Australian Government

Department of Health
Australian Industrial Chemicals Introduction Scheme

Ethylene brassylate and zenolide

Evaluation statement

30 June 2022

Contents

AICIS evaluation statement

Subject of the evaluation

Ethylene brassylate and zenolide

Chemicals in this evaluation

Name	CAS Registry Number
1,4-Dioxacycloheptadecane-5,17-dione	105-95-3
1,4-Dioxacyclohexadecane-5,16-dione	54982-83-1

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to the environment.

Parameters of evaluation

Ethylene brassylate (CAS RN 105-95-3) and zenolide (CAS RN 54982-83-1) have been assessed for their risk to the environment according to the following parameters:

- Default Australian introduction volumes of 100 tonnes per year (t/year) for zenolide.
- Australian introduction volumes of ethylene brassylate based on upper estimates provided by industry sources
- Industrial uses listed below in the ‘Summary of Use’ section
- Expected emission into sewage treatment plants (STPs) due to consumer and commercial use.

These chemicals have been assessed as a group because they are structurally very similar and share the same use patterns.

Summary of evaluation

Summary of introduction, use and end use

Ethylene brassylate and zenolide are used as fragrance ingredients in a variety of cosmetic and consumer use products worldwide, with a combined global use volume in the thousands of tonnes per year.

Ethylene brassylate and zenolide are used in the following products according to domestic and international use data:

- personal care products
- air freshener products
- laundry and dishwashing products

- cleaning and furniture care products.

There are no specific domestic introduction volume data for ethylene brassylate or zenolide. However, according to information provided by IFRA, approximately 1300 tonnes of ethylene brassylate is introduced in the Asia-Pacific region (APAC) (includes Australia) by member companies annually. Further consultation with IFRA indicated that up to 5% of this volume may be introduced into Australia.

Environment

Summary of environmental hazards

According to domestic environmental hazard thresholds and based on the available data ethylene brassylate and zenolide are:

- Not Persistent (not P)
- Not Bioaccumulative (not B)
- Toxic (T)

Environmental hazard classification

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for environmental hazards as follows. This does not consider classification of physical hazards and health hazards:

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short term)	Aquatic Acute 1	H400: Very toxic to aquatic life

Chronic data available for each chemical were insufficient to apply chronic aquatic GHS classifications.

Summary of environmental risk

Ethylene brassylate and zenolide are widely used as fragrance ingredients in personal care and other domestic use products and are released to wastewater as a normal part of their use pattern.

Both chemicals are toxic, not persistent, and have been categorised as not bioaccumulative due to evidence of rapid biotransformation.

The industrial uses of these chemicals are not expected to pose a significant risk to the environment. Exposure modelling based on information provided by IFRA found that the estimated concentrations of ethylene brassylate in Australian river waters are below the level of concern (RQ < 1). Based on measured international concentrations in STP effluent, zenolide is expected to be present in Australian rivers at concentrations below the level of concern.

Conclusions

The conclusions of this evaluation are based on the information described in this Evaluation Statement.

The Executive Director is satisfied that the identified environmental risks can be managed within existing risk management frameworks. 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 and the proposed means of managing the risks identified during this evaluation are implemented.

Note: Obligations to report additional information about hazards under *Section 100 of the Industrial Chemicals Act 2019* apply.

Supporting information

Grouping Rationale

This evaluation considers environmental risks associated with the industrial use of ethylene brassylate and zenolide, two closely related synthetic musks. These chemicals share a common macrocyclic dilactone structure and differ only in the length of the aliphatic carbon chain of the diacid portion connecting the 2 ester groups. The risk evaluation of these substances has been conducted as a group because they both have known applications as synthetic musk fragrances.

Ethylene brassylate and zenolide have moderate to high use volumes internationally (more than 1000 and 100 t/year, respectively), and both have reported uses in consumer products and have been detected in wastewater effluents following STP treatment.

The evaluation selection analysis (ESA) of ethylene brassylate found the potential for adverse effects to aquatic organisms due to emissions to surface waters in the treated effluent discharged from sewage treatment plants (STP), and possible toxic characteristics of the chemical.

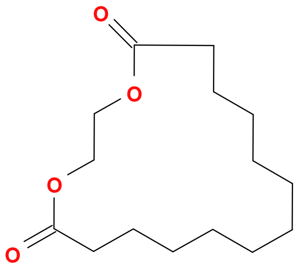
Chemical identity

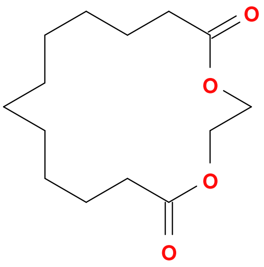
Ethylene brassylate is a 17-membered macrocyclic ring with two ester functional groups, commonly referred to as a macrocyclic dilactone. The chemical belongs to the macrocyclic musk family of fragrances.

