are oxazolidine substituted at the 5 position with ethyl (CAS No 7747-35-5; oxazolidine E) or hydroxymethyl (CAS No 6542-37-6; oxazolidine T) groups. Both chemicals were reported to be used as antimicrobials or biocides in cosmetic products (CosIng). Oxazolidine E is also widely used as a preservative or biocide in domestic products, adhesives, and metal working fluid (Galleria Chemica, SPIN, REACH). The biocidal mechanism involves formaldehyde release into aqueous solutions.

Both chemicals are known formaldehyde donors. Given that the toxicity of these chemicals are based on released formaldehyde, it is appropriate to assess these chemicals together. The hazardous properties of formaldehyde are expected to dominate the toxicity profile of these chemicals despite minor differences in individual chemical solubility in biological systems. The residual aminoalcohols remaining after formaldehyde dissociation are not expected to be toxic at the low concentrations at which the chemicals are used.

Import, Manufacture and Use

Australian

The chemical, oxazolidine T (CAS No 6542-37-6), has reported industrial use as rubbing compounds. The chemical also has reported potential domestic use in automotives after market products.

No specific Australian use, import, or manufacturing information has been identified for oxazolidine E (CAS No 7747-35-5).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH); Galleria Chemica; Substances and Preparations in Nordic countries (SPIN) database;

European Commission Cosmetic Ingredients and Substances

(CosIng) database; and the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary (Personal Care Products Council).

Oxazolidine E (CAS No 7747-35-5)

The chemical has reported uses as UV filter, preservative and antimicrobial in cosmetic products.

The chemical has reported domestic uses as antimicrobial preservative in household cleaning products (dishwashing and laundry liquids, surface cleaners and polishes), and in paints and coatings.

The chemical has reported commercial uses, including:

- as a biocide in cutting fluids, cutting oils, lubricants and additives;
- as an antimicrobial in adhesives;
- as a corrosion inhibitor;
- as a urethane foam catalyst;
- in leather tanning; and
- in heat transferring agents.

Oxazolidine T (CAS No 6542-37-6) (Galleria Chemica)

The chemical has reported use as an antimicrobial in cosmetic products.

The chemical has non-industrial use as a pesticide.

Restrictions

Australian

The chemical is a formaldehyde donor. Formaldehyde donors are specifically included in the definition of free formaldehyde in Part 1, Interpretation in the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) as follows:

“**Free formaldehyde**” includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol and formaldehyde released from formaldehyde donors.

Formaldehyde is listed in Schedules 2, 6 and 10 of the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2017)) as follows:

- in Schedule 2:

'FORMALDEHYDE (excluding its derivatives) for human therapeutic use **except**:

(a) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde; or

(b) in other preparations containing 0.2 per cent or less of free formaldehyde.'

Schedule 2 chemicals are labelled with 'Pharmacy medicines' and are 'substances, the safe use of which may require advice from a pharmacist and should be available from a pharmacy or, from a licensed person'.

- in Schedule 6:

'FORMALDEHYDE (excluding its derivatives) in preparations containing 0.05 per cent or more of free

formaldehyde **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

(d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement: PROTECT CUTICLES WITH GREASE OR OIL;

(e) in all other cosmetic preparations; or

(f) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Schedule 6 chemicals are labelled with 'Poison' and are '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'.

• in Schedule 10:

'FORMALDEHYDE (excluding its derivatives):

(a) in oral hygiene preparations containing more than 0.1 per cent of free formaldehyde;

(b) in aerosol sprays for cosmetic use containing 0.005 per cent or more of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde; or

(d) in all other cosmetic preparations containing 0.05 per cent or more of free formaldehyde **except** in preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Schedule 10 are 'substances of such danger to health as to warrant prohibition of sale, supply and use - Substances which are prohibited for the purpose or purposes listed for each poison.'

International

The chemical, oxazolidine E (CAS No 7747-35-5) is listed on the following (Galleria Chemica):

• ASEAN Cosmetic Directive Annex VI—List of preservatives allowed in cosmetic products;

• EU Cosmetics Directive 76/768/EEC Annex VI—List of UV filters allowed in cosmetic products at a maximum authorised concentration of 0.3%; and

• New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives cosmetic products may contain with restrictions —Table 1: List of preservatives allowed.

No known restrictions have been identified for oxazoline T (CAS No 6542-37-6). However, the chemical is a formaldehyde donor and may be subject to the restrictions on formaldehyde, under certain conditions.

Using formaldehyde in cosmetics in the EU is subject to the restrictions described in EU Regulation, Annex III (List of substances which cosmetic products must not contain except subject to the restrictions laid down) and Annex V (List of preservatives allowed in cosmetic products) (CosIng).

