Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

# Exaltone and related macrocyclic musks

## Evaluation statement

**30 June 2022**

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# AICIS evaluation statement

## Subject of the evaluation

Exaltone and related macrocyclic musks.

## Chemical(s) in this evaluation

| Name | CAS registry number |
|---|---|
| Cyclopentadecanone | 502-72-7 |
| Cyclopentadecanone, 3-methyl- | 541-91-3 |
| 9-Cycloheptadecen-1-one, (*Z*)- | 542-46-1 |
| 8-Cyclohexadecen-1-one | 3100-36-5 |
| Cyclotetradecanone | 3603-99-4 |
| 4-Cyclopentadecen-1-one | 35720-57-1 |
| 4-Cyclopentadecen-1-one, 3-methyl- | 36399-15-2 |
| 5-Cyclohexadecen-1-one | 37609-25-9 |
| 3-Cyclotetradecen-1-one | 55395-13-6 |
| Cyclotridecanone, 3-methyl- | 61415-11-0 |

## Reason for the evaluation

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

## Parameters of evaluation

This evaluation considers the environmental risks associated with the industrial uses of 10 macrocyclic ketone musks: exaltone (CAS RN 502-72-7), muscone (CAS RN 541-91-3), civetone (CAS RN 542-46-1), globanone (CAS RN 3100-36-5), cyclotetradecanone (CAS RN 3603-99-4), exaltenone (CAS RN 35720-57-1), 3-methyl-4-cyclopentadecenone (CAS RN 36399-15-2), ambretone (CAS RN 37609-25-9), 3-cyclotetradecenone (CAS RN 55395-13-6) and 3-methylcyclotridecanone (CAS RN 61415-11-0).

These chemicals have been assessed for their risks to the environment according to the following parameters:

- Australian introduction volumes based on upper estimates provided by industry sources.
- Industrial uses listed in the ‘Summary of Use’ section.

- Expected emission to sewage treatment plants (STPs) following consumer and commercial use.

These chemicals have been assessed as a group as they are structurally similar and have similar use patterns.

# Summary of evaluation

## Summary of introduction, use and end use

Macrocyclic ketone musks are used as fragrance ingredients in a variety of cosmetic and consumer use products worldwide. Exaltone, globanone and ambretone are expected to have the highest use volumes in Australia based on reported international use volumes. There are no specific Australian introduction volume data for any of these chemicals in this group.

Chemicals in this evaluation are used in the following products according to international use data:

- Personal care products
- Air freshener products
- Laundry and dishwashing products
- Cleaning and furniture care products
- Paint and coating products.

Chemicals in this group are used in moderate to low volumes worldwide. Ambretone, globanone and muscone had reported import or manufacture volumes in the USA of 49, 128 and 334 tonnes per annum respectively in 2015. Ambretone and exaltone are registered for use in the European Union (EU) with introduction volumes of 10–100 tonnes per annum. Muscone is also registered in the EU, at 1–10 tonnes per annum.

Exaltone, globanone and ambretone are each introduced at up to 10 tonnes annually in the Asia-Pacific region (APAC) as fragrance ingredients by member companies according to information provided by the International Fragrance Association (IFRA). IFRA also reported annual introduction volumes of 0.1–1 tonnes of muscone, 0.01–0.1 tonnes of civetone, and 0.001–0.01 tonnes of exaltenone in the APAC region.

## Environment

### Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data exaltenone, 3-cyclotetradecenone, 3-methylcyclotridecanone, and cyclotetradecanone are:

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

According to domestic environmental hazard thresholds and based on the available data globanone, exaltone, muscone, civetone, ambretone, 3-methyl-4-cyclopentadecenone are:

- Not Persistent (Not P)

- Bioaccumulative (B)
- Toxic (T).

### Environmental hazard classification

These chemicals satisfy the criteria for classification according to the Globally Harmonized System for 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 |
|---|---|---|
| Acute Aquatic | Acute Aq. – Cat. 1 | H400: Very toxic to aquatic life |

### Summary of environmental risk

Macrocyclic ketone musks are 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.

These chemicals are toxic and not persistent. Globanone, exaltone, muscone, civetone, ambretone, and 3-methyl-4-cyclopentadecenone have also been categorised as bioaccumulative based on calculated bioconcentration factors (BCFs) values that exceed the domestic categorisation threshold (BCF≥2000 L/kg).

Volume information provided by IFRA for the APAC region was used to model concentrations of ambretone, globanone, exaltone, muscone, civetone and exaltenone in Australian environmental surface waters. Of these, the calculated risk quotients marginally exceeded 1 for ambretone and globanone, indicating that they may be present in the environment at concentrations above the level of concern. However, this was a very conservative finding as introduction volumes for ambretone and globanone in Australia are unlikely to be equal to the volume for the entire APAC region. Given this consideration and the marginal nature of the risk quotient (RQ) values, it is concluded that ambretone and globanone are not likely to pose a significant risk to the environment. Exaltone, muscone, civetone and exaltenone are likewise unlikely to pose a significant risk to the environment based on RQ values not exceeding 1.