Zenolide is a 16-membered homologue of ethylene brassylate and is also a member of the macrocyclic musk family of fragrances.

Synthetic access to macrocyclic musks has historically been costly due to the high dilutions required during synthesis to favour macrocyclisation over polymerisation (Williams 1999). However, the process to prepare ethylene brassylate and zenolide involves polymerisation and depolymerisation, enabling high volume synthesis at low cost (Cahill and Rodenberg 1986; Elsasser 1992; Harris and White 1978; Williams 1999).

CAS RN	105-95-3
Chemical name	1,4-dioxacycloheptadecane-5,17-dione
Synonyms	ethylene brassylate ethylene tridecanedioate tridecanedioic acid, cyclic ethylene ester Musk T Musk NN Astratone Emeressence 1150

Structural Formula	
Molecular Formula	$C_{15}H_{26}O_4$
Molecular Weight (g/mol)	270.37
SMILES	C1CCCCCC(=O)OCCOC(=O)CCCCC1
Chemical Description	A 17-membered, unbranched macrocycle with two ester groups in the ring.

CAS RN	54982-83-1
Chemical name	1,4-dioxacyclohexadecane-5,16-dione
Synonyms	Zenolide dioxa, 1,4-cyclohexadecane-5,16-dione ethylene cyclic dodecanedioate Musk C14 MC4 Muskonate
Structural Formula	
Molecular Formula	$C_{14}H_{24}O_4$
Molecular Weight (g/mol)	256.34
SMILES	O=C1OCCOC(=O)CCCCCCCCCC1
Chemical Description	A 16-membered, unbranched macrocycle with two ester groups in the ring.

Relevant physical and chemical properties

Measured physical and chemical property data for ethylene brassylate and zenolide were retrieved from the registration dossiers of each chemical (1,4-dioxacycloheptadecane-5,17-dione and 1,4-dioxacyclohexadecane-5,16-dione) submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the European Union (EU) (REACHb ; REACHc). Henry's Law Constants were calculated with EPISuite using experimental vapour pressure and water solubility values as inputs (US EPA 2017).

Chemical	Ethylene brassylate	Zenolide
Physical Form	Liquid	Liquid
Melting Point	0°C (exp.)	16.7°C (exp.)
Boiling Point	353°C (exp.)	337.3°C (exp.)
Vapour Pressure	0.017 Pa at 20°C (exp.)	0.028 Pa at 25°C (exp.)
Water Solubility	14.8 mg/L at 20°C (exp.)	75 mg/L at 20°C (exp.)
Henry's Law Constant	0.312 Pa·m^3/mol (calc.)	0.096 Pa·m^3/mol (calc.)
Ionisable in the Environment?	No	No
pKa	n/a	n/a
log K_{OW}	4.30 at 25°C (exp.)	3.65 at 20°C (exp.)

Introduction and use

Australia

No specific Australian information on introduction, use and end use has been identified for ethylene brassylate or zenolide.

Based on information in the public domain, ethylene brassylate is readily available for use in Australia as a fragrance ingredient (ABP 2020).

International

Available information indicates that ethylene brassylate and zenolide are used as fragrance ingredients in a range of consumer products worldwide.

Ethylene brassylate and zenolide are listed on the International IFRA Transparency List, which identifies chemicals used as fragrances by member companies (IFRA).

According to information provided by IFRA, approximately 1300 tonnes of ethylene brassylate is introduced in the Asia-Pacific region (APAC) (includes Australia) by member companies annually. Further consultation with IFRA indicated that up to 5% of this volume may be introduced into Australia.

The total use volume of ethylene brassylate in the EU is 1000–10 000 tonnes per year (REACHc). In the United States of America (USA) ethylene brassylate had an annual use volume of 227–454 tonnes in 2016 (US EPA 2016). In the Nordic countries, the average annual use volume over a 5 year period from 2014–2018 was 9.7 tonnes (SPINa). There is some evidence that ethylene brassylate is being used in increasing amounts internationally; in Japan the annual use volume increased from 158 tonnes to 376 tonnes between 2016 and 2018 (NITE 2021).

The total use volume of zenolide in the EU is 100–1000 tonnes/year (REACHb). In the USA zenolide has an annual use volume of less than 454 tonnes (US EPA 2016) and in the Nordic countries there is reported chemical production, but an average use volume of less than one tonne per year (SPINb).