Formaldehyde may be present in the following cosmetic and personal care products (CosIng):

- nail hardening products at a maximum concentration of 5 % in ready for use preparation; if the concentration exceeds 0.05 %, the label must indicate 'Contains formaldehyde'.

- preservatives for oral products with a maximum concentration of 0.1 % as free formaldehyde in ready for use preparation; and
- preservatives for other products with a maximum concentration of 0.2% as free formaldehyde in ready for use preparation.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (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

The chemical, oxazolidine E (CAS No 7747-35-5) has reported use as a preservative in cosmetics, paints and coating, adhesives, and metal working fluids. The chemical is also used as a bactericide in laundry products and household cleaners. The typical concentration of oxazolidine E in various applications ranges from 400 to 2000 ppm. The chemical, oxazolidine T (CAS No 6542-37-6) has also reported use as an antimicrobial in cosmetics and may be used in automotive after market products. In these applications, the biocidal mechanism involves release of formaldehyde into aqueous solutions secondary to hydrolytic degradation of the chemical (Anderson BE et al., 2007). The degree of completeness of formaldehyde release in these products will depend on the concentration of the preservative in the product, the percentage of water in the product, the rate of formaldehyde release from the specific preservative, and the length of time since formulation.

There are limited toxicological data available for oxazolidine T. Where there are data gaps, information from oxazolidine E is considered suitable as read across to oxazolidine T due to their expected similar mode of action. Where data are unavailable or limited for both chemicals, data for formaldehyde have been used for read across to the chemicals. For skin sensitisation and systemic toxicity, it is considered that the formaldehyde released from the hydrolysis of these chemicals will be the critical driver of these modes of toxicity. While the toxicity of the hydrolysis product other than formaldehyde (2-amino-2-ethyl-1,3-propanediol; CAS No 115-70-8 for oxazolidene E) is also relevant and has been considered in this assessment, the EU SCCNFP has previously stated that similar formaldehyde–releasing chemicals used in cosmetics should be regulated based on free formaldehyde (SCCNFP, 2002). Data are not available for 2-amino-2-hydroxymethyl-1,3-propanediol, derived from oxazolidine T; however, the toxiticity is expected to be similar to 2-amino-2-ethyl-1,3-propanediol derived from oxazolidene E.

Toxicokinetics

Oxazolidine E when administered was absorbed, metabolised completely and readily eliminated within 144-168 hours after dosing. The chemical is not expected to bioaccumulate (REACH). There are no toxicokinetic data available for oxazolidine T; however, the chemical is expected to have a similar toxicokinetic profile to oxazolidine E.

The toxicokinetics of oxazolidine E was investigated in Crl:CD Sprague Dawley (SD) rats (4/sex/dose) following oral gavage (5 or 200 mg/kg bw) or dermal application (5 mg/kg bw) of radiolabelled ^{14}C oxazolidine E (radiolabel position unspecified). The oral study was conducted in accordance with the OECD Test Guideline (TG) 417 (Toxicokinetics) and the dermal study was conducted in accordance with OECD TG 427 (Skin Absorption: In vivo Method) (REACH).

In the oral study, groups of SD rats received (1) a single oral dose of 5 mg/kg bw (low dose) radiolabelled oxazolidine E (Groups 1, 3 and 4); (2) a single oral of 200 mg/kg bw (high dose) radiolabelled oxazolidine E (Group 2); (3) and 14 daily oral doses of non-radiolabelled oxazolidine E followed by a single oral dose (5 mg/kg bw) of radiolabelled oxazolidine E on Day 15 (Group 5). Absorption was determined from the amount of radioactivity recovered in the urine, cage wash and animal tissues. Absorption was reported to be higher in Group 5 (96-99%) than in Groups 1,3 and 4 (86-92%). Absorption of single oral high dose (Group 2) was reported to be 85-90% of the administered dose.

Approximately 1% of the administered dose was found in the tissues 144 hours (Group 2) or 168 hours (Groups 1, 3 and 4) after dosing. Similar observations were reported for Group 5. The absorbed chemical was completely metabolised. The metabolite, 2-amino-2-ethyl-1,3-propanediol was found in urine and faecal samples from all dose groups at ≥5% of the administered dose. Four unidentified minor metabolites were also found. The chemical was rapidly excreted in the urine (up to 97%). The majority of the chemical (61-75%) was excreted unchanged within 12 hours (approximately 43% within 6 hours), and 9-12% excreted between 12 to 24 hours of dosing. A small amount (9-15%) was eliminated in the faeces. Very low levels of the radioactivity (1-3% total in the body) were identified, suggesting that accumulation would not occur following exposure to the chemical (REACH).