These RQs were not determined for the remaining chemicals in this evaluation. These chemicals are not expected to pose a significant risk to the environment, as none have hazard characteristics that are significantly different to chemicals named above, and all are likely to be used at relatively negligible volumes in Australia.

## Conclusions

The evaluation conclusions 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

## Rationale

This evaluation considers the environmental risks associated with the industrial uses of 11 macrocyclic ketones. The risk evaluation of these substances has been conducted as a group because they have known or potential applications as synthetic musk fragrances.

Macrocyclic ketone musks were the first examples of musk compounds to be used in perfumery; the use of musk (containing muscone) dates to antiquity (King 2017). Muscone is the main constituent of musk gland secretions of the musk deer (Li D et al. 2016), and other sources of natural musk chemicals include glandular secretions from the civet cat (civetone) and the musk rat (exaltone) (Williams 1999). Due to limits in availability, prohibitively high prices, strict regulation/bans and the desire to protect animals that often must be slain to obtain the scent, the fragrance industry favours the use of synthetic musks (Sommer 2004). The synthesis of macrocyclic musks has previously been costly due to challenging and low-yielding reaction conditions, but advances in synthetic chemistry over the past 3 decades have made these chemicals more accessible for use in perfumery (Williams 1999).

Macrocyclic ketone musks are used as fragrance ingredients in a variety of personal care and household products (CPID 2021; Nakata et al. 2015; REACHc).Their use in these products has potential to result in environmental exposure through emission to sewers following their use, followed by release to the environment in the treated effluents and biosolids produced by STPs.

The Evaluation Selection Analysis (ESA) of the macrocyclic musk exaltone highlighted potential bioaccumulation and toxicity hazard characteristics and a screening RQ above 1, which indicates a high concern for the environment. This evaluation includes further refinement of the risk characterisation, and a more in depth assessment of the available environmental hazard and exposure information for exaltone, and the related chemicals in this group.

## Chemical identity

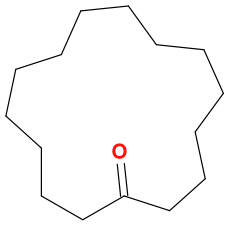
Chemicals in this evaluation are macrocycles with a ring size of 13 to 17 carbons and a single ring carbonyl group. They may also have methyl group substituents or unconjugated alkene groups in the ring.

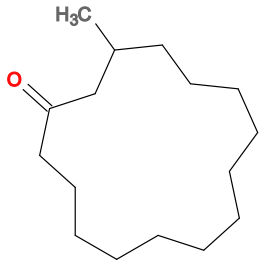
Muscone (CAS RN 541-91-3), 3-methylcyclotridecanone (CAS RN 61415-11-0), and 3-methyl-4-cyclopentadecenone (CAS RN 36399-15-2) have a chiral methyl substituent and can therefore exist as the *R* or *S* enantiomer. Natural muscone produced by the musk deer contains only the *R* enantiomer (Ahmed et al. 2018). However, the stereochemistry of these compounds is not defined on the Australian Inventory of Industrial Chemicals (Inventory), so each compound has been evaluated as the racemic mixture.

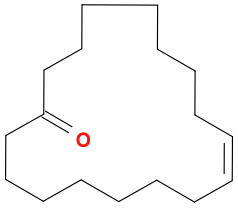
Civetone is listed on the Inventory in its isomerically pure *Z* form. The *E*-isomer (CAS RN 74244-64-7) is not listed on the Inventory.

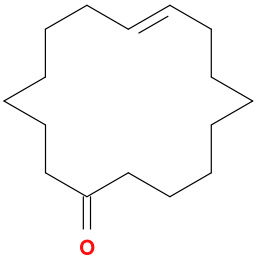
Globanone, exaltenone, 3-methyl-4-cyclopentadecenone, ambretone, and 3-cyclotetradecenone contain an alkene that can exist in either an *E* or *Z* configuration. The

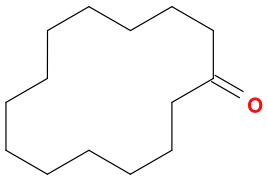
stereochemistry of these compounds is not defined on the Inventory, so each compound has been evaluated as an equal mixture of *E* and *Z* isomers.

