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RIFM fragrance ingredient safety assessment, 3-methyl-1-cyclopentadecanone, CAS Registry Number 541-91-3

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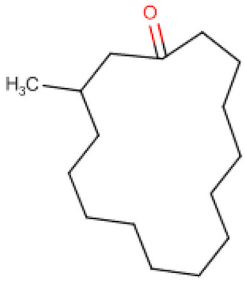

Abbreviation/Definition List:

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

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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.

3-Methyl-1-cyclopentadecanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on 3-methyl-1-cyclopentadecanone and read-across analog 5-cyclotetradecen-1-one, 3-methyl-, (5E)- (CAS # 259854-70-1) show that 3-methyl-1-cyclopentadecanone is not expected to be genotoxic. Data on 3-methyl-1-cyclopentadecanone provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on analog cyclopentadecanone (CAS # 502-72-7) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from analogs 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 259854-70-1) provided a NESIL of 10000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV/Vis spectra; 3-methyl-1-cyclopentadecanone is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material; exposure is below the TTC (0.47 mg/day). 3-Methyl-1-cyclopentadecanone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2004c; RIFM, 2006a)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	Oh (1997)
Reproductive Toxicity: Developmental toxicity: 1000 mg/kg/day. Fertility: 1000 mg/kg/day.	(ECHA REACH Dossier: Cyclopentadecanone; ECHA, 2018)
Skin Sensitization: NESIL = 10000 μg/cm^2.	RIFM, (2006b)
Phototoxicity/Photoallergenicity: Not phototoxic/not expected to be photoallergenic.	(UV/Vis Spectra, RIFM Database; Ohkoshi, 1981; RIFM, 1978; Ogoshi, 1980)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 80% (OECD 301F)	RIFM (2009)
Bioaccumulation: Screening-level: 3996 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.044 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, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.044 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0044 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** 3-Methyl-1-cyclopentadecanone
2. **CAS Registry Number:** 541-91-3
3. **Synonyms:** Cyclopentadecanone, 3-methyl-; 3-Methyl-cyclopentadecanone; Methylexaltone; d,l-Muscone; 3-ﾒﾁﾙｼｸﾛﾍﾟﾝﾀﾃﾞｶﾝ; Methyl cyclopentadecanone; Muscone; 3-Methyl-1-cyclopentadecanone
4. **Molecular Formula:** $C_{16}H_{30}O$
5. **Molecular Weight:** 238.41
6. **RIFM Number:** 867

7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers

2. Physical data

1. **Boiling Point:** >300 °C (Fragrance Materials Association [FMA]), 595±2 K (322±2 °C) at 97.3 kPa (RIFM, 2004d), 335.11 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA), >93 °C (Globally Harmonized System), 155±2 °C (RIFM, 2004d)
3. **Log K_{OW}:** 5.96 (EPI Suite), 6.056 ± 0.079 at 25 ± 1 °C, mean pH 5.647 (RIFM, 2016e)
4. **Melting Point**: 261±0.5 K (−12±0.5 °C) (RIFM, 2004d), 51.13 °C (EPI Suite)
5. **Water Solubility:** 0.2213 mg/L (EPI Suite)
6. **Specific Gravity:** 0.92 (FMA)
7. **Vapor Pressure:** 0.00025 mm Hg at 20 °C (EPI Suite v4.0), 0.001 mm Hg at 20 °C (FMA), 0.000469 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L • mol-1 • cm-1).
9. **Appearance/Organoleptic:** White or colorless or opaque crystalline mass (supercooled, it is colorless, viscous liquid, with very soft, sweet, and extremely tenacious musky odor) (Arctander, 1969)

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 v3.0.3)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.26% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0095 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0032 mg/kg/day (RIFM, 2019)

*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	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** 5-Cyclotetradecen-1-one, 3-methyl-, (5E)- (CAS # 259854-70-1)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Cyclopentadecanone (CAS # 502-72-7)
   d. **Skin Sensitization:** 5-Cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 259854-70-1)
   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-1-cyclopentadecanone 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 04/19/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-methyl-1-cyclopentadecanone 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)	0.77
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	0.37
6	Products with oral and lip exposure	2.5
7	Products applied to the hair with some hand contact	8.8
8	Products with significant ano-genital exposure (tampon)	0.37
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)	3.0
10B	Aerosol air freshener	30
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-1-cyclopentadecanone, the basis was the reference dose of 3.33 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 and use levels, 3-methyl-1-cyclopentadecanone does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3-methyl-1-cyclopentadecanone 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-methyl-1-cyclopentadecanone 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, 2004c). Under the conditions of the study, 3-methyl-1-cyclopentadecanone was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 3-methyl-1-cyclopentadecanone; however, read-across can be made to 5-cyclotetradecen-1-one, 3-methyl-,(5E)- (CAS # 259854-70-1; see Section VI).

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, and this can be extended to 3-methyl-1-cyclopentadecanone.