A dermal dose of 5 mg/kg bw (in polyethylene glycol (PEG) 400) of radiolabelled oxazolidine E was topically applied onto the skin of rats (4/sex/dose) under semi–occlusive dressing for 6 hours, then washed with detergent and water. Low dermal absorption of approximately 25-27% of the dermally applied dose (mean

total) was found. Approximately 3% of the dermal dose was found in the tissues. The peak plasma concentration occurred at 2-3 hours after application. The rate of dermal absorption was 0.14-0.20/hour. The time required for one half of the total amount of the absorbed radioactivity to be eliminated ($t_{1/2}$) was determined to be 0.14 to 0.20 hours. Approximately 17-20% of the applied dose was recovered in the urine within 168 hours, with the majority excreted in the urine within the first 24 hours. Faecal elimination was 4% of the dermal dose (REACH).

Acute Toxicity

Oral

Oxazolidine E has low acute toxicity based on the results from an animal test following oral exposure. The median lethal dose (LD50) in rats was >2000 mg/kg bw. Observed sub-lethal effect included haemorrhagic nasal discharge.

In a non-guideline acute oral study, a solution of oxazolidine E (in distilled water) at doses 0, 2100, 3000, 4200 and 6000 mg/kg bw was administered by gavage as a single dose to Crj:CD Dawley (SD) rats (10/sex/dose). Animals were observed daily for 14 days. At the highest dose, the majority of the animals died within 4 hours.

Surviving animals showed haemorrhagic nasal discharge. The acute oral LD50 was reported to be 5249 and 3674 mg/kg bw for males and females, respectively (REACH).

Dermal

Oxazolidine E has low to moderate acute toxicity based on results from animal tests following dermal exposure. The LD50 in rats is >2000 mg/kg bw.

In an acute dermal study conducted according to OECD TG 402, oxazolidine E (neat) was applied on the shaved skin of rats (5/sex/group) at 2000 mg/kg bw. The application site was covered under occlusive patches for 24 hours and observed for 14 days. There were no mortalities and no local skin reactions reported. A dermal LD50 of >2000 mg/kg bw was reported (REACH).

In a non- guideline study, oxazolidine E was applied on the shaved abdomen of rabbits at 500 (2/sex), 1000 (4/sex), 1500 (4/sex) and 2000 (4/sex) mg/kg bw. The application sites (intact and abraded) were covered under occlusive patches for 24 hours and animals were observed for 14 days. Both intact and abraded skin were severely irritated after 24 hours exposure and remained erythematous and oedematous during the 14-day observation period. The dermal LD50 in rabbits was calculated to be 1948 mg/kg bw (REACH).

The dermal LD50 of the metabolite, 2-amino-2-ethyl-1,3-propanediol (CAS No 115-70-8) in New Zealand White (NZW) rabbits was reported to be >2000 mg/kg bw (REACH).

Inhalation

Oxazolidine E has moderate acute toxicity based on results from an animal test following inhalation exposure, warranting classification (see **Recommendation** section). The median lethal concentration (LC50) in rats is 3.1 mg/L for 4 hours. Observed sub-lethal effects included hunched posture, loss or reduced righting reflex, ataxia, decreased muscle tone, shallow and laboured breathing, and gasping. Lung discolouration was also reported. No data are available for oxazolidine T.

In an acute inhalation study, SD rats (5/sex/dose) were exposed (whole body) to oxazolidine E aerosol at concentrations of 0, 1.6, 2.4, 2.6, 3.3, 4.3 mg/L for 4 hours. An LC50 of 3.1 mg/L was reported (REACH).

Corrosion / Irritation

Skin Irritation

The data available from animal studies indicate that there is potential for skin irritation upon dermal exposure to oxazolidine E, warranting hazard classification (see **Recommendation** section). Oxazolidine E when applied on the intact and abraded rabbit skin for 24 hours produced severe erythema and oedema, which persisted up to 48 hours exposure. Oxazoline T is expected to have similar irritating potential based on the similarity in functional groups and should also be classified unless data are available to demonstrate otherwise.

In a non-guideline skin irritation study, 0.5 mg of undiluted oxazolidine E was applied on the shaved back of albino rabbits (6 rabbits; unspecified sex), under occlusive conditions for 24 hours. The skin on the left side of the middorsal line was left intact and the skin on the right side was abraded with a blunt needle. Observation periods were 24 and 48 hours after dermal application. Erythema and oedema were reported on both intact and abraded skin. The chemical was reported to be a severe irritant to skin (REACH). There is a descrepancy in the study report where the dose was in milligrams (mg); however, the test material was indicated as undiluted.

In another non-guideline study, 0.5 mL of oxazolidine E (94.5% purity) was applied on the back of each rabbit (6 rabbits; unspecified sex), under occlusive patches for four hours. Observation times were 4, 24 and 48 hours after exposure. Slight oedema and erythema were reported (REACH).