Ethylene brassylate is found in a range of fragranced products according to consumer product information and academic studies. International studies have detected ethylene brassylate in perfume and body fragrance (maximum of 24.5 mg/g or 2.5% w/w), fabric softener (maximum of 0.54 mg/g), body soap and lotion (maximum of 0.60 mg/g), antiperspirant (maximum of 0.19 mg/g) and toilet deodoriser (maximum of 11.0 mg/g) (Homem, et al. 2015; Nakata, et al. 2015). Other products containing ethylene brassylate include candles, laundry detergent, cosmetics, sunscreen, air freshener products, and cleaning products (Bothe et al. 2003; EWGa; US EPA 2014a; US EPA 2021b).

International studies have reported the presence of zenolide in perfume and shampoo at maximum concentrations of 32 and 13 µg/g, respectively (Nakata, et al. 2015). Consumer product information has also reported the inclusion of this chemical in moisturisers, fragrances, cleaning agents, soaps, laundry and dishwashing detergents, air freshener products and personal care products (EWGb; US EPA 2014b).

Ethylene brassylate has been approved by the US Food and Drug Administration (FDA) as a synthetic flavouring substance and food adjuvant in accordance with 21 CFR 172.515 (US GPO). The use of this chemical as a pesticide and food additive is beyond the scope of this assessment.

Existing Australian regulatory controls

Environment

Use of ethylene brassylate and zenolide is not subject to any specific national environmental regulations.

International regulatory status

United Nations

Ethylene brassylate and zenolide are not currently identified as Persistent Organic Pollutants (POPs) (UNEP 2001), ozone depleting substances (UNEP 1987), or hazardous substances for the purpose of international trade (UNEP & FAO 1998).

Japan

Ethylene brassylate has been classified as a Priority Assessment Chemical Substance (PACS) under Japan’s Chemical Substances Control Law, indicating that this chemical has been prioritised for assessment. Zenolide has been classified as an existing chemical substance under Japan’s Chemical Substances Control Law (NITE 2021).

United States of America

Ethylene brassylate and zenolide are listed on the US EPA Safer Chemical Ingredients List (the List). This List identifies chemicals deemed to be safer alternatives to other chemicals employed for the same functional use. Criteria for adding chemicals to the List covers a broad range of human health and environmental toxicological effects (US EPA 2021a).

Environmental exposure

Ethylene brassylate and zenolide are expected to be found in household and commercial products available for use in Australia. Formulated products on the Australian market are assumed not to differ significantly from those available internationally. Chemicals used in cosmetics, personal care and cleaning products are typically released to wastewater as a normal part of their use in household and industrial applications.

Depending on degradation and partitioning processes of chemicals in STPs, a fraction of the quantity of chemicals in wastewater entering STPs can be emitted to the air compartment, to rivers or oceans in treated effluent, or to soil by application of biosolids to agricultural land. The emissions of ethylene brassylate and zenolide to environmental surface waters, soil and air are considered in this evaluation.

Environmental fate

Partitioning

Ethylene brassylate and zenolide are expected to preferentially partition to water, sediment and soil when released to the environment. Some volatilisation to air is also possible due to their moderate volatility.

Ethylene brassylate and zenolide are neutral organic chemicals that are moderately soluble in water and moderately volatile. The Henry’s law constants of these chemicals (0.312 and 0.096 $\mathrm{Pa \cdot m^3/mol}$, respectively) suggest they will be moderately volatile from water and moist soil. Ethylene brassylate and zenolide are lipophilic substances with log K_{OW} values of 4.30 and 3.65, and log K_{OC} values of 2.85 and 2.59 L/kg, respectively. These values indicate that these chemicals will have low to medium mobility in soil and will preferentially adsorb to phases in the environment with high organic carbon content (including sediment and soil) (REACHb; REACHc; US EPA 2017).

Following the application of biosolids containing ethylene brassylate or zenolide to agricultural soils, calculations with a standard multimedia partitioning (fugacity) model with sole release to the soil compartment (level III approach) predict that these chemicals will predominately remain in soil (99.1–99.5%) (US EPA 2017).

Following release of these chemicals to surface waters in STP effluent, calculations with a standard multimedia partitioning (fugacity) model with sole release to the water compartment predict that both ethylene brassylate and zenolide will predominantly remain in water (97.4% and 98.4% respectively) (US EPA 2017).

Degradation

Ethylene brassylate and zenolide are degraded in the environment by natural processes.

Ethylene brassylate and zenolide are predicted to undergo rapid abiotic degradation in air but slow abiotic degradation in water. The results of laboratory hydrolysis tests on simple acyclic monoester analogues of ethylene brassylate and zenolide indicate a degradation half life of 2−6 years at neutral pH (Mabey and Mill 1978). Unbranched, linear aliphatic esters were judged to be suitable analogues in preference to lactones with smaller rings where ring-strain could enhance the rate of hydrolysis. Calculated results from standard Quantitative structure-activity relationships (QSARs) predict that both galaxolide and zenolide will rapidly degrade in air following reaction with hydroxyl radicals, with half lives of 7.5 and 8.2 hours, respectively (US EPA 2017).

