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RIFM fragrance ingredient safety assessment, 5-cyclotetradecen-1-one, 3-methyl-,(5E)-, CAS Registry Number 259854-70-1

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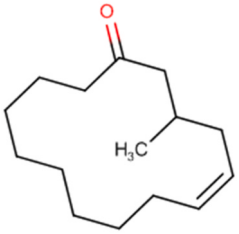
Name: 5-Cyclotetradecen-1-one, 3-methyl-, (5E)-



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CAS Registry Number: 259854-70-1
Additional CAS*: 259854-71-2
5-Cyclotetradecen-1-one, 3-methyl-, (5Z)- (no reported use)
*Included because the materials are isomers

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor

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BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

5-Cyclotetradecen-1-one, 3-methyl-, (5E)- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across material 3-methylcyclopentadecenone (CAS # 82356-51-2) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data provided 5-cyclotetradecen-1-one, 3-methyl-, (5E)- a No Expected Sensitization Induction Level (NESIL) of 10000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material; exposure to 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 5-cyclotetradecen-1-one, 3-methyl-, (5E)- was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2004d; RIFM, 2006a)
Repeated Dose Toxicity: NOAEL = 28.7 mg/kg/day. RIFM (2015)
Reproductive Toxicity: Developmental toxicity NOAEL: 250 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day. RIFM (2003)
Skin Sensitization: NESIL = 10000 μg/cm^2. RIFM (2006b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 75% (OECD 302C) RIFM (2004c)
Bioaccumulation: Screening-level: 1367 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.166 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.166 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0166 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

Chemical Name: 5-Cyclotetradecen-1-one, 3-methyl-, (5E)-	Chemical Name: 5-Cyclotetradecen-1-one, 3-methyl-, (5Z)-
CAS Registry Number: 259854-70-1	**CAS Registry Number:** 259854-71-2
Synonyms: (E)-3-Methylcyclotetradec-5-en-1-one; Cosmone; 5-Cyclotetradecen-1-one, 3-methyl-, (5E)-	**Synonyms:** (Z)-3-Methylcyclotetradec-5-en-1-one; Karmalone; 5-Cyclotetradecen-1-one, 3-methyl-, (5Z)-
Molecular Formula: $C_{15}H_{26}O$	**Molecular Formula:** $C_{15}H_{26}O$
Molecular Weight: 222.37	**Molecular Weight:** 222.37
RIFM Number: 6648	**RIFM Number:** 6648
Stereochemistry: E isomer specified. One chiral center present and 2 total enantiomers possible.	**Stereochemistry:** Z isomer specified. One chiral center present and 2 total enantiomers possible.

2. Physical data

CAS # 259854-70-1	CAS # 259854-71-2
Boiling Point: 322.85 °C (EPI Suite)	**Boiling Point:** Not Available
Flash Point: Not Available	**Flash Point:** Not Available
Log K_{OW}: 5.6 (RIFM, 2004e)	**Log K_{OW}:** 5.6 (RIFM, 2004e)
Melting Point: 44.10 °C (EPI Suite)	**Melting Point**: Not Available
Water Solubility: 1.08E+00 mg/L at 25 °C (WSKOW v1.42 in EPI Suite)	**Water Solubility:** Not Available
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.000404 mm Hg at 20 °C (EPI Suite v4.0)	**Vapor Pressure:** 0.000404 mm Hg at 20 °C (EPI Suite v4.0)

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UV Spectra: No significant absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** Not Available	**UV Spectra:** No significant absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model 3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.32% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0081 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0030 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford, 2015, 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford, 2015, 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	II

2 Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** 3-Methylcyclopentadecenone (CAS # 82356-51-2)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

8. Natural occurrence

5-Cyclotetradecen-1-one, 3-methyl-, (5E)- is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 06/05/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.082
2	Products applied to the axillae	0.23
3	Products applied to the face/body using fingertips	0.16
4	Products related to fine fragrances	4.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.1
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.25
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.33
5D	Baby cream, oil, talc	0.082
6	Products with oral and lip exposure	0.082
7	Products applied to the hair with some hand contact	0.16
8	Products with significant ano-genital exposure (tampon)	0.082
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.2
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.16
10B	Aerosol air freshener	1.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.082
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	41

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 5-cyclotetradecen-1-one, 3-methyl-,(5E)-, the basis was the subchronic reference dose of 0.29 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 10000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 5-cyclotetradecen-1-one, 3-methyl-, (5E)- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and TA102 were treated with 5-cyclotetradecen-1-one, 3-methyl-, (5E)- in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2004d). Under the conditions of the study, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- was not mutagenic in the Ames test.

