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RIFM fragrance ingredient safety assessment, oxacyclohexadecen-2-one, CAS registry number 34902-57-3

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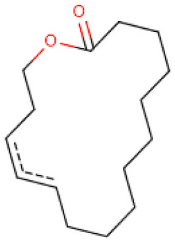

Name: Oxacyclohexadecen-2-one
CAS Registry Number: 34902-57-3
Additional CAS Numbers*:
111879-80-2 Oxacyclohexadec-12-en-2-one, (12E)-99219-32-6 Oxacyclohexadec-13-en-2-one, (13E)- No Reported Use
111879-79-9 Oxacyclohexadec-12-en-2-one, (12Z)- No Reported Use
111879-81-3 Oxacyclohexadec-13-en-2-one, (13Z)- No Reported Use
*Included because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
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., 2021)
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 Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable 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.

(*continued on next page*)

(*continued*)

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

Oxacyclohexadecen-2-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that oxacyclohexadecen-2-one is not genotoxic. Data on oxacyclohexadecen-2-one provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided oxacyclohexadecen-2-one a No Expected Sensitization Induction Level (NESIL) of 7500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; oxacyclohexadecen-2-one is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to oxacyclohexadecen-2-one is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; oxacyclohexadecen-2-one was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2005a; RIFM, 2005c)
Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day. RIFM, (1998b)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day. (RIFM, 2003c; RIFM, 2003b)
Skin Sensitization: NESIL = 7500 μg/cm^2. RIFM (2016)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 95% (OECD 301F) RIFM, (1996b)

Bioaccumulation:
Screening-level: 5338 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Critical Ecotoxicity Endpoint: Fish (chronic NOEC): 0.027 mg/L RIFM, (2003a)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: Fish (chronic NOEC): 0.027 mg/L RIFM, (2003a)
RIFM PNEC is: 2.7 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1

1. Identification

Chemical Name: Oxacyclohexadecen-2-one	Chemical Name: Oxacyclohexadec-12-en-2-one, (12E)-	Chemical Name: Oxacyclohexadec-13-en-2-one, (13E)-	Chemical Name: Oxacyclohexadec-12-en-2-one, (12Z)-	Chemical Name: Oxacyclohexadec-13-en-2-one, (13Z)-
CAS Registry Number: 34902-57-3	**CAS Registry Number:** 111879-80-2	**CAS Registry Number:** 99219-32-6	**CAS Registry Number:**111879-79-9	**CAS Registry Number:**111879-81-3
Synonyms: Habanolide; Cyclopentadecenolide; ｵｷｻｼｸﾛﾍｷｻﾃﾞｾﾝ-2-ｵﾝ; ｵｷｼｼｸﾛﾍｷｻﾃﾞｶ-12-ｴﾝ-2-ｵﾝとｵｷｼｼｸﾛﾍｷｻﾃﾞｶ-13-ｴﾝ-2-ｵﾝの混合物; Globalide; Reaction mass of: (E)-oxacyclohexadec-12-en-2-one, (E)-oxacyclohexadec-13-en-2-one, (Z)-oxacyclohexadec-(12)-en-2-one and (Z)-oxacyclohexadec-(13)-en-2-one; A mixture of: (E)-oxacyclohexadec-12-en-2-one, (E)-oxacyclohexadec-13-en-2-one, (Z)-oxacyclohexadec-(12)-en-2-one, and (Z)-oxacyclohexadec-(13)-en-2-one; E/Z-Oxacyclohexadec-12/13-en-2-one; Oxacyclohexadecen-2-one	**Synonyms:** E-Oxacyclohexadec-12-en-2-one; Oxacyclohexadec-12-en-2-one, (12E)-	**Synonyms:** Oxacyclohexadec-13-en-2-one, (E)-; Oxacyclohexadec-13-en-2-one, (13E)-	**Synonyms:** Oxacyclohexadec-12-en-2-one, (12Z)-; Z-Oxacyclohexadec-12-en-2-one	**Synonyms:** Oxacyclohexadec-13-en-2-one, (13Z)-; (Z)-Oxacyclohexadec-13-en-2-one
Molecular Formula: $C_{15}H_{26}O_2$	**Molecular Formula:** $C_{15}H_{26}O_2$	**Molecular Formula:** $C_{15}H_{26}O_2$	**Molecular Formula:** $C_{15}H_{26}O_2$	**Molecular Formula:** $C_{15}H_{26}O_2$
Molecular Weight: 238.37 g/mol	**Molecular Weight:** 238.37 g/mol	**Molecular Weight:** 238.37 g/mol	**Molecular Weight:** 238.37 g/mol	**Molecular Weight:** 238.37 g/mol
RIFM Number: 6351	**RIFM Number:** 6351	**RIFM Number:** 6351	**RIFM Number:** 6351	**RIFM Number:** 6351