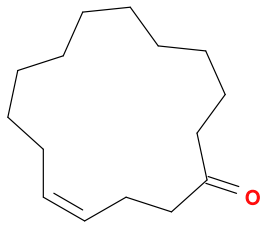
| | |
|---|---|
| CAS RN | 502-72-7 |
| Chemical name | cyclopentadecanone |
| Synonyms | exaltone<br>romanone<br>normuscone<br>cyclopentadecan-1-one |
| Structural formula |  |
| Molecular formula | C15H28O |
| Molecular weight (g/mol) | 224.38 |
| SMILES | O=C1CCCCCCCCCCCCCC1 |
| Chemical description | - |

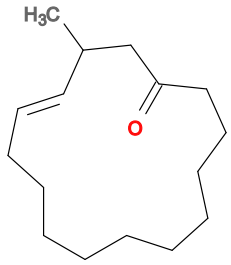
| | |
|---|---|
| CAS RN | 541-91-3 |
| Chemical name | cyclopentadecanone, 3-methyl- |
| Synonyms | muscone<br>muskone<br>methylexaltone<br>3-methylcyclopentadecan-1-one |
| Structural formula |  |
| Molecular formula | C16H30O |
| Molecular weight (g/mol) | 238.41 |
| SMILES | CC1CCCCCCCCCCCCC(=O)C1 |
| Chemical description | - |

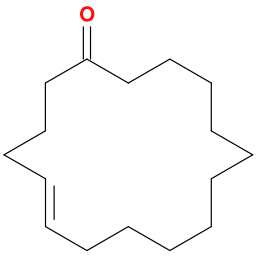
| | |
|---|---|
| CAS RN | 542-46-1 |
| Chemical name | 9-cycloheptadecen-1-one, (*Z*)- |
| Synonyms | civetone<br>*cis*-civetone<br>(*Z*)-9-cycloheptadecen-1-one |
| Structural formula |  |
| Molecular formula | C17H30O |
| Molecular weight (g/mol) | 250.4 |
| SMILES | C1CCC/C=C\CCCCCCCC(=O)CCC1 |
| Chemical description | - |

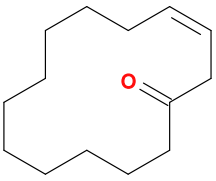
| | |
|---|---|
| CAS RN | 3100-36-5 |
| Chemical name | 8-cyclohexadecen-1-one |
| Synonyms | globanone<br>CHD |
| Structural formula |  |
| Molecular formula | C16H28O |
| Molecular weight (g/mol) | 236.39 |
| SMILES | C1CCCC=CCCCCCCC(=O)CCC1 |
| Chemical description | - |

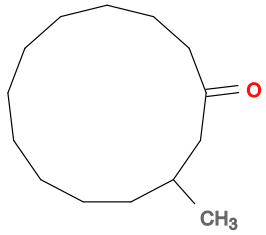
| | |
|---|---|
| CAS RN | 3603-99-4 |
| Chemical name | cyclotetradecanone |
| Synonyms | cyclotetradecan-1-one |
| Structural formula |  |
| Molecular formula | C14H26O |
| Molecular weight (g/mol) | 210.36 |
| SMILES | O=C1CCCCCCCCCCCCC1 |
| Chemical description | - |

| | |
|---|---|
| CAS RN | 35720-57-1 |
| Chemical name | 4-cyclopentadecen-1-one |
| Synonyms | exaltenone<br>musk pentane |
| Structural formula |  |
| Molecular formula | C1CCCCCC(=O)CCC=CCCCC1 |
| Molecular weight (g/mol) | 222.37 |
| SMILES | C15H26O |
| Chemical description | - |

| | |
|---|---|
| CAS RN | 36399-15-2 |
| Chemical name | 4-cyclopentadecen-1-one, 3-methyl- |
| Synonyms | - |
| Structural formula |  |
| Molecular formula | C16H28O |
| Molecular weight (g/mol) | 236.39 |
| SMILES | CC1CC(=O)CCCCCCCCCCC=C1 |
| Chemical description | - |

| | |
|---|---|
| CAS RN | 37609-25-9 |
| Chemical name | 5-cyclohexadecen-1-one |
| Synonyms | ambretone<br>ambrettone<br>velvione<br>musk amberol |
| Structural formula |  |
| Molecular formula | C16H28O |
| Molecular weight (g/mol) | 236.39 |
| SMILES | C1CCCCCC(=O)CCCC=CCCCC1 |
| Chemical description | - |

| | |
|---|---|
| CAS RN | 55395-13-6 |
| Chemical name | 3-cyclotetradecen-1-one |
| Synonyms | 3-cyclotetradecenone |
| Structural formula |  |
| Molecular formula | C14H24O |
| Molecular weight (g/mol) | 208.34 |
| SMILES | C1CCCCCC(=O)CC=CCCCC1 |
| Chemical description | - |

| | |
|---|---|
| CAS RN | 61415-11-0 |
| Chemical name | cyclotridecanone, 3-methyl- |
| Synonyms | 3-methylcyclotridecan-1-one |
| Structural formula |   |
| Molecular formula | CC1CCCCCCCCCCC(=O)C1 |
| Molecular weight (g/mol) | 210.36 |
| SMILES | C14H26O |
| Chemical description | - |