Based on the data available, 5-cyclotetradecen-1-one, 3-methyl-,(5E)- does not present a concern for genotoxic potential, and this can be extended to 3-methyl-1-cyclopentadecanone.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/15/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. The repeated dose toxicity data on 3-methyl-1-cyclopentadecanone are sufficient for the repeated dose toxicity endpoint. In a non-guideline and non-GLP subchronic toxicity study, groups of 10 Sprague Dawley rats/sex/dose were administered 3-methyl-1-cyclopentadecanone via gavage at doses of 0 (vehicle: Tween 80, 0.1%), 10, 100, or 1000 mg/kg/day for 28 days. Observations included mortality, clinical signs, body weight, food consumption, water consumption, urinalysis, hematology, serum biochemistry, organ weights, gross necropsy, and histopathology. No mortality occurred throughout the study period. No treatment-related effects were observed in clinical signs, urinalysis, hematology, or serum biochemistry. Liver weights were significantly increased in both sexes at the highest dose; however, in the absence of correlated blood chemistry data and histopathological findings, these effects were not considered to be toxicologically relevant. In the absence of toxicologically relevant treatment-related effects seen up to the highest dose, the NOAEL was determined to be 1000 mg/kg/day (Oh, 1997).

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-methyl-1-cyclopentadecanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-methyl-1-cyclopentadecanone NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-1-cyclopentadecanone, 333/0.0032, or 104063.

In addition, the total systemic exposure to 3-methyl-1-cyclopentadecanone (3.2 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.

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, 2020) and a reference dose of 3.33 mg/kg/day.

11.1.3. 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-1-cyclopentadecanone was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 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: 03/24/20.

11.1.4. Reproductive toxicity

The MOE for 3-methyl-1-cyclopentadecanone is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.4.1. Risk assessment. There are no reproductive toxicity data on 3-methyl-1-cyclopentadecanone. Read-across material cyclopentadecanone (CAS # 502-72-7; see Section VI) has sufficient data to support the reproductive toxicity endpoint. In an OECD 422/GLP study, groups of 10 Crl:WI(Han) rats/sex/dose were administered cyclopentadecanone via gavage at doses of 0 (corn oil), 100, 300, and 1000 mg/kg bw/day cyclopentadecanone for at least 28 days for males or at least 40 days for females. There were no treatment-related mortalities. Treatment-related alterations in clinical signs, including hunched posture, uncoordinated movements, piloerection, and/or tremors, were reported among mid- and high-dose group animals. One high-dose group female was euthanized moribund on day 23 post coitum due to difficulties with parturition. This was not considered to be treatment-related. There were no adverse effects on fertility or development of the pups among treated animals. Thus, the NOAEL for fertility and developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2018).

Therefore, the 3-methyl-1-cyclopentadecanone MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the cyclopentadecanone NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-1-cyclopentadecanone, 1000/0.0032, or 312500.

In addition, the total systemic exposure to 3-methyl-1-cyclopentadecanone (3.2 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/14/20.

11.1.5. Skin sensitization

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

11.1.5.1. Risk assessment. Limited skin sensitization studies are available for 3-methyl-1-cyclopentadecanone. Based on the existing data and read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 259854-70-1; see Section VI), 3-methyl-1-cyclopentadecanone is considered a skin sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 3-Methyl-1-cyclopentadecanone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens test but positive in the human cell line activation test (h-CLAT) (RIFM, 2016b; RIFM, 2017a; RIFM, 2017b). The read-across material, 5-cyclotetradecen-1-one, 3-methyl-, (5E)-, was found to be negative in an *in vitro* DPRA, KeratinoSens test and positive in an h-CLAT (RIFM, 2016a; RIFM, 2016c; RIFM, 2016d). 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, 2004b). In a guinea pig open epicutaneous test, read-across material 5-cyclotetradecen-1-one, 3-methyl-, (5Z)- did not present reactions indicative of sensitization (RIFM, 2005a). In a human maximization test, no skin sensitization reactions were observed with 3-methyl-1-cyclopentadecanone at 30% (20700 μg/cm^2) (RIFM, 1976). Additionally, 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 read-across material 5-cyclotetradecen-1-one, 3-methyl-, (5Z)- in 3:1 diethyl phthalate:ethanol and dimethyl phthalate, no reactions indicative of sensitization were observed in any of the 97, 103, and 54 volunteers, respectively (RIFM, 2006b; RIFM, 2005b; RIFM, 2004a).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and data on the read-across material 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)-, 3-methyl-1-cyclopentadecanone is a 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, 2020) and a reference dose of 3.33 mg/kg/day.

Additional References: RIFM, 2005a.

Literature Search and Risk Assessment Completed On: 04/14/20.

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

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	20700	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.

11.1.6. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, 3-methyl-1-cyclopentadecanone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6.1. Risk assessment. The UV/Vis spectra for 3-methyl-1-cyclopentadecanone indicate no significant absorbance between 290 and 700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark of concern (1000 L mol^{-1} • cm^{-1}) for phototoxic effects (Henry, 2009). Phototoxic potential of 3-methyl-1-cyclopentadecanone was evaluated in guinea pigs at concentrations of 10%, 20%, and 50% (RIFM, 1978; Ohkoshi, 1981; Ogoshi, 1980) and in rabbits at 10% (RIFM, 1978). There was no evidence of phototoxic activity in these studies. Based on the UV/Vis spectra and *in vivo* studies, 3-methyl-1-cyclopentadecanone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.7. UV spectra analysis

The UV/Vis spectra for 3-methyl-1-cyclopentadecanone indicate minor absorbance between 290 and 700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark of concern (1000 L mol^{-1} • cm^{-1}) for phototoxic effects (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/15/20.

