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RIFM fragrance ingredient safety assessment, 4-cyclopentadecen-1-one, CAS Registry Number 35720-57-1

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Name: 4-Cyclopentadecen-1-one CAS Registry Number: 35720-57-1
Additional CAS*: 14595-54-1
4-Cyclopentadecen-1-one, (Z)-*Included because the materials are isomers

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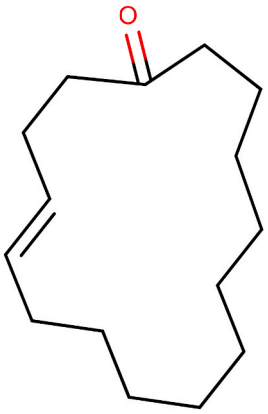

Abbreviation/Definition List:

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

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

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

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

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

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

4-Cyclopentadecen-1-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 5-cyclotetradecen-1-one, 3-methyl-,(5E)- (CAS # 259854-70-1) show that 4-cyclopentadecen-1-one is not expected to be genotoxic and provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data from analog 3-methylcyclopentadecenone (CAS # 82356-51-2) provide a calculated MOE >100 for the reproductive toxicity endpoint. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material, and exposure to 4-cyclopentadecen-1-one is below TTC (0.47 mg/day). Data from read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 259854-70-1) provide 4-cyclopentadecen-1-one a NESIL of 10000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 4-cyclopentadecen-1-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-cyclopentadecen-1-one 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, 2016i; RIFM, 2006a)
Repeated Dose Toxicity: NOAEL = 28.7 mg/kg/day.	RIFM (2015)
Reproductive Toxicity: Developmental toxicity NOAEL: 250 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day.	RIFM (2003)
Skin Sensitization: NESIL = 10000 μg/cm^2.	RIFM (2006b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)	
Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 99.8% (DOC) (OECD 302A) for CAS # 14595-54-1	RIFM (1999a)
Bioaccumulation:	
Screening-level: 1528 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 0.144 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint:: 48-h *Daphnia magna* LC50: 0.144 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0144 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

Chemical Name: 4-Cyclopentadecen-1-one	Chemical Name: 4-Cyclopentadecen-1-one, (Z)-
CAS Registry Number: 35720-57-1	**CAS Registry Number:** 14595-54-1 **Synonyms:** *cis*-4-Cyclopentadecen-1-one; *cis*-4-Cyclopentadecenone; 4-

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Chemical Name: 4-Cyclopentadecen-1-one	Chemical Name: 4-Cyclopentadecen-1-one, (Z)-
Synonyms: Cyclopentadec-4-en-1-one; Musk Z 4; 4-Cyclopentadecen-1-one	Cyclopentadecen-1-one, (4Z)-; 4-Cyclopentadecen-1-one, (Z)-; Exaltenone; Musk Z-4
Molecular Formula: $C_{15}H_{26}O$	**Molecular Formula:** $C_{15}H_{26}O$
Molecular Weight: 222.37	**Molecular Weight:** 222.37
RIFM Number: 5679	**RIFM Number:** 6400
Stereochemistry: No stereocenter possible	**Stereochemistry:** One geometric center, E and Z isomers possible

2. Physical data

CAS # 35720-57-1	CAS # 14595-54-1
Boiling Point: 327.82 °C (EPI Suite)	**Boiling Point:** 284–286 °C corrected to normal atmospheric pressure (1013 hPa) under nitrogen (RIFM, 2016d); 327.82 °C (EPI Suite)
Flash Point: Not Available	**Flash Point:** >100 °C (Globally Harmonized System); >100 °C (Firmenich); 152.0 °C at 1013 hPa (corrected to normal atmospheric pressure and rounded down to nearest multiple of 0.5 °C) (RIFM, 2016h)
Log K_{OW}: 5.33 (EPI Suite)	**Log K_{OW}:** 5.33 (calculated) (EPI Suite); 5.154 ± 0.002 at 25 ± 1 °C, pH 5.410 (RIFM, 2016f)
Melting Point: 45.37 °C (EPI Suite)	**Melting Point**: −38 to 23 °C at 1009 hPa under nitrogen (RIFM, 2016d); 45.37 °C (EPI Suite)
Water Solubility: 0.9369 mg/L (EPI Suite)	**Water Solubility:** 2.91 mg/L at 20 ± 0.5 °C, pH 6 with preincubation at 30 ± 0.5 °C (RIFM, 2016g); 0.9369 (calculated) (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.000303 mm Hg at 20 °C (EPI Suite v4.0), 0.000565 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.13 (interpolated), 0.19 (interpolated) and 1.07 (extrapolated) Pa at 20, 25, and 50 °C, respectively (RIFM, 2016e); 0.000303 mm Hg at 20 °C (EPI Suite v4.0); 0.000565 mm Hg at 25 °C (EPI Suite)
UV Spectra: No significant absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: Not Available	**Appearance/Organoleptic:** Colorless to pale yellow organic liquid (ECHA, 2017a)