The clastogenicity of 5-cyclotetradecen-1-one, 3-methyl-, (5E)- was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung cells were treated with 5-cyclotetradecen-1-one, 3-methyl-, (5E)- in ethanol at concentrations up to 2450 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 2006a). Under the conditions of the study, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/22/20.

11.1.2. Repeated dose toxicity

The MOE for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 5-cyclotetradecen-1-one, 3-methyl-, (5E)-. In a GLP and OECD 407-compliant subchronic study, 5 SPF-bred Wistar rats/sex/dose were administered 5-cyclotetradecen-1-one, 3-methyl-, (5E)- via diet at doses of 0, 1000, 3000, and 10000 ppm (equivalent to 89, 263, and 923 mg/kg/day in males and 86, 268, and 864 mg/kg/day in females; calculations according to the study report) for 28 days (RIFM, 2015). An additional 5 Wistar rats/sex/dose at 0 and 10000 ppm were maintained for 14 days after the treatment period as recovery groups. No mortality was observed throughout the study period. No treatment-related effects were observed in clinical signs, food consumption, or necropsy observations. Changes were seen in bodyweight gain, thyroid follicular cell hypertrophy, and blood parameters, but due to low severity, these effects were not considered toxicologically relevant. Incidence of hepatocellular hypertrophy was increased in males at the low dose and in both sexes at the mid and high doses (0/5 control males, 3/5 low-dose males, 5/5 mid-dose males, 5/5 high-dose males; 0/5 control females, 0/5 low-dose females, 1/5 mid-dose females, 4/5 high-dose females). The severity of the hepatocellular hypertrophy was minimal at the low dose and slight at the mid dose and high doses. Relative liver weights were increased in females at the low dose (9%) and in both sexes at the mid dose (22% in females, 20% in males) and high dose (39% in females, 41% in males). Absolute liver weights were also increased in females at the mid dose (25%) and in both sexes at the high dose (37% in females, 28% in males). Hepatocellular hypertrophy and increased absolute liver weights were reversed during the recovery period (no hepatocellular hypertrophy was seen after the recovery period; absolute liver weights were no longer statistically different from controls), but relative liver weights remained higher. No morphological evidence of liver damage was noted. Liver weight increases were considered to be non-adverse at the low dose but adverse at the mid and high doses based on the magnitudes. α-2u-Globulin nephropathy was seen in males at all doses, but this is specific to male rats and thus not relevant to human health. Based on higher liver weights in both sexes at 3000 and 10000 ppm, the NOAEL for this study was considered to be 1000 ppm (corresponding to 89 and 86 mg/kg/day for males and females, respectively).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 study (ECHA, 2012a). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 86/3, or 28.7 mg/kg/day.

Therefore, the 5-cyclotetradecen-1-one, 3-methyl-, (5E)- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 5-cyclotetradecen-1-one, 3-methyl-, (5E)- NOAEL in mg/kg/day by the total systemic exposure to 5-cyclotetradecen-1-one, 3-methyl-, (5E)-, 28.7/0.003, or 9567.

In addition, the total systemic exposure to 5-cyclotetradecen-1-one, 3-methyl-, (5E)- (3 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1.1. Derivation of subchronic reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic RfD of 0.29 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 28.7 mg/kg/day by the uncertainty factor, 100 = 0.29 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/20.

11.1.3. Reproductive toxicity

The MOE for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 5-cyclotetradecen-1-one, 3-methyl-, (5E)-. Read-across material 3-methylcyclopentadecenone (CAS # 82356-51-2; see Section VI) has sufficient reproductive toxicity data.

