Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

13-Oxabicyclo[10.1.0]trideca-4,8-diene, (1*R*,4*E*,8*Z*,12*R*)-*rel*-

Assessment statement

14 July 2021

Final

Table of contents

Contents

AICIS assessment statement

Chemical in this assessment

Name	CAS registry number
13-Oxabicyclo[10.1.0]trideca-4,8-diene, (1*R*,4*E*,8*Z*,12*R*)-*rel*-	55722-64-0

Reason for the assessment

An application for an assessment certificate under section 31 of the *Industrial Chemicals Act 2019* (the Act)

Certificate Application Type

Very low to low risk

Based on introduction, use and end use information described in the application, the exposure band of the introduction is 4 for human health [table item 6, clause 1] and 3 for the environment [table item 3 clause 3] of Schedule 1 *Industrial Chemicals (General) Rules 2019* (the Rules)]. The isomeric mixture of the assessed chemical (assessed chemical) does not have any of the hazard characteristics in human health hazard bands B and C (Schedule 1, clause 2) and environment hazard bands C and D (Schedule 1, clause 4). In accordance with table item 11 section 28 and table item 13 section 29 of the Rules, the indicative human health and environment risk for the proposed introduction are both in the low risk category.

Defined scope of assessment

The chemical has been assessed:

– as imported into Australia for up to 10 tonnes/annum;

– as introduced neat for reformulation of end use cosmetics and household products at up to 1% concentration in fine fragrances, cosmetics and household products; up to 2% concentration in air fresheners (sprays and aerosols), and less than 10% concentration in electrical air fresheners and candles and

– as a component in formulated end use cosmetic and household products at up to 1% concentration in fine fragrances, cosmetics and household products; up to 2% concentration in air fresheners (sprays and aerosols), and less than 10% concentration in electrical air fresheners and candles.

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will be imported into Australia either in the neat form or as a component of liquid fragrance formulation at up to 10% concentration for reformulation into cosmetic and household products, or as a component in formulated end use cosmetic and household products (at up to 1% concentration in fine fragrances, cosmetics and household products, up to 2% concentration in air fresheners (sprays, aerosols) and less than 10% concentration in electrical air fresheners and candles). End use products containing the assessed chemical at less than 10% concentration will be widely used by consumers and professionals such as hairdressers, workers in beauty salons, and cleaners.

Human health

Summary of health hazards

Based on the available data the assessed chemical is likely to be irritating to the skin (see supporting information) warranting hazard classification (see **Recommendations** section).

No inhalation toxicity data were provided on the assessed chemical. The applicant has determined that the assessed chemical meets the criteria for Specific Target organ Toxicity (STOT) Single Exposure - Category 3, based on the clinical signs noted during the oral study (OECD TG 423) in rats.

The available data also indicates that the assessed chemical:

- is likely to be of low acute oral toxicity
- is non-irritating to eyes and not a skin sensitiser
- is not likely to cause systemic toxicity following repeated oral exposure up to 223 mg/kg bw/day; and
- is not considered to be genotoxic

Health hazard classification

Based on the available data, the assessed chemical warrants hazard classification for human health, according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS, United Nations 2017), as adopted for industrial chemicals in Australia.

Health hazards	Hazard category	Hazard statement
Skin irritation	Category 2	H315: Causes skin irritation

The assessed chemical will not be used in Australia at end use concentrations that warrant the above hazard classifications.

Summary of health risk

Public

When introduced and used in the proposed manner, there will be widespread and repeated exposure of the public to the assessed chemical:

- at less than 10% concentration through the use of a wide range of cosmetic and household products containing the assessed chemical
- the principal route of exposure will be dermal, while ocular and inhalation exposure are also possible, particularly for air care products and if products are applied by spray.

The frequency and extent of public exposure is expected to be lower than that for professional workers.

The assessed chemical is irritating to skin, but given the proposed low use concentrations (at up to 1% concentration in fine fragrances, cosmetics and household products; up to 2% concentration in air fresheners (sprays and aerosols) and less than 10% concentration in electrical air fresheners and candles), irritation effects are not expected.