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 v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance**: 0.32% (RIFM, 2019b)
2. **Inhalation Exposure***: 0.00052 mg/kg/day or 0.031 mg/day (RIFM, 2019b)
3. **Total Systemic Exposure****: 0.0039 mg/kg/day (RIFM, 2019a)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:

a. **Genotoxicity:** 5-Cyclotetradecen-1-one, 3-methyl-,(5E)- (CAS # 259854-70-1)
b. **Repeated Dose Toxicity:** 5-Cyclotetradecen-1-one, 3-methyl-,(5E)- (CAS # 259854-70-1)
c. **Reproductive Toxicity:** 3-Methylcyclopentadecenone (CAS # 82356-51-2)
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.

7.1. Additional References

None.

8. Natural occurrence

4-Cyclopentadecen-1-one is not reported to occur in foods by the VCF*.

4-Cyclopentadecen-1-one, (Z)- 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

4-Cyclopentadecen-1-one (CAS # 35720-57-1) has been pre-registered for 2010; no dossier available as of 04/24/20; 4-cyclopentadecen-1-one, (Z)- (CAS # 14595-54-1) is available; dossier accessed on 04/24/20 (ECHA, 2017a).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4-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)	0.0053
2	Products applied to the axillae	0.23
3	Products applied to the face/body using fingertips	0.18
4	Products related to fine fragrances	4.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.1
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.11
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.21
5D	Baby cream, oil, talc	0.035
6	Products with oral and lip exposure	0.0053
7	Products applied to the hair with some hand contact	0.30
8	Products with significant ano-genital exposure (tampon)	0.035
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.60
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.0053
10B	Aerosol air freshener	1.5
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.035
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	60

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 4-cyclopentadecen-1-one, the basis was the reference dose of 0.29 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 10000 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

Based on the current existing data, 4-cyclopentadecen-1-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 4-cyclopentadecen-1-one was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an equi-reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of structural isomer 4-cyclopentadecen-1-one, (Z)- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 4-cyclopentadecen-1-one, (Z)- in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Small increases in the mean number of revertant colonies were observed in strains TA98 and TA1537 in the absence of an S9 activation system at 5000 μg/plate and 0.5 μg/plate, respectively, when using the preincubation method (RIFM, 2016i). These increases were not considered biologically relevant due to the lack of a dose-response relationship, lack of reproducibility, and only a 1.9-fold maximum increase being observed. Furthermore, the increase observed at 0.5 μg/plate in TA1537 was not observed at higher concentrations. Under the conditions of the study, cyclopentadecen-1-one, (Z)- was not mutagenic in the Ames test (RIFM, 2016i).

There are no studies assessing the clastogenic activity of 4-cyclopentadecen-1-one; 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 4-cyclopentadecen-1-one.

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 4-cyclopentadecen-1-one.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/14/20.

11.1.2. Repeated dose toxicity

The MOE for 4-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 4-cyclopentadecen-1-one. Read-across material 5-cyclotetradecen-1-one, 3-methyl-,(5E)- (CAS # 259854-70-1; see Section VI) has sufficient data to support the repeated dose endpoint. In a GLP and OECD 407-compliant subchronic study, 5 SPF-bred Wistar rats/sex/dose were administered 5-cyclotetradecen-1-one, 3-methyl-,(5E)- via diet at doses of 0, 1000, 3000, and 10000 ppm (equivalent to 89, 263, and 923 mg/kg/day in males; 86, 268, 864 mg/kg/day in females; calculations according to the study report) for 28 days (RIFM, 2015). An additional 5 Wistar rats/sex/dose at 0 and 10000 ppm were maintained for 14 days after the treatment period as recovery groups. No mortality was observed throughout the study period. No treatment-related effects were observed in clinical signs, food consumption, or necropsy observations. Changes were seen in bodyweight gain, thyroid follicular cell hypertrophy, and blood parameters, but due to low severity, these effects were not considered toxicologically relevant. Liver effects included hepatocellular hypertrophy in females at the low dose and in both sexes at the mid and high doses, correlated with increased relative liver weights at the same dose levels. Absolute liver weights were also increased in females at the mid dose and in both sexes at the high dose. Hepatocellular hypertrophy and increased absolute liver weights were reversed during the recovery period, but relative liver weights remained higher. α-2μ-globulin nephropathy was seen in males at all doses but is specific to male rats and thus not relevant to human health. Based on higher liver

weights in both sexes at 3000 and 10000 ppm, the NOAEL for this study was considered to be 1000 ppm (corresponding to 89 and 86 mg/kg/day for males and females, respectively).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 study (ECHA, 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 86/3, or 28.7 mg/kg/day.

