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RIFM fragrance ingredient safety assessment, cyclopentadecanone, CAS Registry Number 502-72-7

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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

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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.

Cyclopentadecanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclopentadecanone is not genotoxic. Data on cyclopentadecanone 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 cyclopentadecanone 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 data and ultraviolet/visible (UV/Vis) spectra; cyclopentadecanone 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 cyclopentadecanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; cyclopentadecanone 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, 1999a; RIFM, 1999b)
Repeated Dose Toxicity: NOAEL = 3.33 mg/kg/day.	(ECHA REACH Dossier: Cyclopentadecanone; ECHA, 2018)
Reproductive Toxicity: Developmental NOAEL: 1000 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day.	(ECHA REACH Dossier: Cyclopentadecanone; ECHA, 2018)
Skin Sensitization: NESIL = 10000 μg/cm^2.	RIFM (2006)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 1986c; RIFM, 1986d)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 70% (OECD 301 B)	(ECHA REACH Dossier: Cyclopentadecanone; ECHA, 2018)
Bioaccumulation: Screening-level: 2119 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 96-h Fish LC50 (OECD 203): 0.17 mg/L	(ECHA REACH Dossier: Cyclopentadecanone; ECHA, 2018)

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: 96-h Fish LC50 (OECD 203): 0.17 mg/L	(ECHA REACH Dossier: Cyclopentadecanone; ECHA, 2018)

RIFM PNEC is: 0.17 μg/L

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

1. Identification

1. **Chemical Name:** Cyclopentadecanone
2. **CAS Registry Number:** 502-72-7
3. **Synonyms:** Exaltone; Normuscone; ｼｸﾛﾍﾟﾝﾀﾃﾞｶﾉﾝ; Musk 15; Cyclopentadecanone
4. **Molecular Formula:** $C_{15}H_{28}O$
5. **Molecular Weight:** 224.38
6. **RIFM Number:** 619

7. **Stereochemistry:** One possible stereoisomer.

2. Physical data

1. **Boiling Point:** 120 at 0.3 mm Hg (Fragrance Materials Association [FMA]), 326.12 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log K_{OW}**: 5.55 (EPI Suite)
4. **Melting Point**: 61 °C (FMA), 44.55 °C (EPI Suite)
5. **Water Solubility:** 0.5989 mg/L (EPI Suite)
6. **Specific Gravity:** 0.897 (FMA)
7. **Vapor Pressure:** 0.000222 mm Hg at 20 °C (EPI Suite v4.0), 0.000418 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:** Colorless or white crystal needles that have a powerful musky odor

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.26% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.011 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0055 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:** 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 and 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

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 03/16/20 (ECHA, 2018).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 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)	0.0054
2	Products applied to the axillae	0.10
3	Products applied to the face/body using fingertips	0.086
4	Products related to fine fragrances	2.7
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.47
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.12
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.20
5D	Baby cream, oil, talc	0.041
6	Products with oral and lip exposure	0.0054
7	Products applied to the hair with some hand contact	0.39
8	Products with significant ano-genital exposure (tampon)	0.041
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.49
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.0054
10B	Aerosol air freshener	0.11
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.041
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	4.5

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 cyclopentadecanone, the basis was the reference dose of 0.033 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, cyclopentadecanone does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 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, TA1538, and *Escherichia coli* strain WP2uvrA were treated with 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, 1999a). Under the conditions of the study, cyclopentadecanone was not mutagenic in the Ames test.