The repeated dose toxicity potential of the assessed chemical was estimated by calculation of the margin of exposure (MoE) using the worst case exposure scenario from use of multiple products by an individual, with total exposure of 2.40 mg/kg bw/day (see human exposure section under **Supporting information**). Using a No–Observed–Adverse-Effect-Level (NOAEL) of 223 mg/kg bw/day for the assessed chemical (derived from a combined repeated/ reproduction/developmental oral toxicity study in rats on an analogue chemical), the MoE was estimated to be 93. A MoE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. As the NOAEL used in the MoE estimation was the highest tested dose in the study with no adverse effects noted, the actual NOAEL for the analogue chemical is considered to be higher than 223 mg/kg bw/day. Therefore, the actual MoE value is expected to be higher than 100 and is considered acceptable.

When introduced in accordance with the terms of the assessment certificate, the assessed chemical is not considered to pose an unreasonable risk to the public.

Workers

Workers may experience exposure to the assessed chemical in its neat form or at up to 10% concentration during weighing and transfer stages, blending, quality control analysis, and cleaning and maintenance of equipment, particularly where manual or open processes are used. Exposure to the assessed chemical in end use products (at less than 10% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hairdressers and workers in beauty salons) or the use of household products in the cleaning industry.

Workers may experience skin irritation if exposed to the assessed chemical at high concentrations during end use product formulation activities. Specific risk management measures (see **Recommendations** section) are required to manage the risks to workers.

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data, the assessed chemical is:

- Not Persistent (P) based on measured half-life in water
- Not Bioaccumulative (B) based on the octanol-water partition coefficient
- Not Toxic (T) based on ecotoxicity data for aquatic organisms

Environmental hazard classification

The assessed chemical is formally classified under the GHS for acute and chronic toxicities based on the ecotoxicological endpoint and lack of rapid biodegradability data (United Nations, 2017).

Environmental Hazard	Hazard Category	Hazard Statement
Acute Aquatic	Category 2	H401: Toxic to aquatic life
Chronic Aquatic	Category 3	H412: Harmful to aquatic life with long lasting effects

Summary of environmental risk

Based on the end use as a fragrance, the majority of the assessed chemical is expected to be released into sewage treatment plants (STPs). The calculated environmental risk quotient for the assessed use of the chemical is less than or equal to 0.07.

Therefore, there are no identified risks to the environment that require specific risk management measures, if the assessed chemical is introduced in accordance with the terms of the assessment certificate.

Conclusions

The conclusions of this assessment are based on the information described in this assessment statement. Obligations to report additional information about hazards under section 100 of the Industrial Chemicals Act 2019 apply.

The Executive Director is satisfied that when the assessed chemical is introduced and used in accordance with the terms of the assessment certificate the human health and environment risks can be managed. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory. The proposed means for managing the risks identified during this assessment are set out in the **Recommendations** section.

Recommendations

Workers

Recommendation to Safe Work Australia

- It is recommended that Safe Work Australia (SWA) update the *Hazardous Chemical Information System* (HCIS) to include classifications relevant to work health and safety (see **Health hazard classification**)

Advice to industry

- The following control measures should be implemented to manage the risk arising from exposure to the assessed chemical during formulation activities:
    - Use of engineering controls such as
        - Enclosed and automated processes if possible
        - Adequate workplace ventilation to avoid accumulation of vapours, mists or aerosols
    - Use of safe work practices to
        - Avoid contact with skin
        - Avoid inhalation of vapours, mists or aerosols
    - Workers should wear the following personal protective equipment (PPE)
        - Impervious gloves
        - Respiratory protection where local ventilation may be inadequate
        - Protective clothing
- The storage of the assessed chemical should be in accordance with the Safe Work Australia *Code of Practice for Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Environment

No specific recommendations for safe use of the assessed chemical are required when the assessed chemical is introduced in accordance with the terms of the assessment certificate.