## Relevant physical and chemical properties

The physical and chemical properties for representative members of this group are tabulated below. Measured physical and chemical property data for ambretone and exaltone were retrieved from the respective registration dossiers for each chemical submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the EU (REACHb; REACHc). Henry's Law constants for these 2 chemicals were calculated from measured values for water solubility and vapour pressure (US EPA 2017). Other physical and chemical properties were calculated using standard quantitative structure property relationships (QSPR) (US EPA 2017). The range of properties for the selected chemicals are expected to encompass the physical and chemical properties of the other chemicals in this evaluation:

| Chemical | Ambretone | Exaltone | 3-Cyclotetradecenone |
|---|---|---|---|
| Physical form | liquid | solid | solid |
| Melting point | 21.8°C (exp.) | 61°C (exp.) | 37°C (calc.) |
| Boiling point | 342°C (exp.) | 246°C (exp.) | 313°C (calc.) |
| Vapour pressure | 0.02 Pa (20°C, exp.) | ≤0.40 Pa (20°C, exp.) | 0.188 Pa (calc.) |
| Water solubility | 0.65 milligrams per litre (mg/L, 20°C, exp.) | 0.58 mg/L (20°C, exp.) | 2.917 mg/L (calc.) |
| Henry's law constant | 7.27 Pa·$m^3$/mol (calc.) | <155.3 Pa·$m^3$/mol (calc.) | 13.4 Pa·m3/mol (calc.) |
| Ionisable in the environment? | no | no | no |
| pKa | n/a | n/a | n/a |
| log $K_{OW}$ | 6.4 (20°C, exp.) | 5.6 (20°C, exp.) | 4.84 (calc.) |

Chemicals in this group differ by alkyl ring size (C13-C17), and the presence of methyl group substituents and/or alkene groups in the ring. Based on experimental and calculated values for the representative chemicals above and for other chemicals in this evaluation, the log $K_{OW}$ (lipophilicity) increases with increasing ring size, increases with a methyl group substitution, and decreases with a ring alkene group.

# Introduction and use

## Australia

No specific Australian import or manufacturing information has been identified for chemicals in this group.

Based on information in the public domain, civetone, globanone and ambretone are readily available for use in Australia as listed fragrance ingredients (Australian Botanical Products). No specific Australian use has been identified for the remaining chemicals in this evaluation.

## International

Chemicals in this group are expected to be used as fragrances.

No international industrial use, import or manufacturing information has been identified for 3-methyl-4-cyclopentadecenone, or 3-cyclotetradecenone. These chemicals do not appear to have widespread use internationally. The remaining chemicals in this group have reported international use as fragrance ingredients (European Commission 2020; US EPA 2014; US EPA 2021a). Of these, 6 chemicals (exaltone, ambretone, muscone, globanone, civetone, exaltenone) are listed on the IFRA transparency list, which identifies chemicals used as fragrance ingredients by member companies (IFRA 2016).

According to information provided by IFRA in 2019, 0.1–1 tonnes per year of muscone, 0.01–0.1 tonnes per year of civetone and 0.001–0.01 tonnes per year of exaltenone were used as fragrance ingredients in the Asia Pacific region (includes Australia) by member companies. Further information provided by IFRA in 2022 indicated that exaltone, globanone, and ambretone were each used at up to 10 tonnes per year in the Asia Pacific region by member companies.

Exaltone, ambretone, muscone and globanone have the highest reported use volumes internationally. Ambretone, globanone and muscone had reported import or manufacture volumes in the USA of 49, 128 and 334 tonnes per year in 2015, respectively (US EPA 2016). Ambretone, exaltone and muscone are registered under REACH in the EU; ambretone and exaltone have reported use volumes of 10–100 tonnes per year, and muscone has a reported use volume of 1–10 tonnes per year (REACHb; REACHc; REACHd). Exaltone, muscone and ambretone had reported use in Canada of less than 0.1 tonnes per year in 2012 (ECCC 2019).

All 4 chemicals have reported international use as fragrances in personal care products (including perfume) and air freshener products. Exaltone, ambretone and globanone have reported use in cleaning and washing products (such as fabric softener, laundry detergent, polishes and waxes), and globanone has reported use in paints, lacquers and varnishes (CPID 2021; ECCC 2019; Nordic Council of Ministers 2021; REACHb; REACHc; US EPA 2014). In Japan, exaltone and muscone were detected in domestic products, such as perfume, body lotion, body soap and shampoo, in maximum concentrations of 21–77 micrograms per gram (µg/g) (Nakata et al. 2015).

Exaltone, globanone, ambretone, muscone and civetone have non-industrial use in pesticides as inert fragrance additives (ECCC 2019; US EPA 2021b). Cyclotetradecanone, muscone and civetone have non-industrial use as food flavouring agents (US EPA 2014). Muscone has reported use in natural health products (ECCC 2019). The use of these chemicals as ingredients in pesticides, food, and health products is beyond the scope of this evaluation.

# Existing Australian regulatory controls

## Environment

The use of these chemicals is not subject to any specific national environmental regulations.

# International regulatory status

## United Nations

Chemicals in this group 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).