The skin irritation potential of the metabolite (2-amino-2-ethyl-1,3-propanediol; CAS No 115-70-8) was assessed in New Zealand White rabbits (6 animals/unspecified sex). The chemical (0.5mL) was applied on the intact skin for 24 hours under occlusive patches and observed for up to 21 days. In all animals, slight erythema, and moderate to severe oedema were reported within 24 and 72 hours. All effects were reversed within 14 days (REACH).

Eye Irritation

Based on the available data, oxazolidine E causes eye irritation, warranting hazard classification (see **Recommendation** section). Irreversible eye irritation effects were reported following exposure to oxazolidine E and the metabolite, 2- amino-2-ethyl-1,3-propanediol. Oxazoline T is expected to have similar irritating potential based on the similarity in functional groups and should also be classified unless data are available to demonstrate otherwise.

In a non-guideline eye irritation study, 0.1 mL of oxazolidine E was instilled into the right eye of rabbits (9 rabbits; unspecified strain) and the untreated left eye served as the control. The eyelids were held closed for 1-2 seconds. Three of the treated eyes

were irrigated with lukewarm water for 20-30 seconds. The eyes were

examined 24, 48 and 72 hours after treatment. The chemical produced irritation to the cornea, iris and conjunctivae in washed and unwashed eyes, and the severity of the irritation persisted up to 72 hours. In some animals, the irritation persisted up to 7 days. The chemical was considered to be an eye irritant (REACH).

The eye irritation potential of the metabolite (2-amino-2-ethyl-1,3-propanediol; CAS No 115-70-8) was assessed using NZW rabbits (Group 1; 6 animals and Group 2; 3 animals). The eyes were instilled with 0.1 mL chemical, and the eyes were either left unwashed (Group 1) or washed 20–30 seconds after instillation (Group 2), and observed for 24 hours. Corneal lesions and severe eye irritation were reported in all animals, and these were reversible only in washed eyes after 21 days. The chemical was reported to be corrosive under the conditions of the study (REACH).

Sensitisation

Skin Sensitisation

Based on the weight of evidence from the available sensitisation studies and human skin patch tests, the chemicals are potential skin sensitisers. In addition, the presence of formaldehyde in solutions containing the chemical should also be taken into account. Formaldehyde is a known skin sensitiser. Overall, the chemicals would; therefore, be considered as skin sensitisers, warranting hazard classification (see **Recommendation** section).

In a guinea pig maximisation test conducted according to OECD TG 406 (Skin Sensitisation), oxazolidine E (5 % as a suspension in distilled water) was injected intradermally on the shaved shoulder of Hartley guinea pig (5/sex/group) and allowed to rest for one week (Induction phase). A week later (day 7), the chemical (25% in distilled water) was topically applied on the skin under occlusive patch for 48 hours. Three weeks after the induction phase (day 21), occlusive patches saturated with the chemical (1 % and 0.5%) were applied on the flanks of the animals for 24 hours. Formaldehyde was used as a positive control. The test area was washed and skin reactions were observed at 3 and 24 hours after the patches were removed. Under the test conditions, the chemical did not induce skin sensitisation in guinea pigs (REACH).

In a guinea pig Buehler test conducted according to OECD TG 406 (Skin Sensitisation), patches containing oxazolidine E (5 % as a suspension in distilled water) were affixed on the skin of Hartley guinea pigs (total of 28 animals) under occlusive conditions for six hours, and repeated weekly for three weeks. The challenge was conducted in the same manner as the induction phase, 11-15 days after the final induction patch. The test area was observed at 24 and 48 hours after the challenge. At 5% concentration challenge, the chemical produced positive skin reactions. A rechallenge using 0.5% concentration also elicited positive response. A third challenge using 0.1% solution produced no evidence of sensitisation. The chemical was determined to be sensitising under the conditions of the study (REACH).

In another maximisation study (TG 406), Harley guinea pigs (n=20) were injected intradermally with oxazolidine E (0.001, 0.01, 0.2 or 1%) (induction phase). After eight days, topical induction patches containing the same chemical concentrations were applied on the shaved skin for 48 hours under occlusive conditions. After 11-15 days (primary challenge) the same concentrations of the chemical were applied on the skin in the same manner as the topical induction. After 24 hours, the test area was examined. Six days after the primary challenge, some animals were re-challenged in the same manner as the primary challenge. Mild skin responses were reported at an induction-challenge concentration of 0.001%. Moderate responses were reported at induction-challenge concentration of 0.01%. Strong responses were reported at an induction-challenge concentration of 0.2%. Extreme responses were reported at an induction-challenge concentration of 1%. The chemical was determined to be a skin sensitiser in guinea pigs (REACH).