Ethylene brassylate is readily biodegradable based on a study conducted according to OECD Test Guideline (TG) 301B. The chemical completely biodegraded under screening test timeframes (100% in 28 days) and the 10 day window was met (biodegradation exceeded 60% within 10 days of the level exceeding 10%) (REACHc). The chemical also readily biodegrades under other standard test conditions, including closed bottle tests (78.1% biodegradation), manometric respiratory tests (OECD 301F, 3 tests, 77-89% biodegradation), and biological oxygen demand tests for insoluble substances (BODIS, 66% biodegradation) (Api, et al. 2016). Zenolide is also readily biodegradable based on a study conducted according to OECD TG 301B (100% degradation in 28 days, 10 day window met) (REACHb).

Mineralisation of ethylene brassylate and zenolide begins with ester hydrolysis followed by degradation via the fatty acid metabolic pathway, as predicted by the University of Minnesota Biocatalysis/Biodegradation database using a model cyclic lactone (EAWAG 2021; Gao et al. 2009).

Bioaccumulation

Ethylene brassylate and zenolide have low potential to bioaccumulate in aquatic life. Both chemicals are lipophilic, but it is anticipated that their potential to bioaccumulate is mitigated by biotransformation processes.

The measured log K_{OW} of zenolide (3.7) is below the domestic categorisation threshold for bioaccumulation hazards (log K_{OW} ≥4.2) (EPHC 2009). The chemical has a calculated BCF of 471 L/kg wet weight (wwt) when the effects of biotransformation are excluded (Arnot-Gobas, upper trophic), indicating low potential to bioaccumulate (US EPA 2017).

The measured log K_{OW} of ethylene brassylate (4.3) exceeds the domestic categorisation threshold for bioaccumulation hazards (log K_{OW} ≥4.2) and results in a calculated BCF of 1995 L/kg wwt (Arnot-Gobas, upper trophic) when the effects of biotransformation are excluded (US EPA 2017). This value is at the upper limit of domestic categorisation thresholds for aquatic bioaccumulation hazards (BCF ≥2000 L/kg wwt) (EPHC 2009).

Biotransformation likely mitigates the bioaccumulation potential of ethylene brassylate. When the effects of biotransformation are included the calculated BCF is 28.6 L/kg wwt (Arnot-Gobas, upper trophic) (US EPA 2017). An in vitro biochemical study found that ethylene brassylate is metabolised in trout hepatocytes with a half life of 6.4 minutes. The authors used this value to extrapolate a half life of 4.2 hours for the whole organism and a BCF of 133 L/kg wwt (Weeks, et al. 2020). This value is below the domestic categorisation threshold for bioaccumulation (BCF ≥2000 L/kg) and indicates that ethylene brassylate has low potential to bioaccumulate due to the mitigating effects of biotransformation (EPHC 2009).

Environmental transport

Ethylene brassylate and zenolide are not expected to undergo long range transport based on their short half lives in the environment.

Ethylene brassylate and zenolide have short predicted atmospheric lifetimes of 7.5 and 8.2 hours, respectively (US EPA 2017) which suggests that long range atmospheric transport is unlikely.

Neither ethylene brassylate nor zenolide have been detected in pristine environmental areas that do not received direct anthropogenic outputs. A Canadian study analysed air samples at a remote location in the arctic, but no confirmed traces of ethylene brassylate or other synthetic musks were detected (Wong et al. 2019).

Predicted environmental concentration (PEC)

Ethylene brassylate is predicted to be present in Australian river water at a concentration of 4.33 micrograms per litre (µg/L) based on standard exposure modelling using reported IFRA APAC region volumes (Struijs 1996). Zenolide is predicted to be present at 0.17 µg/L based on international monitoring data (Vallecillos et al. 2013a). Soil concentrations of 0.011 µg/kg dw ethylene brassylate and 0.0015 µg/kg dry weight (dw) zenolide are predicted based on international measured data (Vallecillos et al. 2013b).

Information provided by IFRA indicated approximately 1300 tonnes of ethylene brassylate is used annually in the APAC region, and that up to 5% of the volume (approximately 65 tonnes) may be introduced into Australia. An introduction volume of 65 tonnes for ethylene brassylate has; therefore, been used as the Australian introduction volume in standard exposure modelling for the release of the chemical to surface waters in STP effluents (Struijs 1996). The calculated concentration of ethylene brassylate in STP effluent based on this modelling was 4.33 µg/L. This value has been used as the maximum concentration of ethylene brassylate in river water in Australia for the purposes of risk characterisation.