# Environmental exposure

Chemicals in this group are expected to be found as fragrance ingredients in household and commercial products available for use in Australia. Formulated products on the Australian market are assumed to be similar to those available internationally. International studies and

consumer product information have reported the use of macrocyclic ketone musks in household and personal care products including perfume, fabric softener, laundry detergent, body soap, shampoo and body lotion (CPID 2021; Nakata et al. 2015; US EPA 2014). An international study measured muscone in perfume in concentrations up to 77 µg/g (0.008% weight/weight [w/w]) and exaltone in body soap in concentrations up to 67 µg/g (0.007% w/w) (Nakata et al. 2015). Chemicals used in 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, some 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 (Struijs 1996). Emissions of macrocyclic ketone musks to environmental surface waters and soil are considered in this evaluation.

## Environmental fate

### Partitioning

Chemicals in this group partition to air, water, sediment and soil when released to the environment.

Macrocyclic ketone musks are neutral organic chemicals that are slightly soluble in water and moderately volatile. The Henry's Law constants of these chemicals are between 7.27 (ambretone) and 155.3 $Pa \cdot m^3/mol$ (exaltone), suggesting they will be moderately to highly volatile from water and moist soil. Chemicals in this group are lipophilic substances with log $K_{OW}$ values ranging from 4.84 to 6.4 and log soil adsorption coefficients ($K_{OC}$) values ranging from 3.80 to 4.66, indicating that they will be immobile in soil and will preferentially adsorb to phases in the environment with high organic carbon content (including sediment and soil) (REACHb; REACHc; REACHd; US EPA 2017).

Chemicals in this group may be emitted to the soil compartment through application of biosolids from STP processes. 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 (> 99.7%) (US EPA 2017).

Following release to surface waters in STP effluent, calculations with a fugacity model with sole release to the water compartment predict that these chemicals will predominately remain in water (59.7–89.2%) or partition to sediment (9.33–40.2%) (US EPA 2017). The more lipophilic the chemical (high values of log $K_{OW}$) the more partitioning to sediment is favoured.

### Degradation

Chemicals in this group are degraded in the environment by natural processes.

Exaltone, ambretone, muscone, and exaltenone are expected to biodegrade based on studies conducted according to standard ready biodegradability test methods. An OECD TG 301B study using exaltone found 70% mineralisation within 28 days, passing the 10 day ready biodegradability window (REACHc). An OECD TG 301F study with ambretone found 86% mineralisation within 28 days, passing the 10 day ready biodegradability window (REACHb). An OECD TG 301F study with muscone found 80% mineralisation within 28 days, passing the 10 day ready biodegradability window (REACHd). Finally, an OECD TG

301B study with the *Z*-isomer of exaltenone (CAS RN 14595-54-1) found 84% mineralisation within 28 days, passing the 10 day ready biodegradability window (REACHa). It is expected that both the *Z*- and *E*-isomers of exaltenone will be readily biodegradable based on this result.

The structural variety accounted for by the 4 chemicals above includes chemicals with ring sizes of C15 and C16, chemicals with methyl substituents, and chemicals with cyclic alkene functional groups. The ready biodegradability test results for these 4 chemicals (exaltone, ambretone, muscone, and exaltenone) are expected to read across to the remaining chemicals in this group, due to their high structural and functional group similarity.

Chemicals in this group are predicted to undergo rapid abiotic degradation in air. Calculated results from standard quantitative structure activity relationships (QSARs) predict that these chemicals will rapidly degrade in air following reaction with hydroxyl radicals, with half-lives of 1.58–5.49 hours. Macrocycles with an unconjugated double bond are predicted to react more rapidly with ozone (half-life of 1.38 hours), and may undergo initial degradation by this pathway (US EPA 2017).

### Bioaccumulation

Chemicals in this group have a low to moderate potential to bioaccumulate in aquatic life.

The log $K_{OW}$ values of chemicals in this group range from 4.84 to 6.4, which exceeds the domestic categorisation threshold for bioaccumulation hazards (log $K_{OW} \geq 4.2$), indicating that these chemicals have the potential to bioaccumulate (EPHC 2009).

Experimental BCFs have not been identified for chemicals in this group, so BCF values that take into account the mitigating effects of biotransformation were calculated for all chemicals (Arnot-Gobas, upper trophic) (US EPA 2017).

Exaltenone, 3-cyclotetradecenone, 3-methylcyclotridecanone, and cyclotetradecanone have calculated BCF values ranging from 1073 to 1560 litres per kilogram wet weight (L/kg wwt), which is below domestic categorisation thresholds for aquatic bioaccumulation hazards (BCF≤2000 L/kg wwt) and indicates that these chemicals will have a low potential to bioaccumulate (EPHC 2009; US EPA 2017).