In a non–guideline sensitisation study conducted in male guinea pigs (30 animals/unspecified strain), oxazolidine E was tested using induction by intradermal injection (0.5% suspension in water). At challenge, intradermal injection of the chemical (0.5% suspension in water) caused mild skin reactions which reversed within 48 hours. The chemical was considered to be non-sensitising under the test conditions (REACH).

Observation in humans

Patch testing was conducted in patients referred for allergic contact dermatitis testing. Out of 210 patients, 24 showed positive reactions to patch testing using formaldehyde, various Bioban products (including oxazolidine E) and other formaldehyde releasers. A high rate of cross reactivity amongst formaldehyde, various Bioban products and other formaldehyde releasers was reported. Thirteen patients (6.2 %) reacted positively to oxazolidine E (Anderson BE et al., 2007).

Metal workers (n=408) in Germany were patch tested against various Bioban products (including oxazolidine E). Positive reactions were reported in 14/408 workers (3.4 %), with 2.0 % showing positive patch tests for oxazolidine E. The study concluded that positive patch test reactions to Bioban products among metal workers were not unusual; however, the results were "often weak and not reproducible". Cross-reactivity to various Bioban products and formaldehyde may contribute to the positive patch tests (Brinkmeier T et al., 2002).

In Spain, 2184 patients with occupational contact dermatitis from two contact dermatitis clinics were investigated. Out of 2184 patients, 72 (64 men and 8 women) metal workers aged between 27 and 50 years were tested with chemotechnique cutting oil series (including oxazolidine E). Positive reactions were reported in 8 patients patch tested using the cutting oil series. Twenty four of the 72 patients were also tested using dilutions of their own cutting oil. No patients reacted to their own cutting oil (Camarasa JG, 1993).

Repeated Dose Toxicity

Oral

Considering the effects reported in various repeated oral dose toxicity studies using oxazolidine E, as well as the lack of systemic toxicity of formaldehyde in oral studies (NICNAS), repeated oral exposure to the chemicals are not considered to cause serious damage to health.

In a repeat dose toxicity study conducted according to OECD TG 408 (Repeated dose 90–day oral toxicity in rodents), Crl:CD (SD) rats (10/sex/dose) were dosed daily by gavage with oxazolidine E (in corn oil) at 0, 10 (low), 50 (mid) and 250 (high) mg/kg bw/day for 13 weeks. Animals from mid and high dose groups were left untreated for 28 days following treatment period (recovery groups). At the highest dose (250 mg/kg bw/day), salivation and statistically higher mean reticulocyte counts were reported. Increased incidence and severity of blood in urine was also reported in females. Thickened limiting ridge of the stomach was

observed in high and mid dose groups. Microscopic observations of the glandular mucosa of the stomach included subacute to chronic inflammation, hypertrophy of the surface epithelial cells, increased numbers of mitotic figures in the mucosa cells, multifocal erosions, focal ulcer and focal necrosis. These effects were considered a direct result of irritation to the gastric mucosa. Partial recovery of the effects in the stomach was reported following 28 days of recovery period. The No Observed Effect Level (NOEL) was 10 mg/kg bw/day based on local gastric irritation. The NOEL for local gastric toxicity was determined to be 50 mg/kg bw/day (REACH).

In a 90-day study conducted according to OECD TG 409 (Repeated dose 90–day oral toxicity study in non–rodents), beagle dogs (4/sex/dose) were dosed daily by gavage with oxazolidine E (in corn oil) at 1.5, 5 and 15 mg/kg bw/day for 90 days. Intermittent vomiting due to nausea was reported in all treated animals. A NOEL was not determined. The no observed adverse effect level (NOAEL) as reported to be 15 mg/kg bw/day (REACH).

In a sub-acute toxicity study conducted according to OECD TG 407 (Repeated dose 28–day oral toxicity study in rodents), Crl:CD SD rats (5/sex/dose) were dosed daily by gavage with oxazolidine E (in corn oil) at 0, 50, 100, 300 or 1000 mg/kg bw/day for 28 days Treatment–related salivation was observed in all treated animals. Statistically significant reduction in body weight was reported at 1000 mg/kg bw/day. Treatment–related higher mean relative organ weights (liver, adrenal, heart, kidney, brain, spleen, thymus) were reported. In males, a treatment–related liver effect consisting of slight centrilobular hypertrophy of hepatocytes at 1000 mg/kg bw/day was reported. Abnormalities in erythrocytes consisting of polychromasia, hypochromia, and a decrease in size of erythrocytes were also noted. Statistically significant changes in haematology were reported at 300 and 1000 mg/kg bw/day in males. The stomach was found to be the most sensitive target organ, with dose-related localised irritation reported at all doses. Hyperplasia of the limiting ridge of the stomach was observed in the majority of treated animals. Gastric irritation was considered to be caused by the presence of formaldehyde, which is a degradation product of the chemical in the acidic environment of the stomach. A NOAEL was not determined in this study, based on hyperplasia of the gastric mucosa at all doses (REACH).