Ethylene brassylate has been detected in STP influent and effluent internationally. The chemical has been detected at maximum concentrations of 11.76 µg/L in influent, 8.94 µg/L in effluent following secondary treatment, and 0.19 µg/L in effluent following tertiary treatment (reverse osmosis) (Homem et al. 2016; Vallecillos et al. 2013a; 2014). The removal efficiencies of ethylene brassylate at individual international STPs are 24–96%, depending on the level of treatment. Ethylene brassylate has also been quantified in sea water at average concentrations of 307 ng/L (Homem et al. 2016).

For zenolide, standard exposure modelling assuming a default introduction volume of 100 tonnes per year gives calculated concentrations of 6.18 µg/L in STP effluents (Struijs 1996). However, this is likely to overestimate the concentration of zenolide in Australian surface waters. Zenolide was measured in STP samples in two studies in maximum influent and effluent concentrations of 0.82 µg/L and 0.17 µg/L, respectively (Vallecillos et al. 2012; Vallecillos et al. 2013a). A further study did not detect zenolide above the limit of detection (*ca.* 0.03 µg/L) in influent or effluent from three urban STPs (Vallecillos et al. 2014). A value of 0.17 µg/L has been used as the predicted concentration of zenolide in river water in Australia for the purposes of risk characterisation, with a worst case estimate of 0.82 µg/L.

Ethylene brassylate and zenolide adsorb to biosolids in STPs, and maximum concentrations of 1.45 and 0.19 µg/kg dw, respectively, have been measured internationally (Vallecillos et al. 2013b). These values were used to calculate the concentration of each chemical in soil amended with biosolids. Calculations gave maximum soil concentrations for ethylene brassylate and zenolide of 0.011 and 0.0015 µg/kg dw, respectively, using typical biosolids application rates and a soil bulk density of 1300 kilograms per cubic metre (kg/m^3) (EPHC 2009; Langdon et al. 2010).

Environmental effects

Effects on aquatic life

Ethylene brassylate and zenolide are expected to cause toxic effects at low concentrations in aquatic organisms across multiple trophic levels.

The toxicity of ethylene brassylate towards aquatic organisms was guided by read across from zenolide and an analogue, cervolide (CAS RN 6707-60-4). Toxicity data for ethylene brassylate in aquatic organisms are available (REACHc), but were not used because the results were concluded to be unreliable. In short term toxicity studies towards fish, invertebrates and algae, concentrations of the test substance were measured at the beginning and end of the test. Rapid loss of the substance was evident by low measured concentrations upon test completion. The true concentration of the test substance during the test was unknown and was likely to be far lower than reported nominal concentrations or calculated values (arithmetic or geometric means) based on initial measured concentrations. Therefore, the reported toxicity results are considered to be unreliable.

The toxicity of zenolide and cervolide are suitable to be read across to ethylene brassylate for the following reasons:

- *Structural Similarity*: ethylene brassylate and zenolide are homologous dilactones, while cervolide is a monolactone containing an ether group in place of one of the ester groups.
- *Hydrophobicity*: all chemicals are neutral organics with similar experimental log K_{OW} values, decreasing from cervolide (4.4) to ethylene brassylate (4.3) to zenolide (3.7) (REACHa).
- *Mode-of-Action (MoA):* all chemicals share the same MoA for acute toxicity. Profiling with the OECD QSAR Toolbox identified that all three chemicals have unspecific reactivity class 3 according to the Verhaar scheme, while OASIS and ECOSAR identified that all three chemicals will have the ecotoxicity characteristics of esters (OECD 2020). The ether group in cervolide confers non-specific toxicity and is not expected to change the MoA.
- *Degradants:* All chemicals are predicted to degrade by initial ester hydrolysis, with ultimate degradation by fatty acid metabolism.

Where data are available for both zenolide and cervolide, cervolide was preferentially used as read across for ethylene brassylate. For esters there is a direct relationship between the toxicity of the chemical and its hydrophobicity (US EPA 2017). Read across from cervolide (log K_{OW} = 4.4) will slightly overestimate the toxicity of ethylene brassylate (log K_{OW} = 4.3), providing a conservative measure. This is preferential over read across from zenolide (log K_{OW} = 3.7), which will likely underestimate the toxicity of ethylene brassylate.