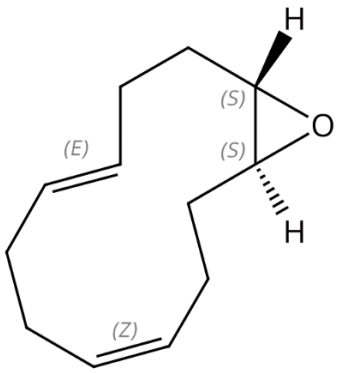
Supporting information

Chemical identity

The assessed chemical has a typical degree of purity of greater than 90%. It contains two diastereomers in an approximately 1:1 ratio, individually identified as follows:

Chemical Name (Diastereomer)	13-Oxabicyclo[10.1.0]trideca-4,8-diene, (1*R*,4*E*,8*Z*,12*R*)-
Chemical Name (Diastereomer)	13-Oxabicyclo[10.1.0]trideca-4,8-diene, (1*S*,4*E*,8*Z*,12*S*)-

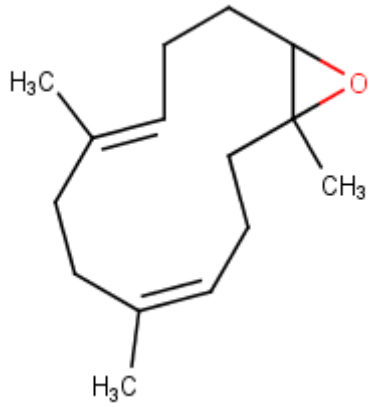
Other Chemical Identity Information

Synonyms	(1*RS*,4*Z*,8*E*,12*RS*)-13-oxabicyclo[10.1.0]trideca-4,8-diene (IUPAC name)
Structural formula	 *Relative stereochemistry shown*
Molecular formula	C12H18O
Molecular weight (g/mol)	178.27
SMILES	O1C2CCC=CCCC=CCCC12

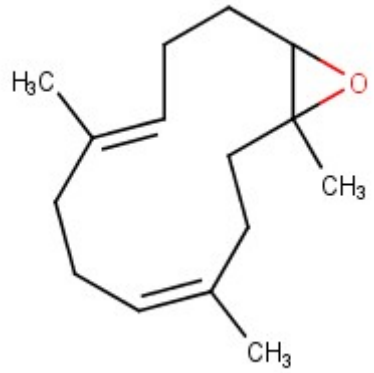
Analogue Chemical Identity Information

Chemical Name	1,5,10-Trimethylcyclododeca-1,5,9-triene, epoxidised (IUPAC name)
CAS Number	Not assigned
Structural formula	The chemical is a UVCB substance with the following composition: Constituent 1 (greater than 50): 13-Oxabicyclo[10.1.0]trideca-4,8-diene, 1,5,8-trimethyl-, (4*Z*,8*E*)- (CAS RN 2561530-02-5)

MW = 220.35 g/mol



Constituent 2 (less than 20%):
13-Oxabicyclo[10.1.0]trideca-4,8-diene, 1,4,8-trimethyl-, (4*Z*,8*E*)- (CAS RN 2561530-03-6)
MW = 220.35 g/mol



Other constituents (less than 15%):
Mixture of regio- and geometrical isomers of racemic mono- and diepoxides of 1,5,10-trimethylcyclododeca-1,5,9-triene

Relevant physical and chemical properties

All measured values are based on the studies provided on the assessed chemical and conducted according to OECD test guidelines.

Physical form	Colourless liquid
Melting point	-11.5°C
Boiling point	274.0°C
Density	978 kg/m^3 at 20 °C

Physical form	Colourless liquid
Vapour pressure	0.82 Pa at 20 °C and 1.5 Pa at 25 ºC
Water solubility	204 mg/L at 20 °C (moderate soluble)
Flash point	124 °C
Auto flammability	260 °C
Hydrolysis as a function of pH	Hydrolytically stable under environmental pH (4-9)
Ionisable in the environment?	No
Acid dissociation constant (pKa)	N/A
Octanol-water partition coefficient (log K_{ow})	3.3 at 25 ºC and 3.47 at 30 ºC (estimated)
Adsorption coefficient (log Koc)	2.99

Introduction and use

Australia

The assessed chemical will be imported into Australia either in the neat form or as a component of liquid fragrance formulations (up to 10% concentration) for reformulation of end use cosmetics and household products or as a component in formulated end use cosmetic and household products (at up to 1% concentration in fine fragrances, cosmetics and household products, up to 2% concentration in air fresheners (sprays, aerosols) and less than 10% concentration in electrical air fresheners and candles).