In another sub-acute toxicity study, SD rats (5/sex/dose) were dosed daily by gavage with oxazolidine E (in water) at 0, 100, 300 or 1000 mg/kg bw/day for 28 days. Excessive salivation, piloerection, lower body weight gain and decreased food consumption were observed at the highest dose tested (1000 mg/kg bw/day). At 300 mg/kg bw/day, generalised anaemia was observed in males. Macroscopic examination revealed prominent or swollen stomach limiting ridge. Local alterations of the stomach were also reported microscopically at ≥300 mg/kg bw/day (REACH).

Beagle dogs (2/sex/dose) were dosed daily by gavage with oxazolidine E (in corn oil) at 0. 1.5, 5 and 15 mg/kg bw/day for 28 days. At 15 mg/kg bw/day, nausea and decreases in relative thymus weight were reported. The NOAEL was reported to be 15 mg/kg bw/day (REACH).

Dermal

Considering the effects reported in repeated dermal dose toxicity study, the chemicals are not considered to cause serious damage to health from repeated dermal exposure.

In a repeat dose study similar to OECD TG 410 (Repeated dose dermal toxicity: 21/28-day study), Wistar rats (3/sex/dose) received daily dermal applications of 0, 30, 100 and 300 mg/kg bw/day under occlusive patches, 6 hours/day for 21 days. No mortalities or signs of systemic toxicity were reported. Dose–related necrotic erythema and eschar formation were seen in all animals in the mid and high dose groups. Erythema and crust formation were 56, 34, 16 and 3% for high, mid, low and control groups, respectively. Microscopic observations included erosion, chronic dermatitis, and local subepidermal infiltrate. The NOEL was reported to be 100 mg/kg bw/day (REACH).

Inhalation

Although, oxazolidine E demonstrated acute toxicity following inhalation exposure, it is not expected to be hazardous at the low concentrations present in products containing the chemical.

Based on the lack of conclusive evidence of systemic toxicity of formaldehyde in inhalation studies (NICNAS), and the low volatility of formaldehyde from dilute aqueous solutions, the chemicals are not expected to be harmful due to repeated inhalation exposure to the formaldehyde released from products containing the chemicals.

Genotoxicity

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

In vitro

In an in vitro bacterial mutation assay in *Salmonella typhimurium* (TA 98, TA100, TA1535, TA1537 and TA1538), oxazolidine E (6.0 to 600 µg/plate) gave negative results in all strains tested, in the presence or absence of metabolic activation, S9 (REACH).

In an in vitro mammalian cell gene mutation assay in mouse lymphoma (L5178Y TK+/-) cells, oxazolidine E induced dose–dependent and reproducible increases in mutation frequency at concentrations 0.5 to 100 µg/ml in the absence of S9 and 1.25 to 100 µg/ml in the presence of S9 (REACH). The positive results were reported to be due to the in situ formaldehyde generation. Therefore, a modified mammalian mouse lymphoma assay was conducted in the presence of formaldehyde dehydrogenase (FDH). The addition of FDH in the modified assay was found to completely inhibit the mutagenic response of the chemical in the mouse lymphoma assay, which indicates that the increases in mutation frequency were due to the presence of formaldehyde. (REACH).

In an in vitro DNA damage and repair assay (unscheduled DNA synthesis–UDS) in mammalian cells using rat hepatocytes, oxazolidine E at concentrations of 0.5, 1, 5, 10, 50 and 100 µL/ml without metabolic activation gave a negative result (REACH).

In an in vitro mammalian chromosome aberration assay in Chinese hamster ovary (CHO) cells, oxazolidine E (0.0125 to 0.2 µL/ml with or without S9) did not cause a significant increase in the number of chromosome aberrations with or without metabolic activation. (REACH).

In vivo

In an in vivo mammalian erythrocyte micronucleus test, CD1 male mice were given oxazolidine E at 0, 500, 1000 or 2000 mg/kg bw/day by gavage for two consecutive days. Bone marrow cells were collected 24 hours after dosing. There were no statistically significant increases in the number of micronucleated erythrocytes in any group (REACH).

In an in vivo UDS assay, Fischer 344 rats (5/dose) were dosed with 1000 and 2000 mg/kg bw oxazolidine E in corn oil by a single oral gavage. Hepatocytes were collected at 2–4 hours or 14–16 hours after treatment. The chemical did not cause statistically significant effects (REACH).