Acute toxicity

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms across three trophic levels exposed to ethylene brassylate (EB) and zenolide (Z) were retrieved from REACH registration dossiers for zenolide and cervolide (REACHa ; REACHb):

Taxon	Endpoint	Method
Fish	EB: 96 h LC50 = 0.88 mg/L	Read-across from zenolide *Oncorhynchus mykiss* (rainbow trout) Flow-through conditions, test substance concentrations measured OECD TG 203
	Z: 96 h LC50 = 0.88 mg/L	*Oncorhynchus mykiss* Flow through conditions, test substance concentrations measured OECD TG 203
Invertebrates	EB: 48 h EC50 = 10.3 mg/L	Read across from cervolide *Daphnia magna* (water flea) Semi-static conditions, test substance concentrations measured OECD TG 202
	Z: 48 h EC50 > 14 mg/L	*Daphnia magna* Static conditions, test substance concentrations measured OECD TG 202
Algae	EB: 72 h EC50 = 1.2 mg/L	Read-across from cervolide *Raphidocelis subcapitata* (microalgae) Static conditions, test substance concentrations measured OECD TG 201
	Z: 72 h EC50 = 17 mg/L	*Raphidocelis subcapitata* Static conditions, test substance concentrations measured OECD TG 201

Chronic toxicity

The following measured 10% effective concentration (EC10) values for algae were retrieved from REACH registration dossiers for zenolide and cervolide (REACHa; REACHb). No data were available to assess the chronic toxicity of ethylene brassylate, zenolide or suitable analogues towards fish or invertebrates:

Taxon	Endpoint	Method
Algae	EB: 72 h EC10 = 0.48 mg/L	Read-across from cervolide *Raphidocelis subcapitata* (microalgae) Static conditions, test substance concentrations measured OECD TG 201
	Z: 72 h EC10 = 0.61 mg/L	*Raphidocelis subcapitata* Static conditions, test substance concentrations measured OECD TG 201

Predicted no-effect concentration (PNEC)

The PNEC for ethylene brassylate in water is 4.8 µg/L.

The 72 h EC10 value for *Raphidocelis subcapitata* (read-across from cervolide) was used to derive the PNEC for this chemical. An assessment factor of 100 was applied to the pivotal endpoint as there are reliable acute ecotoxicity data available from read across over three trophic levels (fish, invertebrates, and algae) and chronic data for one taxon (algae) (EPHC 2009).

The PNEC for zenolide in water is 6.1 µg/L.

The 72h EC10 value for *Raphidocelis subcapitata* was used to derive the PNEC for this chemical. An assessment factor of 100 was applied to the pivotal endpoint as there are reliable acute ecotoxicity data available over three trophic levels (fish, invertebrates and algae) and chronic toxicity data for one taxon (algae) (EPHC 2009).

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemicals according to domestic environmental hazard thresholds is presented below (EPHC 2009):

Persistence

Not Persistent (Not P). Based on results from standard biodegradability tests that show ready biodegradability, both ethylene brassylate and zenolide are categorised as Not Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on low calculated bioconcentration factors (BCF) in fish, and evidence of biotransformation for ethylene brassylate, both ethylene brassylate and zenolide are categorised as Not Bioaccumulative.

Toxicity

Toxic (T). Based on acute ecotoxicity values below 1 mg/L, both ethylene brassylate and zenolide are categorised as Toxic.

Environmental risk characterisation

Ethylene brassylate and zenolide are Not Persistent, Not Bioaccumulative and Toxic. The risk quotients (RQ = PEC ÷ PNEC) below for the riverine compartment have been calculated based on the PEC and PNEC values determined for ethylene brassylate and zenolide:

Chemical	PEC (µg/L)	PNEC (µg/L)	RQ
Ethylene brassylate	4.33	4.8	0.9
Zenolide	0.17	6.1	0.03

The RQ value for each chemical is less than 1. This indicates that environmental concentrations of these chemicals are not expected to pose a significant risk to the environment based on the estimated emissions, as environmental concentrations are below levels likely to cause harmful effects.

The calculated RQ for zenolide considering the worst-case PEC of 0.82 µg/L is 0.13, indicating that zenolide is not expected to pose a high risk to the environment even at worst case concentrations in the freshwater aquatic compartment.

Insufficient ecotoxicity data are available to characterise the risks posed by release of these chemicals to the soil or sediment compartments.

Uncertainty

This evaluation was conducted based on a set of information that may be incomplete or limited in scope. Some relatively common data limitations can be addressed through use of conservative assumptions (OECD 2019) or quantitative adjustments such as assessment factors (US EPA 1984). Others must be addressed qualitatively, or on a case by case basis (OECD 2019). The most consequential areas of uncertainty for this evaluation are discussed below.

- No domestic STP or inland surface water monitoring data were available for these chemicals in this evaluation. In lieu of these data, estimates based on standard modelling approaches using default introduction volume assumptions and international monitoring were used to calculate the RQ for these chemicals in this assessment. Data on actual domestic introduction volumes or domestic monitoring data for these chemicals may therefore significantly change aspects of the risk characterisation.
- There are insufficient ecotoxicity data available to fully characterise the toxicity characteristics of ethylene brassylate. In lieu of these data, read across from structural analogue chemicals was used to generate the RQ for this chemical. The risk characterisation may significantly change if additional ecotoxicity data for ethylene brassylate becomes available.
- There are minimal ecotoxicity data on soil and sediment dwelling organisms available for these chemicals in this evaluation. The risk profiles of these chemicals may change should new ecotoxicity data or exposure data become available to indicate that they may be present in Australian soil and sediment above levels of concern.

