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RIFM fragrance ingredient safety assessment, 3-methyl-5-cyclopentadecen-1-one, CAS registry number 63314-79-4

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Additional CAS Numbers*:
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*Included because the materials are isomers

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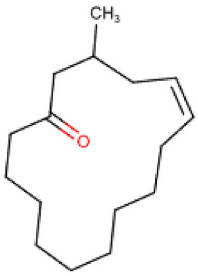

Abbreviation/Definition List:

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

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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.

3-Methyl-5-cyclopentadecen-1-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3-methyl-5-cyclopentadecen-1-one is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analogs 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2 and 259854-70-1) provided 3-methyl-5-cyclopentadecen-1-one 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/visible (UV/Vis) spectra; 3-methyl-5-cyclopentadecen-1-one 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 II material, and the exposure to 3-methyl-5-cyclopentadecen-1-one is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 3-methyl-5-cyclopentadecen-1-one 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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2005c; RIFM, 1995c; RIFM, 2004a; RIFM, 2006a)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM (1996)
Reproductive Toxicity: Developmental toxicity NOAEL: 250 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day.	RIFM (2003a)
Skin Sensitization: NESIL = 10000 μg/cm^2.	RIFM (2006b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 81% (OECD 301F)	RIFM (2009c)
Bioaccumulation:	
Screening-level: 2883 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 28-day fathead minnow NOEC: 0.00098 mg/L	(RIFM, 2003c)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 28-day Fathead minnow NOEC: 0.00098 mg/L	RIFM (2003c)
RIFM PNEC is: 0.098 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1	

1. Identification

Chemical Name: 3-Methyl-5-cyclopentadecen-1-one	Chemical Name: 3-Methylcyclopentadecenone
CAS Registry Number: 63314-79-4	**CAS Registry Number:** 82356-51-2
Synonyms: 3-Methylcyclopentadec-5-en-1-one; Muscenone dextro; 5-Cyclopentadecen-1-one, 3-methyl; 3-Methyl-5-cyclopentadecen-1-one	**Synonyms:** Muscenone Delta; 3-Methylcyclopentadecenone
Molecular Formula: $C_{16}H_{28}O$	**Molecular Formula:** $C_{16}H_{28}O$
Molecular Weight: 236.39	**Molecular Weight:** 238.41

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RIFM Number: 7001 **Stereochemistry:** One stereocenter and 2 possible stereoisomers	**RIFM Number:** 6444 **Stereochemistry:** One stereocenter and 2 possible stereoisomers

2. Physical data

CAS # 63314-79-4	CAS # 82356-51-2
Boiling Point: 610 ± 2 K(337 O+/ 0 2 °C) at 97.2 kPa (RIFM, 2010)	**Boiling Point:** 316.8–339.8 °C at 988.6 mbar (RIFM, 1992a)
Flash Point: 160 °C (Globally Harmonized System [GHS]), 173 +/0 2 °C (RIFM, 2010), greater than 100 °C (RIFM, 2009a)	**Flash Point:** 160 °C (GHS), 160 °C (RIFM, 1992a)
Log K_{OW}: 6.32 (RIFM, 2010), 6.57 (RIFM, 2009c), 6.57 (RIFM, 2009b), 6.57 (RIFM, 2009c)	**Log K_{OW}:** Log10 Pow > 4.88 (RIFM, 1994)
Melting Point: <253.0 ± 0.5 K(<-20.0 ± 0.5 °C) at 96.9 kPa (RIFM, 2010)	**Melting Point**: less than 253 ± 0.5 K (RIFM, 1995a), less than 253 ± 0.5 K (RIFM, 2008)
Water Solubility: 100 μg/L (RIFM, 2009b); low, 840 μg/L in algal medium (RIFM, 2009a); 100 μg/L at 20 °C, pH 7 (RIFM, 2009c)	**Water Solubility:** Not Available
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.000164 mm Hg at 20 °C (EPI Suite v4.0)	**Vapor Pressure:** 0.0000916 mm Hg at 20 °C (EPI Suite v4.0)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: Not Available	**Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0.4)***

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.36% (RIFM, 2019)
2. **Inhalation Exposure****: 0.00024 mg/kg/day or 0.018 mg/day (RIFM, 2019)
3. **Total Systemic Exposure*****: 0.0043 mg/kg/day (RIFM, 2019)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

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

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
II*	III	III

*See Appendix below for additional details.