An OECD 415/GLP 1-generation reproduction toxicity study was conducted in Sprague Dawley rats. Groups of 28 rats/sex/dose were exposed to the test material 3-methylcyclopentadecenone at doses of 50, 250, or 1000 mg/kg via oral gavage. No treatment-related effects were seen for reproductive performance, fertility, offspring viability, growth, or development. In addition, postmortem findings showed no treatment-related effects on reproductive organs. Further, no treatment-related effects were seen in offspring growth and physical growth during lactation. A reduction in offspring viability was seen at the highest dose between days 7 and 14 of lactation, and that resulted in a slightly smaller mean litter size between days 14 and 21; this effect was not statically

significant but can be considered as adverse. In addition, total postnatal loss in the highest-dose group is 2.7 per litter compared to 1.6 per litter in the control group. Thus, taking a conservative approach, the NOAEL for developmental toxicity was considered to be 250 mg/kg/day, based on a reduction in offspring viability and total postnatal loss seen at the highest dose. The fertility NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003). **Therefore, the 5-cyclotetradecen-1-one, 3-methyl-,(5E)- MOE for the developmental toxicity endpoint can be calculated by dividing the 3-methylcyclopentadecenone NOAEL in mg/kg/day by the total systemic exposure to 5-cyclotetradecen-1-one, 3-methyl-,(5E)-, 250/0.003, or 83333.**

5-Cyclotetradecen-1-one, 3-methyl-, (5E)- MOE for the fertility endpoint can be calculated by dividing the 3-methylcyclopentadecenone NOAEL in mg/kg/day by the total systemic exposure to 5-cyclotetradecen-1-one, 3-methyl-, (5E)-, 1000/0.003, or 333333.

In addition, the total systemic exposure to 5-cyclotetradecen-1-one, 3-methyl-, (5E)- (3 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/20.

11.1.4. Skin sensitization

Based on the existing data, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is considered a sensitizer with defined NESIL of 10000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins directly as well as through metabolites and autoxidation products (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2; TIMES-SS v2.28.16). Contrary to the *in silico* prediction, 5-cyclotetradecen-1-one, 3-methyl-, (5E)-, was found to be negative in an *in vitro* DPRA and KeratinoSens tests but positive in the h-CLAT (RIFM, 2016a; RIFM, 2016b; RIFM, 2016c). In a murine local lymph node assay (LLNA), 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- was found to be sensitizing with an EC3 value of 16.4% (4100 μg/cm^2) (RIFM, 2004g). In a guinea pig open epicutaneous test (OET), 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- did not present reactions indicative of sensitization (RIFM, 2005a). In 3 Confirmation of No Induction in Humans tests (CNIHs) with 20% (10000 μg/cm^2), 10% (5000 μg/cm^2), and 6% (3000 μg/cm^2) of 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- in 3:1 diethyl phthalate:ethanol and dimethyl phthalate, no reaction indicative of sensitization was observed in any of the 97, 103, and 54 volunteers, respectively (RIFM, 2006b; RIFM, 2005b; RIFM, 2004f).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is a weak sensitizer with a WoE NESIL of 10000 μg/cm^2 (see Table 1).

Table 1
Data summary for 5-cyclotetradecen-1-one, 3-methyl-, (5E)-.

LLNA Weighted Mean EC3 Value [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c]
4100 [1]	Weak	10000	NA	NA	10000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic reference dose of 0.29 mg/kg/day.

Additional References: ECHA, 2012b

Literature Search and Risk Assessment Completed On: 05/08/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV absorbance spectra, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- in experimental models. UV absorption spectra indicate no absorption between 290 and 500 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance in the critical range, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available spectra indicate no significant absorbance in the range of 290–500 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to the lack of appropriate data. The exposure level for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 5-cyclotetradecen-1-one, 3-methyl-, (5E)-. Based on the Creme RIFM Model, the inhalation exposure is 0.0081 mg/day. This exposure is 58 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 5-cyclotetradecen-1-one, 3-methyl-, (5E)- was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating

the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 5-cyclotetradecen-1-one, 3-methyl-, (5E)- was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 5-cyclotetradecen-1-one, 3-methyl-, (5E)- as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on current VoU (2015), 5-cyclotetradecen-1-one, 3-methyl-, (5E)- presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. **RIFM, 2004b:** The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Biodegradation of 70% was observed after 28 days and 73% after 34 days.