The remaining chemicals in this group (globanone, exaltone, muscone, civetone, ambretone and 3-methyl-4-cyclopentadecenone) have calculated BCF values ranging from 2069 to 3321 L/kg wwt, indicating a moderate potential for bioaccumulation (US EPA 2017). However, experimental evidence suggests that macrocyclic ketone musks may undergo rapid depuration by fish. The depuration half life of globanone (log $K_{OW}$ = 5.82, calculated BCF = 2663 L/kg) in rainbow trout (*Oncorhynchus mykiss*) following a single dietary exposure to the chemical was measured to be 1.36 days (first order rate constant = 0.509 $d^{-1}$) (Chen et al. 2018). As such, the bioaccumulation of these chemicals may be overestimated. Taking a conservative approach, these chemicals are expected to have a moderate potential to bioaccumulate in aquatic life.

### Environmental transport

Chemicals in this group are not expected to undergo long range transport based on their short half lives in the environment.

## Predicted environmental concentration (PEC)

The estimated concentration in Australian river water is 0.34 micrograms per litre (µg/L) for exaltone, globanone and ambretone; 0.034 µg/L for muscone, 0.0034 µg/L for civetone, and 0.00045 µg/L for exaltenone. A PEC was not determined for the remaining chemicals in this evaluation.

Information was provided by IFRA on the approximate introduction volumes of exaltone, globanone, ambretone, muscone, civetone, and exaltenone in the Asia Pacific region. These values have been conservatively used as the Australian introduction volumes in standard exposure modelling for the release of these chemicals to surface waters in STP effluents (Struijs 1996). The resulting predicted concentrations in STP effluents are 0.34 µg/L each for exaltone, globanone, and ambretone (introduction volume of 10 tonnes/y each), 0.034 µg/L for muscone (introduction volume of one tonne per year), 0.0034 µg/L for civetone (0.1 tonne per year), and 0.00045 µg/L for exaltenone (0.01 tonne per year).

No use volume or experimental monitoring data were identified for the remaining chemicals in this evaluation. As IFRA makes up the majority of fragrance producers it is assumed that the volume of use of these chemicals will be lower than those above. Therefore, the concentrations of the remaining chemicals in this evaluation in STP effluent are assumed to be negligible.

Some chemicals in this group have been quantified in international STPs. In a study on samples taken from secondary STP effluent in a Spanish STP, exaltone was found at concentrations in the range of <0.005–2.26 µg/L, muscone at <0.0025–0.43 µg/L, and civetone at <0.00075–1.79 µg/L (Vallecillos et al. 2013). A second study found concentrations in the range of <0.012 – 0.48 µg/L for exaltone, <0.018 – 1.75 µg/L for muscone, and <0.012 µg/L for civetone (Vallecillos et al. 2014).

Exaltone, muscone and civetone adsorb to biosolids in STPs. Maximum concentrations of 80, 2000 and 130 nanograms per kilogram dry weight (ng/kg dw), respectively, were measured in a study conducted in Spain (Vallecillos et al. 2013). The calculated exaltone, muscone and civetone concentrations in soil amended with biosolids are 0.53, 13.33 and 0.87 ng/kg dw, respectively. This is based on measured international biosolids concentrations, typical biosolids application rates and a soil bulk density of 1500 kilograms per cubic metre ($kg/m^3$) (EPHC 2009; Langdon et al. 2010).

# Environmental effects

## Effects on Aquatic Life

Chemicals in this group are expected to cause toxic effects at low concentrations in aquatic organisms across multiple trophic levels.

With the exception of 3-cyclotetradecenenone, chemicals in this evaluation are expected to have a common toxicity mode of action (MoA). Profiling with the OECD QSAR toolbox identified that these chemicals all possess narcosis or baseline toxicity (class 1) according to the Verhaar scheme, while OASIS and ECOSAR identified that the listed chemicals all have similar ecotoxicity characteristics of base surface narcotics/neutral organics.

Experimental data were identified for exaltone (acute fish, invertebrate and algae; chronic algae) and ambretone (acute invertebrate and algae; chronic algae). Toxicity of the

remaining chemicals in this group were read across from either exaltone or ambretone. These chemicals are suitable for read across due to:

- *Structural similarity*: all chemicals are macrocyclic ketones with ring sizes of C13-C17. Some chemicals in the group have unconjugated alkenes and/or β-methyl substitution.
- *Hydrophobicity*: chemicals in this group are neutral organics with similar log $K_{OW}$ values, decreasing from ambretone (6.4) to 3-methylcyclotridecanone (4.98).
- *MoA*: all chemicals share the same toxicity MoA
- *Degradants*: All chemicals are predicted to degrade by lactone formation, followed by ester hydrolysis and ultimate degradation by the fatty acid mechanism.

Choosing whether toxicity of the target chemical was read across from exaltone or ambretone was based on the log $K_{OW}$. Chemicals with log $K_{OW}$<5.6 (3-methylcyclotridecanone, cyclotetradecanone, exaltenone) were read across from exaltone (log $K_{OW}$ = 5.6), while those with log $K_{OW}$ 5.6–6.4 (3-methyl-4-cyclopentadecenone, globanone, muscone, civetone) were read across from ambretone (log $K_{OW}$ = 6.4). There is a direct relationship between toxicity and hydrophobicity up to the chemical's water solubility limit for neutral organics that exhibit base surface narcosis (US EPA 2017) and read across from chemicals with higher hydrophobicity overestimates the toxicity, providing a conservative estimate.