Carcinogenicity

There is insufficient information available to determine hazard classification of the chemicals for carcinogenicity. While formaldehyde is classified as a carcinogen category 1B (May cause cancer), this applies to inhaled formaldehyde, at high concentrations (NICNAS). Formaldehyde is not likely to be volatile from the low concentrations present in products containing the chemicals; therefore, there are no inhalation carcinogenicity concerns relating to these products. During formulation of the products, formaldehyde gas may be present.

Reproductive and Developmental Toxicity

The chemicals do not show 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 (Two-generation reproduction toxicity study), SD rats (27/sex/group) were dosed daily by gavage with oxazolidine E (in corn oil) at 0, 5, 25 and 150 mg/kg bw/day prior to mating (10 weeks), during mating (2 weeks), gestation (3 weeks) and lactation (3 weeks) for each of two generations. At 150 mg/kg bw/day (highest dose), a treatment-related decrease in body weight gains during the entire lactation period was reported in parental generation 1 (P1) and parental generation 2 (P2) females. Stomach irritation consisting of non–glandular mucosal thickening was reported. Histopathological observations including hyperplasia of the limiting ridge epithelium; hyperplasia, hypertrophy, and increased mitotic figures in the glandular mucosa; and subacute to chronic inflammations of the glandular mucosa and submucosa were reported in the majority of animals. Similar effects, albeit of lesser severity and incidence, were seen in animals treated at 25 mg/kg bw/day. Slight increases in absolute and relative thyroid gland weights without related histopathological effects were reported in high dose P1 and P2 males. In high dose P1 males, increased absolute and relative liver weights were accompanied by histological findings of slightly altered tinctorial properties (increased eosinophilia) of centrilobular hepatocytes. The NOEL for systemic toxicity was determined to be 5 mg/kg bw/day for both P1 and P2 generations. There were no effects or any of the reproductive parameters, performance, offspring or survival on any dose level tested. The NOEL for reproductive toxicity was determined to be 150 mg/kg bw/day (REACH).

Developmental toxicity

In a range finding study, SD rats (unspecified number) were dosed daily with oxazolidine E at 0, 250, 500, 750, 1000 and 15600 mg/kg bw/day by gavage from GD 6–15. All treated animals survived. However, dose–related decrease in body weight gains was reported at doses 500 mg/kg bw/day and above. Adverse effects including decreased mean number of viable foetuses, increased mean post implantation loss and very high incidence of foetal anomalies were also reported. Based of the effects found in the range finding study, dose levels of 50, 250 and 650 mg/kg bw/day were selected for the developmental study (REACH).

In a developmental study conducted similar to OECD TG 414 (Prenatal developmental toxicity study), Crl:CD BR rats (25/sex/group) were dosed daily by gavage with oxazolidine E (in deionised water) at 0, 50, 250 and 650 mg/kg bw/day on gestation days (GD) 6–15. Animals were observed twice daily from GD 0–21. At 650 mg/kg bw/day (high dose), mean maternal body weight was decreased. No maternal deaths were reported. At this dose, foetal malformations consisting of abdominal wall defects and/or cleft palate were clustered in 2 litters. Late resorptions with similar malformations as above were also reported from another litter. Mean foetal weight was also slightly decreased. There was an increase in the percentage of foetuses with delayed ossification of sternebrae 5 and 6. At 50 and 250 mg/kg bw/day, the incidences of foetal anomalies and developmental variations were comparable with the concurrent control and historical control data at the testing facility. The NOAEL for maternal

toxicity was determined to be 250 mg/kg bw/day. The lowest observed adverse effect level (LOAEL) was reported to be 650 mg/kg bw/day (the highest dose tested) (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from inhalation exposure) and local effects (skin and eye irritation and skin sensitisation).

The released formaldehyde in cosmetic and domestic products containing the chemicals are also considered in the risk characterisation. The critical health effects from released formaldehyde is skin sensitisation.

For workers, health hazards can arise from the presence of formaldehyde gas during formulation of products containing these chemicals or sensitisation while using these chemicals as oils or lubricants when cutting metal workpieces (NICNASa, de Groot A et al, 2010).

Public Risk Characterisation

The chemical, oxazolidine T (CAS No 6542-37-6), has potential domestic use as rubbing compounds and in automotive after market products in Australia.

The chemicals in this group are reported to be used in cosmetic and domestic products overseas with typical concentrations ranging from 400 to 2000 ppm (Anderson BE et al., 2007). In these instances, the general public may be exposed to low concentrations of the chemicals through the dermal, ocular and inhalation routes. In addition, the potential risk of skin sensitisation attributed to released formaldehyde from products containing the chemicals, is also of concern. The SUSMP specifies limits for the levels of formaldehyde in cosmetic and domestic products (SUSMP, 2017). The current controls are considered adequate to minimise the risk to public health posed by domestic and cosmetic products containing the chemicals. Therefore, the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the 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.