The assessed chemical will be imported and distributed in tightly closed lacquered drums of varying sizes: 5 kg, 10 kg, 25 kg, 50 kg, 100 kg or 180 kg. Reformulation/re-packaging activity will not occur at the applicant's facility in Australia. The drums will be transported mainly by road to the warehouse for storage and later distributed to the formulators by road. Finished consumer products containing the assessed chemical at various concentration will be packaged in containers suitable for retail sale.

Human exposure

Workers

Reformulation

Typically, reformulation processes may incorporate blending operations that are highly automated and occur in a fully enclosed/contained environment, followed by automated filling using sealed delivery systems into containers of various sizes. Dermal, ocular and may be inhalation exposure (if aerosols or mists are formed) of workers to the assessed chemical in its neat form or at up to 10% concentration is possible during weighing and transfer stages, blending, quality control analysis, packaging, cleaning and during maintenance of equipment.

However, the exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of PPE such as protective clothing, eye protection, impervious gloves and appropriate respiratory protection.

Professional End Use

Exposure to the assessed chemical in end use products (at less than 10% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hairdressers and workers in beauty salons) or the use of household products in the cleaning industry. These products, depending on their nature, could be applied in a number of ways, such as by hand, using an applicator or sprayed. The principal route of exposure will be dermal and inhalation (for air care products), while ocular exposure is also possible. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the end use products containing less than 10% of the assessed chemical.

Public

There will be widespread and repeated exposure of the public to the chemicals (at less than 10% concentration) through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and/or inhalation exposures are also possible, particularly if the products are applied by spray or when used in air fresheners.

Data on typical use patterns of products (SCCS 2012; Cadby et al. 2002; ACI 2010; Loretz et al. 2006) in which the assessed chemical may be used are shown in the following tables. For the purposes of exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) rate of 100% and a lifetime average female body weight (BW) of 70 kg (enHealth 2012) were used for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Steiling et al. 2014; Rothe et al. 2011; Earnest Jr. 2009). An adult inhalation rate of 20 m^3/day (enHealth 2012) was used and it was conservatively assumed that the fraction of the assessed chemical inhaled is 50%.

Cosmetic products (dermal exposure)

Product type	**Amount** (mg/day)	**C** (%)	**RF** (unitless)	**Daily systemic exposure** (mg/kg bw/day)
Body lotion	7820	1	1	1.2219
Face cream	1540	1	1	0.2406
Hand cream	2160	1	1	0.3375
Fine fragrances	750	1	1	0.1172
Deodorant	1500	1	1	0.2344
Shampoo	10460	1	0.01	0.0163
Conditioner	3920	1	0.01	0.0061
Shower gel	18670	1	0.01	0.0292
Hand soap	20000	1	0.01	0.0313
Hair styling products	4000	1	0.1	0.0625
Total				**2.2970**

C = maximum intended concentration of assessed chemical; RF = retention factor
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household products (Indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	1	0.95	10	0.0341
Fabric softener	90	1	0.95	10	0.0134
Total					**0.0475**

C = maximum intended concentration of assessed chemical
Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact area (cm^2)	Product use C (g/cm^3)	Film thickness (cm)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	1	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	1	1980	0.009	0.01	0.03	0.0025
All-purpose cleaner	1	1	1980	1	0.01	0.007	0.0217
Total							**0.0245**

C = maximum intended concentration of assessed chemical
Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × DA)/BW

Hair spray (inhalation exposure)

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure duration (Zone 1) (min)	Exposure duration (Zone 1) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	1	20	1	20	50	1	10	**0.0322**

C = maximum intended concentration of assessed chemical
Total daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the assessed chemical at the maximum intended concentrations specified by the applicant in various product types. This would result in a combined internal dose of 2.40 mg/kg bw/day for the assessed chemical. It is acknowledged that inhalation exposure to the assessed chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, the combination of the conservative hair spray inhalation exposure assessment parameters used and the aggregate exposure from use of the dermally applied products (using a conservative 100% dermal absorption rate), are sufficiently protective to cover additional inhalation exposure to the assessed chemical from use of other spray cosmetic and household products containing it with low exposure (e.g. air fresheners).

Health hazard information

Toxicokinetics

Given the low molecular weight (178.27 g/mol) and the partition coefficient (log Pow = 3.3 at 25 °C) of the assessed chemical, absorption across biological membranes is possible.