The toxicity mode of action (MoA) of 3-cyclotetradecenone is expected to differ from the other chemicals in the group. Ecotoxicity endpoints for 3-cyclotetradecenone were calculated using standard QSARs (ECOSAR 2.0) within the vinyl/allyl/propargyl ketones chemical class.

### Acute toxicity

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms across 3 trophic levels were retrieved from REACH registration dossiers for exaltone and ambretone (REACHb; REACHc). Endpoints for 3-cyclotetradecenone were calculated with standard QSARs (US EPA 2017).

| Taxon | Endpoint | Method |
|---|---|---|
| Fish | Exaltone and log $K_{OW}$<5.6 chemicals:<br>96 h LC50 = 0.17 mg/L | Experimental<br>*Cyprinus Carpio* (common carp)<br>semi-static, geometric mean measured concentrations<br>OECD TG 203 |
| | 3-Cyclotetradecenone:<br>96 h LC50 = 1.45 mg/L | Calculated<br>Vinyl/allyl/propargyl ketones class |
| Invertebrate | Exaltone and log $K_{OW}$<5.6 chemicals:<br>48 h EC50 = 0.18 mg/L | Experimental<br>*Daphnia magna* (water flea), mobility<br>static, geometric mean measured concentrations<br>OECD TG 202 |
| | Ambretone and log $K_{OW}$>5.6 chemicals:<br>48 h EC50 = 0.24 mg/L | Experimental<br>water flea, mobility<br>semi-static, measured concentrations (arithmetic mean), solubilised with DMF<br>OECD TG 202 |
| | 3-Cyclotetradecenone:<br>48 h LC50 = 0.40 mg/L | Calculated<br>Vinyl/allyl/propargyl ketones class |
| Algae | Exaltone and log $K_{OW}$<5.6 chemicals:<br>72 h EC50 > 0.17 mg/L | Experimental<br>*Raphidocelis subcapitata* (green algae)<br>growth<br>Static, measured concentrations (time weighted average)<br>OECD TG 201 |
| | Ambretone and log $K_{OW}$>5.6 chemicals:<br>72 h EC50 = 0.15 mg/L | Experimental<br>microalgae, yield<br>static, solubilised with DMF, measured concentrations<br>OECD TG 201 |
| | 3-Cyclotetradecenone:<br>96 h EC50 = 0.41 mg/L | Calculated<br>Vinyl/allyl/propargyl ketones class |

Muscone causes developmental and heart toxicity in zebra fish embryos in concentrations that exceed environmentally relevant concentrations. A study observed that *R*-muscone exposure leads to a decrease in the hatching rate and heart rate of zebrafish embryos (Li M et al. 2020). These adverse effects could be observed at concentrations of 2.38 (8% decrease in rate) and 1.1 mg/L (15% decrease in rate), respectively. These effects were more significant at higher concentrations of *R*-muscone. At concentrations of 7.2 mg/L there was a 40% decrease in hatching rate, and at concentrations of 47.9 mg/L there was a 64% decrease in heart rate.

### Chronic toxicity

The following measured no observed effect concentrations (NOEC) for model organisms across 3 trophic levels were retrieved from REACH registration dossiers for exaltone and ambretone (REACHb; REACHc):

| Taxon | Endpoint | Method |
|---|---|---|
| Algae | Exaltone and log $K_{OW}$<5.6 chemicals:<br>72 h NOEC = 0.17 mg/L | Experimental<br>*Raphidocelis subcapitata* (green algae)<br>growth<br>static<br>measured concentrations (time weighted average)<br>OECD TG 201 |
| | Ambretone and log $K_{OW}$>5.6 chemicals:<br>72 h NOEC = 0.015 mg/L | Experimental<br>microalgae, yield<br>static, solubilised with DMF, mean measured concentrations<br>OECD TG 201 |

### Predicted no-effect concentration (PNEC)

The PNEC for 3-methyl-4-cyclopentadecenone, ambretone, muscone, civetone and globanone in water is 0.15 µg/L.

The 72 h NOEC value for the exposure of ambretone to *Raphidocelis subcapitata* was used to derive the PNEC for these chemicals. An assessment factor of 100 was applied to the pivotal endpoint as there are reliable acute ecotoxicity data available over 2 trophic levels (invertebrates and algae) and chronic data for one taxon (algae) (EPHC 2009).

The PNEC for exaltone, exaltenone, cyclotetradecanone and 3-methylcyclotridecanone in water is 1.7 µg/L.