Where these chemicals are handled in pure or highly concentrated form during formulation and in cutting metal work pieces, formaldehyde gas may be present and pose unreasonalbe risk to workers unless adequate control measures to minimise inhalation exposure to the chemicals are implemented. The chemicals should be appropriately classified and labelled and the appropriate risk management measures for formaldehyde should be applied in these cases.

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

NICNAS Recommendation

Assessment of these chemicals are 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 chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2017).

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. 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 inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (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 dermal, ocular and 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 chemical[s], 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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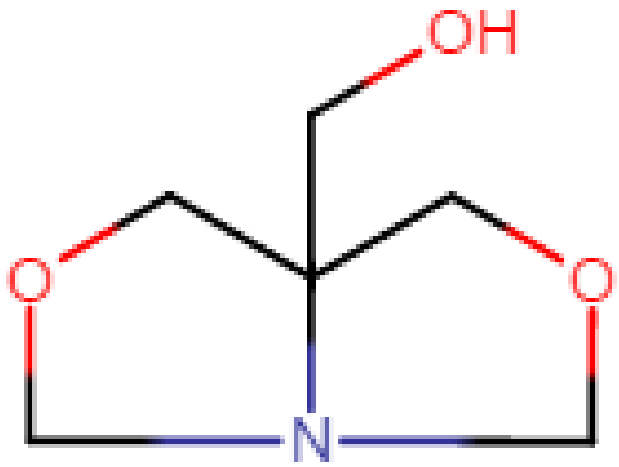
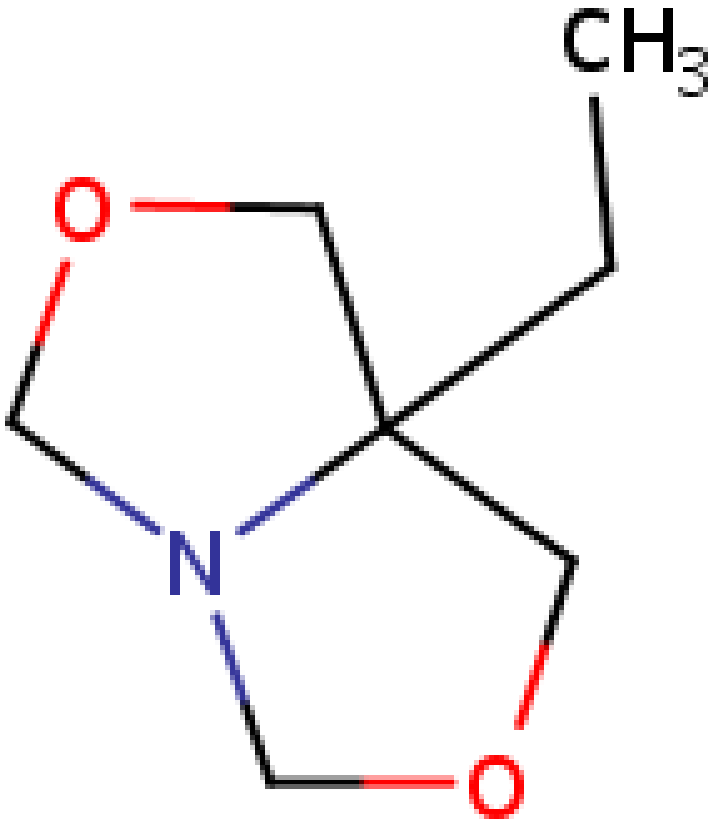
Last Update 26 October 2018

Chemical Identities

Chemical Name in the Inventory and Synonyms	**1H,3H,5H-Oxazolo[3,4-c]oxazole-7a(7H)-methanol** 1-aza-3,7-dioxa-5-hydroxymethylbicyclo[3.3.0]octane oxazolidine T hydroxymethyl dioxoazabicyclooctane bioban CS-1246
CAS Number	6542-37-6
Structural Formula	

	
Molecular Formula	C6H11NO3
Molecular Weight	145.158

Chemical Name in the Inventory and Synonyms	**1H,3H,5H-Oxazolo[3,4-c]oxazole, 7a-ethyldihydro-** 1-aza-5-ethyl-3,7-dioxabicyclo(3.3.0)octane bioban CS-1246 oxazolidine E 7-ethylbicyclooxazolidine
CAS Number	7747-35-5
Structural Formula	

	
Molecular Formula	C7H13NO2
Molecular Weight	143.186

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