Acute toxicity

Oral

No acute oral toxicity data was submitted for the assessed chemical.

The applicant, however, submitted an acute oral toxicology study of an analogue chemical, which was read-across to the assessed chemical. The read-across is based on the hypothesis that the analogue chemical and the assessed chemical have common structural features in the same relative positions and therefore, expected to have similar physio-chemical and toxicological properties.

The median lethal dose (LD50) of the analogue chemical was determined to be greater than 2000 mg/kg bw in rats (OECD TG 423), indicating that the assessed chemical is likely to be of low acute oral toxicity.

While there was no mortalities in acute oral toxicity study, clinical signs of systemic toxicity noted during the study were hunched posture (6/6 females), lethargy (4/6), ataxia (4/6), increased salivation, (2/6), decreased respiratory rate (2/6), and noisy respiration (1/6). All effects were transient in nature and females appeared normal on two, three or four days after dosing. Based on this study, the applicant has determined that the assessed chemical meets the criteria of Specific Target organ Toxicity (STOT) Single Exposure (Category 3: Narcotic effects: H336 - May cause drowsiness or dizziness) according to GHS criteria as adopted in Australia for industrial chemicals.

Dermal

No acute dermal toxicity data was available for the assessed chemical.

Inhalation

No acute or chronic inhalation toxicity data were provided for the assessed chemical.

Corrosion/Irritation

Skin irritation

The assessed chemical was determined not to be corrosive in an *in vitro* skin corrosion test using the EpiDerm™ reconstructed human epidermis tissue model (EpiDerm Skin Model (EPI-200)) (OECD TG 431). The mean relative tissue viability for the test item was 93 percent (after 3 min exposure) and 121 percent (after 60 min exposure).

However, the assessed chemical has been determined to be irritating to the skin in an *in vitro* skin irritation test using the EPISKIN TM reconstructed human epidermis tissue model (EPISKIN TM Small Model) (OECD TG 439). Since the mean relative tissue viability for the assessed chemical was below 50 percent after 15 minutes treatment, the assessed chemical is considered to be a skin irritant.

Based on the available information, the assessed chemical warrants hazard classification for Skin Irritant (Category 2, H315: Causes skin irritation) according to GHS criteria as adopted in Australia for industrial chemicals.

Eye irritation

The assessed chemical was tested using reconstructed Human EpiOcular™ Cornea-like Epithelial Model (OECD TG 492) to determine whether it is not an eye irritant or requires classification for serious eye damage. The relative mean tissue viability obtained after 30 ± 2 minutes treatment with the test item compared to the negative control tissues was < 60 percent (56 percent). Based on these results and as per the test guideline, no prediction can be made regarding the irritant potential of the assessed chemical and further testing is required using other test guidelines.

The assessed chemical was further tested for eye irritating potential using the isolated chicken eye (ICE) test method (OECD TG 438). The test measured the ability of the assessed chemical to cause corneal opacity, swelling and fluorescein retention in an enucleated chicken eye (ICE classes). The negative and the positive controls performed appropriately. Under the conditions of this study, the assessed chemical was found to be non-irritating to the eyes.

Overall, based on the available information, the assessed chemical is not classified as an eye irritant.

Sensitisation

Skin sensitisation

One *in chemico* and one *in vitro* cell based assays were conducted to evaluate the skin sensitisation potential of the assessed chemical. These tests are part of Integrated Approach to Testing and Assessment (IATA) which address specific events of the Adverse Outcome Pathway (AOP) leading to development of skin sensitisation (OECD, 2016). The tests are thus considered relevant for assessment of the skin sensitisation potential of the assessed chemical, along with other supporting information.

The assessed chemical showed negative responses in both *in chemico* direct peptide reactivity assay (DPRA) (OECD TG 442C) and *in vitro* ARE-Nrf2 (OECD 422D) tests of the AOP for skin sensitisation. An *in vivo* guinea pig maximisation test (GPMT) conducted on the analogue chemical also showed no signs of skin sensitisation.

Overall, on the basis of the available information, the assessed chemical is not considered to be a skin sensitiser.

Repeat dose toxicity

Oral

Repeated dose toxicology information was not submitted for the assessed chemical. The applicant, however, submitted a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) of an analogue chemical. Details of the reproduction/developmental toxicity screening test are described in the respective section.