The clastogenicity of cyclopentadecanone 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 cyclopentadecanone in DMSO at concentrations up to 500 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, 1999b). Under the conditions of the study, cyclopentadecanone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, cyclopentadecanone does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for cyclopentadecanone 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 cyclopentadecanone. In an OECD 422 and GLP-compliant study, groups of 10 Crl:WI(Han) rats/sex/dose were administered cyclopentadecanone via gavage at doses of 0, 100, 300, and 1000 mg/kg/day. Males were treated for approximately 31 days, whereas females were treated for 42–54 days. In the highest dose group, 1 female died due to complications during parturition; this was not considered to be treatment related. No treatment-related effects were observed in water consumption, hematology, clinical biochemistry, behavior, or immunology. Clinical signs, including hunched posture, uncoordinated movements, piloerection, and tremors, were noted in both sexes in the mid- and high-dose groups. Additionally, slight lethargy and ptosis were noted in 2 females in the high-dose group. Increases in body weight, bodyweight gain, and food consumption in high-dose females were statistically significant but within the normal range of biological variation, so they were not considered to be adverse. Food consumption increase was not considered adverse, even though it was slightly higher in males of the mid-dose group; it lacked a dose-dependence or any correlated body weight changes. Dose-dependent increases in absolute and relative liver weights were observed in males at all doses and in high-dose females with correlating hepatocellular hypertrophy. Absolute and relative weights of the thyroid gland increased dose-dependently in males, but this effect was only statistically significant in the highest dose group, with correlating thyroid gland enlargement and follicular cell hypertrophy. Absolute and relative kidney weights were increased in high-dose group males with increased hyaline droplet accumulation; however, no information on immunohistochemistry or Heidenhain's hematoxylin staining was available. This was accompanied by kidney discoloration in 9/10 animals in the same group. The hyaline droplet accumulation was attributed to α-2u-globulin nephropathy, which is a sex- and species-specific effect and not considered a human health concern. In the high-dose females, vacuolation of zona glomerulosa and slight thymus lymphoid atrophy were also reported. Based on the reported clinical signs at doses >100 mg/kg/day, dose-dependent increases in relative liver weight, hepatocellular hypertrophy, thyroid weight, and thyroid follicular cell hypertrophy at all doses, a NOAEL could not be determined. Thus, the lowest dose of 100 mg/kg/day was considered as the LOAEL (ECHA, 2018).

A safety factor of 10 is applied when deriving a NOAEL from a LOAEL (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the NOAEL is calculated by 100/10, or 10 mg/kg/day.

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 10/3, or 3.33 mg/kg/day.

Therefore, the cyclopentadecanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the cyclopentadecanone NOAEL in mg/kg/day by the total systemic exposure to cyclopentadecanone, 3.33/0.0055, or 605.5.

In addition, the total systemic exposure to cyclopentadecanone (5.5 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.

Derivation of 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, 2020) and a reference dose of 0.033 mg/kg/day.

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 cyclopentadecanone was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 3.33 mg/kg/day by the uncertainty factor, 100 = 0.033 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.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on cyclopentadecanone. 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 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 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. The NOAEL for fertility and developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2018).

Therefore, the 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 cyclopentadecanone, 1000/0.0055, or 181818.

In addition, the total systemic exposure to cyclopentadecanone (5.5 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.

11.1.4. Skin sensitization

Based on the existing data and read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2 and 259854-70-1), cyclopentadecanone 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 cyclopentadecanone. Based on the existing data and read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2 and 25984-70-1); see Section VI), cyclopentadecanone is considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts, 2007; OECD Toolbox v4.2). Cyclopentadecanone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens test and positive in the human Cell Line Activation Test (h-CLAT) (RIFM, 2016a; RIFM, 2017; RIFM, 2018). The read-across material, 5-cyclotetradecen-1-one, 3-methyl-, (5E)-, was found to be negative in an *in vitro* DPRA and KeratinoSens test and positive in the h-CLAT (RIFM, 2016b; RIFM, 2016c; RIFM, 2016d). In a guinea pig open epicutaneous test (OET), cyclopentadecanone did not present reactions indicative of sensitization (RIFM, 1986a). However, in a Freund's complete adjuvant test (FCAT) with cyclopentadecanone, reactions indicative of sensitization were observed (RIFM, 1986b). 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 OET, 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 cyclopentadecanone at 10% (6900 μg/cm^2) (RIFM, 1975). Additionally, in a Confirmation of No Induction in Humans (CNIH) test at 2% cyclopentadecanone in dimethyl phthalate (DMP), no reactions indicative of sensitization were observed in any of the 54 volunteers (RIFM, 1972). 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 (DEP:EtOH), DEP:EtOH, and DMP, respectively, no reaction indicative of sensitization was observed in any of the 97, 103, and 54 volunteers, respectively (RIFM, 2006; RIFM, 2005b; RIFM, 2004a).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and data on the read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)-, 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 0.033 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 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	6900	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.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available *in vivo* data, cyclopentadecanone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). The existing *in vivo* data demonstrate that cyclopentadecanone does not present a concern for phototoxicity/photoallergenicity (RIFM, 1978; RIFM, 1986c; RIFM, 1986d). Based on the available *in vivo* data and the lack of absorbance in the critical range, cyclopentadecanone 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 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: Ohkoshi (1981); Ogoshi (1980).