The 72 h NOEC value for the exposure of exaltone to *R. subcapitata* was used to derive the PNEC for these chemicals. An assessment factor of 100 was applied to the pivotal endpoint as there are reliable acute ecotoxicity data available over 3 trophic levels (fish, invertebrates and algae) and chronic data for one taxon (algae) (EPHC 2009).

The PNEC for 3-cyclotetradecenone in water is 0.40 µg/L.

The calculated 48 h LC50 value for daphnids was used to derive the PNEC for this chemical. An assessment factor of 1000 was applied to the pivotal endpoint due to minimal data being available and the chemical having a specific mode of action (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 and reliable read across, chemicals in this evaluation are categorised as Not Persistent.

## Bioaccumulation

### Exaltenone, 3-cyclotetradecenone, 3-methylcyclotridecanone, cyclotetradecanone

Not Bioaccumulative (Not B). Based on calculated BCFs in fish that do not exceed the domestic categorisation threshold, these chemicals are categorised as Not Bioaccumulative.

### Globanone, exaltone, muscone, civetone, ambretone, 3-methyl-4-cyclopentadecenone

Bioaccumulative (B). Based on calculated BCFs in fish that exceed the domestic categorisation threshold, these chemicals are categorised as Bioaccumulative.

## Toxicity

### Exaltone, ambretone

Toxic (T). Based on experimental acute ecotoxicity values below 1 mg/L and evidence of high chronic toxicity, exaltone and ambretone are categorised as Toxic.

### Exaltenone, 3-cyclotetradecenone, 3-methylcyclotridecanone, cyclotetradecanone, muscone, civetone, globanone, 3-methyl-4-cyclopentadecenone

Toxic (T). Based on reliable read across from available acute ecotoxicity values below 1 mg/L and evidence of high chronic toxicity, exaltenone, 3-cyclotetradecenone, 3 methyltridecanone, cyclotetradecanone, muscone, civetone, globanone and 3-methyl-4-cyclopentadecenone are categorised as Toxic.

# Environmental risk characterisation

Chemicals in this group are Not Persistent, variously Bioaccumulative or 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 chemicals in this group:

| Chemical | PEC (µg/L) | PNEC (µg/L) | RQ |
|---|---|---|---|
| Exaltone | 0.34 | 1.7 | 0.20 |
| Ambretone | 0.34 | 0.15 | 2.27 |
| Muscone | 0.034 | 0.15 | 0.23 |
| Civetone | 0.0034 | 0.15 | 0.02 |
| Globanone | 0.34 | 0.15 | 2.27 |
| Exaltenone | 0.00045 | 1.7 | 0.0003 |

The RQ values for ambretone and globanone are greater than one, indicating that the environmental concentrations of these chemicals may exceed levels that cause ecotoxic effects in exposed organisms in Australian surface waters. However, the PECs selected for these chemicals were conservative based on standard exposure modelling using Australian introduction volumes equal to the total reported introduction volume in the Asia Pacific region (up to 10 tonnes each annually). The total Australian introduction volume of these 2

chemicals is likely to be much lower than that of the APAC region. Therefore, these RQ values are likely to overestimate the risk posed by these chemicals. In addition, the calculated RQ values for these 2 chemicals are relatively marginal. Ambretone and globanone are; therefore, not expected to pose a significant risk to the environment.

Exaltone, muscone, civetone and exaltenone RQ values are less than one, indicating that they are unlikely to pose a significant risk to the environment.

For cyclotetradecanone, 3-methyl-4-cyclopentadecenone, 3-cyclotetradecenone, and 3-methylcyclotridecanone, RQs were not calculated. These chemicals are not expected to pose a significant risk to the environment, as none have hazard characteristics that are significantly different to chemicals accounted for in the table above, and all are likely to be used at relatively negligible volumes in Australia.

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 (OECD 1995). 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 introduction volume, STP or inland surface water monitoring data were available for chemicals in this evaluation. Use volume information provided by IFRA enabled conservative introduction volumes for 8 of the 11 chemicals to be deduced, provided information could not be used to predict domestic use volumes for the 3 highest volume chemicals (exaltone, globanone and ambretone). In lieu of these data, estimates based on standard modelling approaches using conservative introduction volume assumptions were used to calculate the RQ for these chemicals. It is expected that these assumptions overestimate domestic use volumes, and actual use volume data for Australia would significantly change aspects of the risk characterisation.
- There are insufficient experimental data to fully characterise the bioaccumulation potential of these chemicals. In lieu of these data, standard QSARs were used to calculate predicted bioconcentration factors. It is expected that chemicals in this evaluation will undergo biotransformation in biota, which is not adequately accounted for in calculations. The categorisation of some of these chemicals as bioaccumulative may change if experimental BCF values become available.
- There are insufficient ecotoxicity data available to fully characterise the toxicity characteristics of 9 of the 11 chemicals in this evaluation. In lieu of these data, read across or the results from standard QSARs were used to generate the RQ for these chemicals. The risk characterisation may significantly change if additional ecotoxicity data becomes available.

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