The repeated dose study was performed in rats by dietary administration of the analogue chemical for at least six weeks with additional subgroups used to assess reversibility, persistence or delayed effects for 14 days post treatment. Animals (n= 5-10/sex/dose group) received dietary doses of 0 (control), 417, 1250 or 3750 ppm test material/day.

No clinical signs of toxicity or mortality were observed throughout the treatment and recovery period up to 3750 ppm (equivalent to 223 mg/kg bw/day for males and 225 mg/kg bw/day for females). There were no treatment-related adverse effects on clinical chemistry, haematology or urinalysis and no treatment- related macroscopic findings were observed during necropsy. Microscopic findings related to treatment for 6 weeks (males and females) were seen in the liver (centrilobular hepatocyte hypertrophy) and thyroid follicular cell hypertrophy at all treatment concentrations. Following the 2-week recovery period, centrilobular hepatocyte hypertrophy demonstrated a partial and a near full recovery in males and females, respectively, indicating the effect as an adaptive response to the treatment. Similarly, follicular cell hypertrophy in the thyroids had not completely recovered in males but complete recovery was seen in females.

Changes in the thyroid glands were considered to be a consequences of hepatic enzyme induction and consequential disruption of the normal feedback control of the thyroid gland. As hepatic enzymes have a recognised role in thyroid hormone metabolism and clearance, an increase in enzyme activity can result in increased compensatory thyroid hormone production (Greaves 2012). Thyroid changes observed in this study were considered to be of little relevance to humans since the hormone binding profiles differ in humans and the rate of metabolic clearance of thyroxine is much slower in humans than in rats (Gopinath 1995). Consequently, the thyroid gland in humans is not expected to markedly influenced by hepatic enzyme induction. It was therefore considered that the effects were non-adverse (adaptive effects) and/or of little toxicological relevance to humans.

Based on the above findings, the NOAEL for systemic toxicity of the analogue chemical was established as 3750 ppm (mean achieved dose: 223 mg/kg bw/day) in male/female rats based on the absence of treatment related adverse effects up to the highest dose tested. Therefore, the assessed chemical is expected to have a NOAEL of greater than 3750 ppm (or 223 mg/kg bw/day).

Genotoxicity

The assessed chemical was found to be non-mutagenic in a bacterial reverse mutation assay using *S.typhimurium* strains TA98, TA100, TA1535, TA1537 and *E.coli* strain WP2uvrA- in both the presence and absence of S9 -mix (OECD TG 471). The assessed chemical was also determined to be non-clastogenic and non-aneugenic in an *in vitro* mammalian micronucleus test using human lymphocytes (OECD TG 487).

Reproductive toxicity

Reproductive toxicology information was not submitted for the assessed chemical. The applicant, however, submitted a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test of an analogue chemical.

Dietary administration of the analogue chemical to rats for 6 weeks at concentrations up to and including 3750 ppm was generally well tolerated by the toxicity phase males/females, and reproductive phase females and their offspring. No reproductive/developmental toxicity effects related to the test item were observed in parental males/females or offspring during the study.

Reproductive performance, fertility and offspring survival were unaffected by parental treatment. From Day 7 of age, growth was slightly reduced in offspring of the groups receiving 1250 or 3750 ppm; this was associated with the slightly larger litter sizes in these treatment groups and was considered not to be an effect of the treatment.

The NOAEL for reproductive/developmental toxicity was considered to be above 3750 ppm (mean doses of 259 mg/kg bw/day during gestation and 598 mg/kg bw/day during lactation).

Human health risk characterisation

Public risk

The MoE of the assessed chemical was estimated to be 93 using a NOAEL of 223 mg/kg bw/day and the worst case exposure scenario from use of multiple products by an individual, with total exposure of 2.40 mg/kg bw/day. As no adverse effects were noted at NOAEL of 223 mg/kg bw/day (highest dose tested), the actual MoE value is expected to be higher than 100 and is considered acceptable. Therefore, the assessed chemical is unlikely to pose risk to public.

Environmental exposure

The assessed chemical is not expected to be significantly released into the environment during reformulation, transport or storage. Based on the assessed use as a fragrance in various consumer products, the majority of the assessed chemical is expected to be released to sewers.