References

ABP (Australian Botanical Products) (2020) *Aromatic Chemicals List*, ABP, accessed February 2021.

Api AM, Belsito D, Bhatia S, Bruze M, Calow P, Dagli ML, Dekant W, Fryer AD, Kromidas L, La Cava S, Lalko JF, Lapczynski A, Liebler DC, Politano VT, Ritacco G, Salvito D, Schultz TW, Shen J, Sipes IG, Wall B and Wilcox DK (2016). RIFM fragrance ingredient safety assessment, ethylene brassylate, CAS Registry Number 105-95-3. *Food and Chemical Toxicology,* **97**, pp S192-S200.

Bothe F, Dettmer K and Engewald W (2003). Determination of perfume oil in household products by headspace solid-phase microextraction and fast capillary gas chromatography. *Chromatographia,* **57**(1), pp S199-S206.

Cahill J, Jr. and Rodenberg HG (1986) *Process for the production of macrocyclic esters by the depolymerization of polyesters (US 4709058)*, National Distillers and Chemical Corporation, accessed January 2022.

EAWAG (Swiss Federal Institute of Aquatic Science and Technology) (2021) *Biocatalysis/Biodegradation Database*, EAWAG, accessed April 2021.

Elsasser AF, Jr. (1992) *Process for controlled depolymerization of feed material to produce a product with lower molecular weight (WO09215573)*, Henkel Corporation, accessed January 2021.

EPHC (Environment Protection and Heritage Council) (2009) *Environmental Risk Assessment Guidance Manual for Industrial Chemicals*, EPHC, accessed March 2021.

EWGa (Environmental Working Group) (n.d.) *EWG's Skin Deep Cosmetics Database Products Containing Ethylene Brassylate*, EWG website, accessed March 2021.

EWGb (Environmental Working Group) (n.d.) *EWG's Skin Deep Cosmetics Database Products Containing Ethylene Dodecanedioate*, EWG website, accessed March, 2021.

Gao J, Ellis LBM and Wackett LP (2009). The University of Minnesota Biocatalysis/Biodegradation Database: improving public access. *Nucleic Acids Research,* **38**(suppl_1), pp D488-D491.

Harris EG and White JF (1978) *Process for the production of macrocyclic esters (US 4218379)*, Emery Industries, Inc., accessed January 2021.

Homem V, Silva E, Alves A and Santos L (2015). Scented traces – Dermal exposure of synthetic musk fragrances in personal care products and environmental input assessment. *Chemosphere,* **139**, pp 276-287.

Homem V, Alves A, Alves A and Santos L (2016). Ultrasound-assisted dispersive liquid–liquid microextraction for the determination of synthetic musk fragrances in aqueous matrices by gas chromatography–mass spectrometry. *Talanta,* **148**, pp 84-93.

IFRA (International Fragrance Association) (n.d.) *Transparency List*, IFRA website, accessed February 2021.

Langdon K, Warne M and Kookana R (2010). Aquatic hazard assessment for pharmaceuticals, personal care products, and endocrine-disrupting compounds from biosolids-amended land. *Integrated Environmental Assessment and Management,* **6**(4), pp 663-76.

Mabey W and Mill T (1978). Critical review of hydrolysis of organic compounds in water under environmental conditions. *Journal of Physical and Chemical Reference Data,* **7**(2), pp 383-415.

Nakata H, Hinosaka M and Yanagimoto H (2015). Macrocyclic-, polycyclic-, and nitro musks in cosmetics, household commodities and indoor dusts collected from Japan: Implications for their human exposure. *Ecotoxicology and Environmental Safety,* **111**, pp 248-255.

NITE (National Institute of Technology and Evaluation) (2021) *Japan Chemicals Collaborative Knowledge database (J-Check)*, NITE, accessed March 2021.

OECD (The Organisation for Economic Co-operation and Development) (2019) *Guiding Principles and Key Elements for Establishing a Weight of Evidence for Chemical Assessment, Series on Testing and Assessment No. 311, Environment, Health and Safety Division, Environment Directorate* , OECD, accessed March 2021.

OECD (2020) *The OECD QSAR Toolbox 4.4.1*, The Laboratory of Mathematical Chemistry (LMC) for the Organisation for Economic Co-Operation and Development (OECD), accessed December 2020.

REACHa (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.) *Registered dossier for CAS No. 6707-60-4*, European Chemicals Agency website, accessed March 2021.