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 5-Cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 25984-70-1)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

3-Methyl-5-cyclopentadecen-1-one and 3-methylcyclopentadecenone are 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

3-Methyl-5-cyclopentadecen-1-one has not been pre-registered; no dossier available as of 04/22/21. Available for 3-methylcyclopentadecenone; accessed 10/06/20 (ECHA, 2015).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-methyl-5-cyclopentadecen-1-one 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)	0.15
2	Products applied to the axillae	0.23
3	Products applied to the face/body using fingertips	4.6
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	1.1
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	1.1
5D	Baby cream, oil, talc	0.037
6	Products with oral and lip exposure	0.15
7	Products applied to the hair with some hand contact	2.5
8		0.37

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Products with significant ano-genital exposure (tampon)	
9	Products with body and hand exposure, primarily rinse-off (bar soap)	8.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	2.7
10B	Aerosol air freshener	28
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.37
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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 3-methyl-5-cyclopentadecen-1-one, the basis was the reference dose of 2.50 mg/kg/day, a predicted skin absorption value of 10%, 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, 3-methyl-5-cyclopentadecen-1-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3-methyl-5-cyclopentadecen-1-one was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity without metabolic activation, and positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity with metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of additional material (isomer) 3-methylcyclopentadecenone 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3-methylcyclopentadecenone 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, 2005a). Under the conditions of the study, 3-methylcyclopentadecenone was not mutagenic in the Ames test.

The clastogenicity of additional material (isomer) 3-methylcyclopentadecenone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with 3-methylcyclopentadecenone in DMSO at concentrations up to 2280 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, 1995c). Under the conditions of the study, 3-methylcyclopentadecenone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, 3-methylcyclopentadecenone does not present a concern for genotoxic potential.

Additional References: RIFM, 1991, RIFM, 2001.

Literature Search and Risk Assessment Completed On: 10/06/20.

11.1.2. Repeated dose toxicity

The MOE for 3-methyl-5-cyclopentadecen-1-one is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-methyl-5-cyclopentadecen-1-one. Additional material (isomer) 3-methylcyclopentadecenone (CAS # 82356-51-2) has sufficient data to support the repeated dose endpoint. In a GLP-compliant subchronic study, 6 Crl:CD(SD)BR rats/sex/dose were administered 3-methylcyclopentadecenone via gavage at doses of 0, 250, 500, and 1000 mg/kg/day for 28 days. An additional 6 Crl:CD(SD)BR rats/sex/dose were maintained as recovery groups at 0 and 1000 mg/kg/day for 2 weeks after the treatment period. Parameters examined included body weights, food consumption, ophthalmoscopy, hematology, urinalysis, necropsy, organ weights, microscopic examinations, and gross lesions. No mortality was observed during the treatment period. No treatment-related changes were discovered in clinical signs, body weights, bodyweight gains, food consumption, ophthalmoscopy, urinalysis, organ weights, or macroscopic or microscopic findings. Activated partial prothrombin time (PTT) levels were increased in males at the mid and high doses (21% and 34%, respectively). Fibrinogen levels were increased in males at the high dose (15%). Both effects were reversed during the recovery period. Cholesterol levels were increased in females at all doses and in males at the high dose; however, this effect was not dose-related. Since no toxicologically relevant, treatment-related effects were observed up to the highest dose, the NOAEL for this study was considered to be 1000 mg/kg/day (RIFM, 1996).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3, or 333 mg/kg/day.