RIFM, 2004c: The inherent biodegradability of the test material was determined by the manometric respirometry test according to the OECD 302C method. Under the conditions of the study, biodegradation of 75% was observed after 28 days.

11.2.3.2. Ecotoxicity. **RIFM, 2004a:** A 48-h *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value was reported to be 0.58 mg/L (95% CI: 0.53–0.68 mg/L) based on nominal concentrations.

RIFM, 2011: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. In order to assess the toxicity of the multi-component test material and following a non-GLP range finding test, water accommodated fractions (WAFs) with the loading rates of 0.32, 1.0, 3.2, 10, 32, and 100 mg/L were tested. The dispersions were stirred for 96 h to dissolve a maximum amount of the different components of the test material in the dispersion. Then, the dispersions were filtered through membrane filters (0.45 μm), and the undiluted filtrates were tested as WAFs. Based on the loading rate, the 72-h EC50 values were reported to be 67 mg/L (95% CI: 45–123 mg/L) for growth rate and 3.8 mg/L (95% CI: 3.1–4.6 mg/L) for yield. Based on time-weighted mean measured concentrations, 72-h EC50 values were reported to be 2.6 mg/L (95% CI: 2.2–3.2 mg/L) for growth rate and 0.55 mg/L (0.44–0.66 mg/L) for yield.

11.2.3.3. Other available data. 5-Cyclotetradecen-1-one, 3-methyl-, (5E)- has been registered for REACH with no additional information available at this time.

11.2.3.3.1. Risk assessment refinement. Since 5-Cyclotetradecen-1-one, 3-methyl-, (5E)- has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.6	5.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

*Combined Regional Volumes of use for both CAS #s.

The RIFM PNEC is 0.0166 μg/L. The revised PEC/PNECs for EU and NA are <1. Therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/08/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/21/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.221			1000000	0.000221	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.217	0.166	0.430	10000	0.0166	Neutral Organics

known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112977.

Appendix

Read-across Justification

Methods

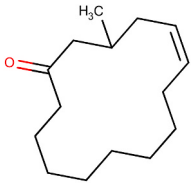
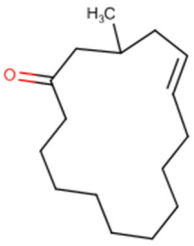
The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	5-Cyclotetradecen-1-one, 3-methyl-, (5E)-	3-Methylcyclopentadecenone
CAS No.	259854-70-1	82356-51-2
Structure		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
		
Similarity (Tanimoto Score)		1.00
Endpoint		Reproductive toxicity
Molecular Formula	$C_{15}H_{26}O$	$C_{16}H_{28}O$
Molecular Weight	222.372	238.415
Melting Point (°C, EPI Suite)	44.10	51.13
Boiling Point (°C, EPI Suite)	322.85	329.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.00E-01	6.25E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.08E+00	2.21E-01
Log K_{OW}	5.26	5.96
J_{max} (μg/cm^2/h, SAM)	0.16	0.03
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.84E+01	8.81E+01
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 4-cyclopentadecen-1-one (CAS # 35720-57-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 3-methylcyclopentadecenone (CAS # 82356-51-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 3-Methylcyclopentadecenone (CAS # 82356-51-2) was used as a read-across analog for the target material 4-cyclopentadecen-1-one (CAS # 35720-57-1) for the reproductive endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a family of musk lactones (macrolactones).
  - o The key difference between the target material and the read-across analog is that the read-across analog is a mixture of materials with a varying position of the vinylene group. The structure shown represents 1 of the possibilities. In contrast, the target material's structure has been identified with a vinylene group at the 5 position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no alerts for the read-across analog and the target material. Therefore, the i*n silico* alerts are consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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