REACHb (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.) *Registered dossier for CAS No. 54982-83-1*, European Chemicals Agency website, accessed March 2021.

REACHc (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.) *Registered dossier for CAS No. 105-95-3*, European Chemicals Agency website, accessed August 2020.

SPINa (Substances in Preparations in Nordic Countries) (n.d.) *SPIN Database for CAS RN 105-95-3*, SPIN website, accessed August 2020.

SPINb (Substances in Preparations in Nordic Countries) (n.d.) *SPIN Database for CAS RN 54982-83-1*, SPIN website, accessed March 2021.

Struijs J (1996). *SimpleTreat 3.0: a model to predict the distribution and elimination of chemicals by sewage treatment plants*. National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

UNEP (United Nations Environment Programme, Ozone Secretariat) (1987) *The Montreal Protocol on Substances that Deplete the Ozone Layer*, UNEP, accessed October 2020.

UNEP (United Nations Environment Programme, Secretariant of the Stockholm Convention) (2001) *The Stockholm Convention on Persistent Organic Pollutants*, UNEP, accessed October 2020.

UNEP & FAO (United Nations Environment Programme and Food and Agriculture Organization of the United Nations) (1998) *The Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade*, UNEP & FAO, accessed October 2020.

US EPA (1984) *Estimation of "concern levels" for concentrations of chemical substances in the environment. A report from Health and Environmental Review Division, Environmental Effects Branch*, United States Environmental Protection Agency, accessed March 2021.

US EPA (United States Environmental Protection Agency) (2014a) *Chemical and Product Categories (CPCat) Chemical Use for 1,4-dioxacycloheptadecane-5,17-dione (CAS RN 105-95-3)*, PubChem website, accessed February 2021.

US EPA (United States Environmental Protection Agency) (2014b) *Chemical and Product Categories (CPCat) Chemical Use for 1,4-dioxacyclohexadecane-5,16-dione (CAS RN 54982-83-1)*, PubChem website, accessed February 2021.

US EPA (2016). *2016 Chemical Data Reporting (CDR) Industrial Processing and Use Database*. United States Environmental Protection Agency, Washington DC, USA. accessed August 2020.

US EPA (United States Environmental Protection Agency) (2017) *Estimations Programs Interface (EPI) SuiteTM for Microsoft Windows®* v 4.11, [Computer software], US EPA, accessed March 2021.

US EPA (United States Environmental Protection Agency) (2021a) *Safer Chemical Ingredients List*, US EPA, accessed February 2021.

US EPA (2021b) *CompTox Chemicals Dashboard entry for 1,4-Dioxacycloheptadecane-5,17-dione*, United States Environmental Protection Agency, accessed February 2021.

US GPO (United States Government Publishing Office) *Electronic Code of Federal Regulations (e-CFR): Title 21, 172.515 (Food Additives Permitted for DIrect Addition to Food For Human Consumption, Subpart F - Flavoring Agents and Related Susbtances* , US GPO, accessed March 2021.

Vallecillos L, Pocurull E and Borrull F (2012). Fully automated determination of macrocyclic musk fragrances in wastewater by microextraction by packed sorbents and large volume injection gas chromatography–mass spectrometry. *Journal of Chromatography A,* **1264**, pp 87-94.

Vallecillos L, Borrull F and Pocurull E (2013a). An automated headspace solid-phase microextraction followed by gas chromatography–mass spectrometry method to determine macrocyclic musk fragrances in wastewater samples. *Analytical and Bioanalytical Chemistry,* **405**(29), pp 9547-9554.

Vallecillos L, Pocurull E and Borrull F (2013b). A simple and automated method to determine macrocyclic musk fragrances in sewage sludge samples by headspace solid-phase microextraction and gas chromatography–mass spectrometry. *Journal of Chromatography A,* **1314**, pp 38-43.

Vallecillos L, Borrull F and Pocurull E (2014). On-line coupling of solid-phase extraction to gas chromatography–mass spectrometry to determine musk fragrances in wastewater. *Journal of Chromatography A,* **1364**, pp 1-11.

Weeks J, Li AP, Doshi U, Johanning K and Guiney PD (2020). In vitro evaluation of the metabolic stability of nine fragrance chemicals in trout and human hepatocytes. *Journal of Applied Toxicology,* **40**(10), pp 1421-1434.

Williams AS (1999). The Synthesis of Macrocyclic Musks. *Synthesis,* **1999**(10), pp 1707-1723.

Wong F, Robson M, Melymuk L, Shunthirasingham C, Alexandrou N, Shoeib M, Luk E, Helm P, Diamond Miriam L and Hung H (2019). Urban sources of synthetic musk compounds to the environment. *Environmental Science: Processes & Impacts,* **21**(1), pp 74-88.