Therefore, the 3-methylcyclopentadecenone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-methylcyclopentadecenone NOAEL in mg/kg/day by the total systemic exposure to 3-methylcyclopentadecenone, 333/0.0043, or 77442.

In addition, the total systemic exposure to 3-methylcyclopentadecenone (4.3 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

*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: 10/06/20.

11.1.3. Reproductive toxicity

The MOE for 3-methyl-5-cyclopentadecen-1-one 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 3-methyl-5-cyclopentadecen-1-one. Additional material (isomer) 3-methylcyclopentadecenone (CAS # 82356-51-2) 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. Fertility NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003a). **Therefore, the 3-methyl-5-cyclopentadecen-1-one 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 3-methyl-5-cyclopentadecen-1-one, 250/0.0043, or 58140.**

3-Methyl-5-cyclopentadecen-1-one MOE for the fertility endpoint can be calculated by dividing the 3-methylcyclopentadecenone NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-5-cyclopentadecen-1-one, 1000/0.0043, or 232558.

In addition, the total systemic exposure to 3-methyl-5-cyclopentadecen-1-one (4.3 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

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 reference dose of 2.50 mg/kg/day.

Derivation of reference dose (RfD)

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for 3-methyl-5-cyclopentadecen-1-one was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 250 mg/kg/day by the uncertainty factor, 100 = 2.50 mg/kg/day.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 25984-70-1), 3-methyl-5-cyclopentadecen-1-one is considered a skin sensitizer with a defined NESIL of 10000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 3-methyl-5-cyclopentadecen-1-one. Based on the existing data and read-across material 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 25984-70-1; see Section VI), 3-methyl-5-cyclopentadecen-1-one is considered a skin sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins directly as well as through metabolites and autoxidation products (Roberts, 2007; OECD Toolbox v4.2; TIMES-SS v2.28.16). 3-Methyl-5-cyclopentadecen-1-one was found to be positive in an *in vitro* Direct peptide reactivity assay (DPRA) (RIFM, 2016b). 3-Methylcyclopentadecenone was found to be negative in KeratinoSens and positive the in human cell line activation test (h-CLAT) (RIFM, 2016d; RIFM, 2017b). The read-across material, 5-cyclotetradecen-1-one, 3-methyl-, (5E)-, was found to be negative in an *in vitro* DPRA, and KeratinoSens but positive in the human cell line activation test (h-CLAT) (RIFM, 2016a; RIFM, 2016c; RIFM, 2016e). In a murine local lymph node assay (LLNA), read-across material 5-cyclotetradecen-1-one, 3-methyl-, (5Z)- was found to be sensitizing with an EC3 value of 16.4% (4100 μg/cm^2) (RIFM, 2004c). In a guinea pig maximization test, 3-methylcyclopentadecenone did not lead to skin sensitization reactions (RIFM, 2000). In a guinea pig Buehler test, 3-methylcyclopentadecenone did not present reactions indicative of sensitization (RIFM, 1999b). In a guinea pig open epicuataneous test (OET), read-across material 5-cyclotetradecen-1-one, 3-methyl-, (5Z)- did not present reactions indicative of sensitization (RIFM, 2005a). In 2 Confirmation of No Induction in Humans tests (CNIHs) with 10% (5000 μg/cm^2) and 20% (10000 μg/cm^2) 3-methylcyclopentadecenone in diethyl phthalate (DEP), no reactions indicative of sensitization were observed in any of the 102 and 108 volunteers, respectively, (RIFM, 1995b; RIFM, 1999a). Similarly, in 3 CNIHs with 20% (10000 μg/cm^2), 10% (5000 μg/cm^2), and 6% (3000 μg/cm^2) of read-across material 5-cyclotetradecen-1-one, 3-methyl-, (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, 2004b).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and data from read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)-, 3-methyl-5-cyclopentadecen-1-one is a weak sensitizer with a WoE NESIL of 10000 μg/cm^2 (see Table 1). 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 reference dose of 2.50 mg/kg/day.