11.1.8. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-methyl-1-cyclopentadecanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.8.1. Risk assessment. There are insufficient inhalation data available on 3-methyl-1-cyclopentadecanone. Based on the Creme RIFM Model, the inhalation exposure is 0.0095 mg/day. This exposure is 49.5 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: Gilbert (1996); Jacob (2002).

Literature Search and Risk Assessment Completed On: 04/14/20.

12. Environmental endpoint summary

12.1. Screening-level assessment

A screening-level risk assessment of 3-methyl-1-cyclopentadecanone 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-1-cyclopentadecanone 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-1-cyclopentadecanone as not possibly persistent but 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.

12.1.1. Risk assessment

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

12.1.2. Key studies

12.1.2.1. Biodegradation. RIFM, 2009: The ready biodegradability of the test material was conducted using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 80% was observed after 28 days.

Ecotoxicity: No data available.

12.1.2.2. Other available data. 3-Methyl-1-cyclopentadecanone has been registered for REACH with no additional data available at this time.

A robust summary of available environmental data has been published by Salvito et al. (Salvito, 2011).

12.1.2.3. 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 Framework: Salvito, 2002).**

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.056	6.056
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0044 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 volumes of use.

Literature Search and Risk Assessment Completed On: 04/15/20.

13. 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.095			1000000	0.000095	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.054	0.044	0.15	10000	0.0044	Neutral Organics

- **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 04/19/21.

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.2021.112622.

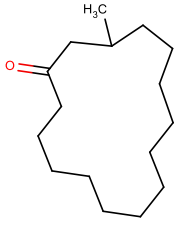
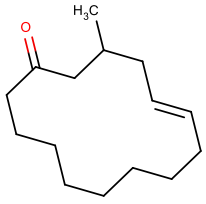
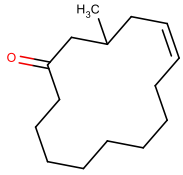
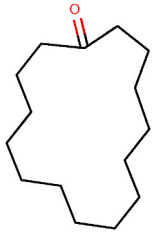
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization 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).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	3-Methyl-1-cyclopentadecanone	5-Cyclotetradecen-1-one, 3-methyl-,(5E)-	5-Cyclotetradecen-1-one, 3-methyl-, (5Z)-	Cyclopentadecanone
CAS No.	541-91-3	259854-70-1	259854-71-2	502-72-7
Structure				
Similarity (Tanimoto Score)		0.54	0.54	0.78
Endpoint		• Genotoxicity • Skin sensitization	• Skin sensitization	• Reproductive toxicity
Molecular Formula	$C_{16}H_{30}O$	$C_{15}H_{26}O$	$C_{15}H_{26}O$	$C_{15}H_{28}O$
Molecular Weight	238.41	222.37	222.37	224.39
	51.13	44.10	44.10	63

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Melting Point (°C, EPI Suite)				
Boiling Point (°C, EPI Suite)	329.00	322.85	322.85	326.12
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.06	0.10	0.10	0.056
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.22	1.08	1.08	0.60
Log K_{OW}	5.96	5.26	5.26	5.55
J_{max} (μg/cm^2/h, SAM)	0.03	0.16	0.16	0.094
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	88.05	58.36	58.36	66.37
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	No alert found		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found		
Oncologic Classification	Not classified	Not classified		
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group			Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)			Non-toxicant (low reliability)
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	See Supplemental Data 4

Summary

There are insufficient toxicity data on 3-methyl-1-cyclopentadecanone (CAS # 541-91-3). 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), 5-cyclotetradecen-1-one, 3-methyl-, (5Z)- (CAS # 259854-71-2), and cyclopentadecanone (CAS # 502-72-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 5-Cyclotetradecen-1-one, 3-methyl-, (5E)- (CAS # 259854-70-1) was used as a read-across analog for the target material 3-methyl-1-cyclopentadecanone (CAS # 541-91-3) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of ketones.
  - o The key difference between the target material and the read-across analog is that the read-across has an additional double bond at the fifth position. Moreover, the target material has a slightly larger cyclic ring than the read-across. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score presented in the table above. The differences in the structures which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.

- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- 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-1-cyclopentadecanone (CAS # 541-91-3) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of ketones.
  - The key difference between the target material and the read-across analog is that the read-across has an additional double bond at the fifth position. Moreover, the target material has a slightly larger cyclic ring than the read-across. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - 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-1-cyclopentadecanone 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.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Cyclopentadecanone (CAS # 502-72-7) was used as a read-across analog for the target material 3-methyl-1-cyclopentadecanone (CAS # 541-91-3) for the reproductive toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of ketones.
  - The key difference between the target material and the read-across analog is the presence of a methyl substituent at the third position in the target, which is missing in the read-across analog. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score presented in the table above. The differences in the structures responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - 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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