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

11.1.6. Local respiratory toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on cyclopentadecanone. Based on the Creme RIFM Model, the inhalation exposure is 0.011 mg/day. This exposure is 42.7 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: Pinching (1974); Gilbert (1996).

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 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, 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 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.

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1997: The inherent biodegradability of the test material was evaluated using the modified SCAS test and sealed vessel test according to the OECD 302A guideline. Biodegradation of 66.7% was observed after 28 days.

RIFM, 1998: The ultimate biodegradability of the test material was evaluated using the CO_2 production test according to the OECD 301 B guideline. Biodegradation of 56.7% was observed after 28 days.

Ecotoxicity: No data available.

11.2.2.1.2. Other available data. Cyclopentadecanone has been registered for REACH with following additional data available at this time (ECHA, 2018):

The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 70% was observed after 28 days.

The fish (*Cyprinus carpio*) acute toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value based on the mean measured concentration was reported to be 0.17 mg/L (95% CI: 0.088–0.22 mg/L).

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on the mean measured concentration was reported to be 0.18 mg/L (95% CI: 0.15–0.20 mg/L).

The growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on the time-weighted average for growth rate was reported to be 0.17 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 Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.55	5.55
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.17 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: 04/13/20.

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 05/13/21.

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)**	0.25			1,000,000	0.00025	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.121	0.095	0.274	10,000	0.0095	Neutral Organics
Tier 3: Measured Data Including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.17			1000	0.17	
Daphnia		0.18				
Algae		>0.17				

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.2021.112474.

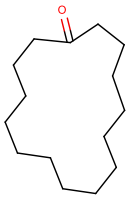
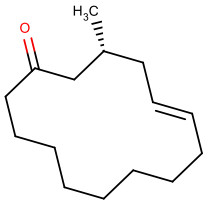
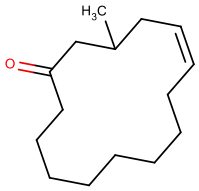
Appendix

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
Principal Name	Cyclopentadecanone	5-Cyclotetradecen-1-one, 3-methyl-,(5E)-	5-Cyclotetradecen-1-one, 3-methyl-, (5Z)-
CAS No.	502-72-7	259854-70-1	259854-71-2
Structure			
Similarity (Tanimoto Score)		0.42	0.42
Endpoint		• Skin sensitization	• Skin sensitization
Molecular Formula	$C_{15}H_{28}O$	$C_{15}H_{26}O$	$C_{15}H_{26}O$
Molecular Weight	224.39	222.37	222.37
Melting Point (°C, EPI Suite)	63.00	44.10	44.10
Boiling Point (°C, EPI Suite)	326.12	322.85	322.85
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.06	0.10	0.10
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.60	1.08	1.08
Log K_{OW}	5.55	5.26	5.26
Jmax (mg/cm^2/h, SAM)	0.09	0.16	0.16
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	66.37	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 cyclopentadecanone (CAS # 502-72-7). 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-1-cyclopentadecanone (CAS # 541-91-3) for the skin sensitization 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.
  - 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.

- 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), 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.

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