Additional References: RIFM, 1992b; RIFM, 2003b; RIFM, 2017a.

Literature Search and Risk Assessment Completed On: 05/14/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3-methyl-5-cyclopentadecen-1-one 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 3-methyl-5-cyclopentadecen-1-one in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 3-methyl-5-cyclopentadecen-1-one does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in

Table 1
Data summary for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- as read-across materials for 3-methyl-5-cyclopentadecen-1-one.

LLNA Weighted Mean EC3 Value μg/cm^2 (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] μg/cm^2
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.

the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/06/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to the lack of appropriate data. The exposure level for 3-methyl-5-cyclopentadecen-1-one 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 3-methyl-5-cyclopentadecen-1-one. Based on the Creme RIFM Model, the inhalation exposure is 0.018 mg/day. This exposure is 26.1 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 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 3-methyl-5-cyclopentadecen-1-one was performed following the RIFM Environmental Framework (Salvito, 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, 3-methyl-5-cyclopentadecen-1-one 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) identified 3-methyl-5-cyclopentadecen-1-one 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). 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 the current Volume of Use (2015), 3-methyl-5-cyclopentadecen-1-one presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. **Biodegradation**

RIFM, 2009c: The biodegradation of 5-cyclopentadecen-1-one, 3-methyl- was investigated over a 28-day period in a manometric respirometry test according to OECD guideline 301F. Under the conditions of the study, biodegradation of 81% was observed.

Ecotoxicity

RIFM, 2009a: An algae growth inhibition study was conducted according to the OECD 201 method. Nominal loadings of the test material were 100, 50, 25, 12.5, and 6.25 mg/L. The algae were exposed under static conditions in tightly closed culture vessels for 72 h. The EC10 values for growth rate and yield were calculated to be 0.754 mg/L. The 72-h ErC50 (growth rate) was greater than 0.715 mg/L (mean measured concentration). The 72-h NOEC for growth rate and yield was 0.371 mg/L (mean measured concentration).

RIFM, 2009b: A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. Based on the time-weighted means (TWM) concentrations, the 21-day NOEC for adult growth, age of first brood, and the intrinsic rate were reported to be 0.0898 mg/L. The reproduction EC50 was reported to be 0.253 mg/L based on TWM.

RIFM, 1995e: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 based on nominal concentration was reported to be 0.39 mg/L.

RIFM, 1995d: A 96-h fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method under static conditions, and the LC50 based on the arithmetic mean measured concentration was reported to be 0.22 mg/L.

RIFM, 1995f: An algae growth inhibition study was conducted according to the OECD 201 method. The 72-h NOEC, based on the nominal concentration, was reported to be > 30 mg/L.

RIFM, 2003c: A fish early-life stage toxicity test was conducted on freshly hatched larvae of the Fathead minnow, following the OECD 210 guidelines. The NOECs based on nominal test concentration were considered to be 0.002 mg/L and 0.00098 mg/L based on the mean measured test concentration of the centrifuged test media. These low measured test concentrations were considered to be due to the low solubility of the test material in water and the associated problems with dosing materials of low solubility using auxiliary solvents and possible losses due to volatility.

Other available data

3-Methyl-5-cyclopentadecen-1-one (CAS # 82356-51-5) has been registered under REACH, and the following data are available (ECHA, 2015):

A fish short-term toxicity test on embryo and sac-fry stages were conducted according to the OECD 212 method. The 10-day EC10 based on the arithmetic mean measured concentration was 0.18 mg/L.

11.2.3. Risk assessment refinement

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.0577			1000000	5.78E-05	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.084	0.067	0.209	10000	0.0067	Neutral organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.22		0.00098	10	0.098	
Daphnia		0.253	0.0898			
Algae		0.715	0.371			

Framework: Salvito, 2002).