Therefore, the 4-cyclopentadecen-1-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the 5-cyclotetradecen-1-one, 3-methyl-,(5E)- NOAEL in mg/kg/day by the total systemic exposure to 4-cyclopentadecen-1-one, 28.7/0.0039, or 9567.

In addition, the total systemic exposure to 4-cyclopentadecen-1-one (3.9 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

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 0.29 mg/kg/day.

Derivation of reference dose (RfD)

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for 4-cyclopentadecen-1-one was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 28.7 mg/kg/day by the uncertainty factor, 100 = 0.29 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/28/20.

11.1.3. Reproductive toxicity

The MOE for 4-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 4-cyclopentadecen-1-one. Read-across material 3-methylcyclopentadecenone (CAS # 82356-51-2; see Section VI) has sufficient reproductive toxicity data.

An OECD 415/GLP 1-generation reproduction toxicity study was conducted in Sprague Dawley rats. Groups of 28 rats/sex/dose were exposed to the test material 3-methylcyclopentadecenone at doses of 50, 250, or 1000 mg/kg via oral gavage. No treatment-related effects were seen for reproductive performance, fertility, offspring viability, growth, or development. In addition, post-mortem 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, 2003). Therefore, the 4-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 4-cyclopentadecen-1-one, 250/0.0039, or 64103.

The 4-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 4-cyclopentadecen-1-one, 1000/0.0039, or 256410.

In addition, the total systemic exposure to 4-cyclopentadecen-1-one (3.9 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across materials 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- (CAS # 259854-71-2, 259854-70-1), 4-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 4-cyclopentadecen-1-one. 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); see Section VI), 4-cyclopentadecen-1-one is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly, as well as through the metabolites and autoxidation products (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2; TIMES-SS v2.28.1). 4-Cyclopentadecen-1-one was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) and the human cell line activation test (h-CLAT), but negative in the KeratinoSens test (RIFM, 2016b; RIFM, 2017; RIFM, 2018a). The read-across material 5-cyclotetradecen-1-one, 3-methyl-, (5E)-, was found to be negative in an *in vitro* DPRA and KeratinoSens and positive in the h-CLAT (RIFM, 2016a; RIFM, 2016b; RIFM, 2016c). A guinea pig maximization test with 4-cyclopentadecen-1-one, (Z)- did not present reactions indicative of sensitization (ECHA, 2017a; RIFM, 1998a). 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 Confirmation of No Induction in Humans tests (CNIHs) at 10% (5000 μg/cm^2) 4-cyclopentadecen-1-one, (Z)- in DEP and 2% (1101 μg/cm^2) 4-cyclopentadecen-1-one, (Z)- in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 106 and 51 volunteers, respectively (RIFM, 1998b; RIFM, 1998c). 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, 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)-, 4-cyclopentadecen-1-one 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, 2020b) and a reference dose of 0.29 mg/kg/day.

Additional References: None.

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 4-cyclopentadecen-1-one would not be expected to present a concern for phototoxicity or

Table 1
Data summary for 5-cyclotetradecen-1-one, 3-methyl-, (5E)- and (5Z)- as read-across material for 4-cyclopentadecen-1-one.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[2] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
4100 [1]	Weak	10000	NA	NA	10000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from CNIH test or HMT.
[3]WoE NESIL limited to 2 significant figures.

photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 4-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 et al., 2009). Based on the lack of absorbance, 4-cyclopentadecen-1-one does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-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 4-cyclopentadecen-1-one. Based on the Creme RIFM Model, the inhalation exposure is 0.031 mg/day. This exposure is 15.2 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

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

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-cyclopentadecen-1-one was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 4-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) did not identify 4-cyclopentadecen-1-one as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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), 4-cyclopentadecen-1-one presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **For CAS # 14595-54-1**

RIFM, 1999b: The inherent biodegradability of the test material was evaluated using the modified SCAS test according to the OECD 302A guidelines. Removal of the test material at 20 mg C/L in activated sludge ranged from 96.0% to 101.8%, with an average removal of 99.8% over a 28-day test period.