Environmental fate

The assessed chemical is moderately soluble in water, moderately lipophilic and have medium mobility in soil based on the measured endpoints conducted according to OECD test guidelines. The assessed chemical is not readily biodegradable based on the results of a stringent test (0% degradation over 28 days, OECD TG 301F study), and was found to be hydrolytically stable under environmental pH range (pH 4 – 9) in water based on the results of supplied screening test. However, the assessed chemical underwent fast primary degradation and partial mineralisation under realistic environmental conditions typical for surface water-sediment systems in the simulation test performed in accordance with OECD TG 309. The ^{3}H labelled part of parent chemical showed clear evidence of mineralisation to $^{3}H2O$ and degraded with half-lives (DT50) of between 10.5 and 21 days in biotic conditions at two different nominal concentrations (0.5 and 2.5 µg/L) and temperatures of 12 and 20 ºC. The assessed chemical also underwent rapid degradation under abiotic conditions but it's a less relevant pathway for degradation under the environmental conditions. Given the uncertainty in the influences on the rate of degradation on the test substance, the most conservative DT50 was used to determine persistence. The assessed chemical was found not persistent with a DT50 lower than two months in water according to domestic environmental hazard thresholds, but not rapidly degraded (>16 days) for GHS environment hazard classification purposes (United Nations, 2017).

A majority of the assessed chemical will be disposed of into STPs and released to environment with effluent from STPs. The assessed chemical is expected to undergo rapid primary degradation and ultimately biodegrade in the environment. The assessed chemical is not expected to bioaccumulate in the environment based on its measured low octanol-water partition coefficients (log Kow = 3.3 – 3.47). The assessed chemical is moderately volatile (Henry's Law Constant = 7.11 × 10-1 Pa-m3/mole, 20 ºC) and the estimated half-life in air is 1.1 h based on AOP Program v 1.92 (US EPA, 2012).

Predicted environmental concentration (PEC)

The predicted environmental concentrations (PEC) in water (receiving environments) have been calculated based on 100% release of the assessed chemical (from the introduction volume) into sewer systems nationwide over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in STP processes is based on its physico-chemical properties and its tested biodegradability, modelled by SimpleTreat 3.0 (Struijs, 1996) and is estimated to be 6%. Therefore 94% of the total introduction volume is estimated to be released to the aquatic environment. The calculation of the PEC is detailed in the table below:

Total Annual Import Volume	10,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	10,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	27.40	kg/day
Water use	200.0	L/person/day
Population of Australia	24.386	million
Removal within STP	6%	mitigation
Daily effluent production	4877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	5.28	µg/L
PEC - Ocean	0.53	µg/L

Environmental effects

Effects on Aquatic Life

Acute toxicity

The results from the supplied ecotoxicological studies conducted on the assessed chemical are summarised in the table below.

Taxon	Endpoint	Method
Fish	96 h LC50 = 14 mg/L	OECD TG 203
Invertebrate	48 h EC50 = 16 mg/L	OECD TG 202
Algae	72 h ErC50 = 7.4 mg/L	OECD TG 201
Algae	72 h NOEC = 1.6 mg/L	OECD TG 201

The assessed chemical is toxic to algae, the most sensitive taxonomic group to toxic effects based on these data.

Predicted no-effect concentration (PNEC)

A Predicted No-Effect Concentration (PNEC) was calculated based on the above acute endpoint for algae using an assessment factor of 100 as three acute trophic endpoints are available. The resulting PNEC is 74 µg/L.

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below:

Persistence

Not Persistent (P). Based on measured half-life in water lower than two months, the assessed chemical is categorised as Not Persistent

Bioaccumulation

Not Bioaccumulative (B). Based on the measured log Kow value (log Kow less than 4.2), the assessed chemical is categorised as Not Bioaccumulative.

Toxicity

Not Toxic (T). Based on the available acute and chronic ecotoxicity values above 1 mg/L, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

The risk quotient (RQ = PEC/PNEC) for the assessed chemical is calculated to be 0.07 for riverine compartments and less than 0.01 for oceanic compartments. Therefore, the assessed chemical is unlikely to pose significant risk to aquatic life.

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