Exposure	Europe	North America
Log K_{ow} Used	6.3	6.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional Volume of Use.

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

The RIFM PNEC is 0.098 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 10/07/20.

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 04/22/21.

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 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.2021.112427.

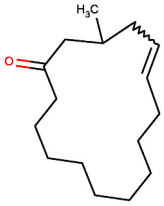
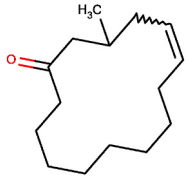
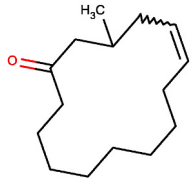
Appendix

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, 2017).

- 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	Read-across Material
Principal Name	3-Methyl-5-cyclopentadecen-1-one	5-Cyclotetradecen-1-one, 3-methyl-,(5E)-	5-Cyclotetradecen-1-one, 3-methyl-, (5Z)-
CAS No.	63314-79-4	259854-70-1	259854-71-2
Structure			
Similarity (Tanimoto Score)		0.96	0.96
Endpoint		• Skin sensitization	• Skin sensitization
Molecular Formula	$C_{16}H_{28}O$	$C_{15}H_{26}O$	$C_{15}H_{26}O$
Molecular Weight	236.40	222.37	222.37
Melting Point (°C, EPI Suite)	51.94	44.10	44.10
Boiling Point (°C, EPI Suite)	336.72	322.85	322.85
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.04	0.10	0.10
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.35	1.08	1.08
Log K_{OW}	5.75	5.26	5.26
J_{max} (μg/cm^2/h, SAM)	0.05	0.16	0.16
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	77.41	58.36	58.36
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones	Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones	Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 3-methyl-5-cyclopentadecen-1-one (CAS # 63314-79-4). 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, 5-cyclotetradecen-1-one, 3-methyl-,(5E)- (CAS # 259854-70-1) and 5-cyclotetradecen-1-one, 3-methyl-, (5Z)- (CAS # 259854-71-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 5-Cyclotetradecen-1-one, 3-methyl-,(5E)- (CAS # 259854-70-1) and 5-cyclotetradecen-1-one, 3-methyl-, (5Z)- (CAS # 259854-71-2) were used as read-across analogs for the target material 3-methyl-5-cyclopentadecen-1-one (CAS # 63314-79-4) for the skin sensitization endpoint.
  - o The target material and the read-across analogs are structurally similar and belong to the structural class of ketones.
  - o The key difference between the target material and the read-across analogs is that the macrocycle in the read-across analogs is 1 carbon smaller than that in the target material. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analogs is indicated by the Tanimoto score presented in the table above. The differences in the structures that are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - o The physical–chemical properties of the target material and the read-across analogs 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 analogs.
  - o The target material and the read-across analogs have an alert for undergoing nucleophilic addition to carbon-hetero double bonds in carbonyl compounds by the protein Binding (OASIS v1.1 QSAR Toolbox v4.2) *in silico* model for skin sensitization. A chemical with this structural alert could interact with proteins via nucleophilic addition to ketones. Simple ketones are usually too weakly reactive to sensitize unless log P is very high. This is taken into account in the TIMES-SS model by defining a threshold of log K_{ow} >4 for weak skin sensitizers. Both the target and the read-across analogs are simpler ketones with log K_{ow} >4. Based on the existing data and read-across to 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 25984-70-1), 3-methyl-5-cyclopentadecen-1-one is considered a skin sensitizer with a defined NESIL of 10000 μg/cm^2. Therefore, based on the structural similarity between the target material and the read-across analogs as well as the data for the read-across analogs, the *in silico* alerts on these materials are superseded by the 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.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? No.
Q23. Aromatic? No.
Q24. Monocarbocyclic with simple substituents? No.
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No.
Q26. Monocycloalkanone* or a bicyclo compound? Yes. Class II (Class intermediate)

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