RIFM, 1999a: The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guidelines. Biodegradation of 83.9% (CO_2 evolution) was observed after 28 days.

11.2.2.1.2. Ecotoxicity. **For CAS # 14595-54-1**

RIFM, 2018b: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. Due to the low water solubility of the test material, it was dosed via a passive dosing system. The 48-h EC50 value based on measured concentrations was reported to be 0682 mg/L (95% CI: 0.627–0.753 mg/L).

11.2.2.1.3. Other available data. 4-Cyclopentadecen-1-one (CAS # 14595-54-1) has been registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

Since 4-Cyclopentadecen-1-one has passed the screening criteria,

measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.14	5.14
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 material is < 1. No further assessment is necessary.

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

The RIFM PNEC is 0.0144 µg/L. The revised PEC/PNECs for EU and NA are <1. Therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/11/20.

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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112561.

Appendix

Read-across Justification

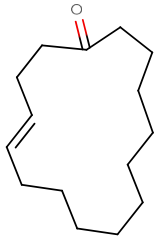
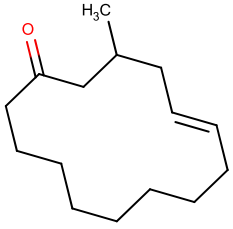
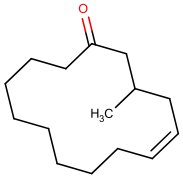
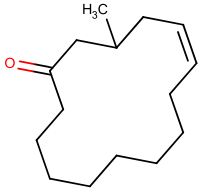
Methods

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.56			1000000	0.0056	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.186	0.144	0.382	10000	0.0144	Neutral Organics

are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

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

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	4-Cyclopentadecen-1-one	5-Cyclotetradecen-1-one, 3-methyl-,(5E)-	5-Cyclotetradecen-1-one, 3-methyl-, (5Z)-	3-Methylcyclopentadecenone
CAS No.	35720-57-1	259854-70-1	259854-71-2	82356-51-2
Structure				
Similarity (Tanimoto Score)		0.65	0.65	0.65
Endpoint		Skin sensitization Genotoxicity Repeated dose toxicity	Skin sensitization	Reproductive toxicity
Molecular Formula	$C_{15}H_{26}O$	$C_{15}H_{26}O$	$C_{15}H_{26}O$	$C_{16}H_{30}O$
Molecular Weight	222.372	222.372	222.372	238.415
Melting Point (°C, EPI Suite)	45.37	44.10	44.10	51.13
Boiling Point (°C, EPI Suite)	327.82	322.85	322.85	329.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.53E-02	1.00E-01	1.00E-01	6.25E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	9.37E-01	1.08E+00	1.08E+00	2.21E-01
Log K_{OW}	5.33	5.26	5.26	5.96
J_{max} (μg/cm^2/h, SAM)	0.14	0.16	0.16	0.03
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.84E+01	5.84E+01	5.84E+01	8.81E+01
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		
Repeated Dose Toxicity				
Repeated Dose (HESS)	Cuprizone (Hepatotoxicity) Alert	Not categorized		
Reproductive Toxicity				

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
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)
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 4-cyclopentadecen-1-one (CAS # 35720-57-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 3-methylcyclopentadecenone (CAS # 82356-51-2), 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) was used as a read-across analog for the target material 4-cyclopentadecen-1-one (CAS # 35720-57-1) for the genotoxicity and repeated dose toxicity endpoints.
  - 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 analog has a methyl substitution at the third position, which is missing in the target material. Moreover, the double bond in the target material is at the fourth position, whereas the read-across analog has a double bond at the fifth position. 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 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 4-cyclopentadecen-1-one (CAS # 35720-57-1) for the skin sensitization endpoint.
  - The target material and the read-across analogs 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 analogs have a methyl substitution at the third position, which is missing in the target material. Moreover, the double bond in the target material is at the fourth position, whereas the read-across analogs have a double bond at the fifth position. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analogs 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 analogs.
  - 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 material 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), 4-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.

- The target material and the read-across analogs 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 analogs and the target material.

- 3-Methylcyclopentadecenone (CAS # 82356-51-2) was used as a read-across analog for the target material 4-cyclopentadecen-1-one (CAS # 35720-57-1) for the reproductive 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 that the read-across analog has a methyl substitution at the third position, which is missing in the target material. Moreover, the double bond in the target material is at the fourth position, whereas the read-across analog has a double bond at the fifth position. 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 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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