2. Physical data

Chemical Name: Oxacyclohexadecen-2-one	Chemical Name: Oxacyclohexadec-12-en-2-one, (12E)-	Chemical Name: Oxacyclohexadec-13-en-2-one, (13E)-	Chemical Name: Oxacyclohexadec-12-en-2-one, (12Z)-	Chemical Name: Oxacyclohexadec-13-en-2-one, (13Z)-
CAS Registry Number: 34902-57-3	CAS Registry Number: 111879-80-2	CAS Registry Number: 99219-32-6	CAS Registry Number:111879-79-9	CAS Registry Number:111879-81-3
1. Boiling Point: 333 °C at 1013 hPa (RIFM, 2004d), 364.47 °C (EPI Suite), 283.5–331.3 °C max. at 948.4 mbar (RIFM, 1992a)	**1. Boiling Point:** 366 °C (EPI Suite)	**1. Boiling Point:** Not available	**1. Boiling Point:** Not available	**1. Boiling Point:** Not available
2. Flash Point: 156.5 °C at 1013.3 hPa (RIFM, 2004b), t1/2(25 °C) pH 4 & 7 >1a; t1/2(50 °C) pH 9 = 61.3 h (RIFM, 2005e), 157 °C (RIFM, 1992a)	**2. Flash Point:** 157 °C (Globally Harmonized System)	**2. Flash Point:** Not available	**2. Flash Point:** Not available	**2. Flash Point:** Not available
3. Log K_{OW}: 6.15 (EPI Suite), >3.94 at 22 °C (RIFM, 1994), >6.20 (RIFM, 2000)	**3. Log K_{OW}:** 4.88 (EPI Suite)	**3. Log K_{OW}:** Not available	**3. Log K_{OW}:** Not available	**3. Log K_{OW}:** Not available
4. Melting Point: 46 °C at 1013.3 hPa (RIFM, 2004c), 26.06 °C (EPI Suite)	**4. Melting Point**: 26.84 °C (EPI Suite)	**4. Melting Point**: Not available	**4. Melting Point**: Not available	**4. Melting Point**: Not available
5. Water Solubility: 0.1484 mg/L (EPI Suite), 9.64 x 10($^{-4}$) g/L of solution at 20.0 ± 0.5 °C (RIFM, 2001b), 1.2 mg/L in purified H_2O; 0.63 mg/L in *Daphnia* med (RIFM, 2012)	**5. Water Solubility:** 1.859 mg/L (EPI Suite)	**5. Water Solubility:** Not available	**5. Water Solubility:** Not available	**5. Water Solubility:** Not available
6. Specific Gravity: Not Available	**6. Specific Gravity:** Not Available	**6. Specific Gravity:** Not available	**6. Specific Gravity:** Not available	**6. Specific Gravity:** Not available
7. Vapor Pressure: 0.039 Pa at 20 °C; 0.076 Pa at 25 °C; 1.6 Pa at 50 °C (RIFM, 2004e), 5.17e-005 mm Hg at 25 °C (EPI Suite), 0.16 Pa at 25 °C (RIFM, 1995a)	**7. Vapor Pressure:** 5.29E-005 mm Hg at 25 °C (EPI Suite), 2.68E-005 mm Hg at 20 °C (EPI Suite v4.0)	**7. Vapor Pressure:** Not available	**7. Vapor Pressure:** Not available	**7. Vapor Pressure:** Not available
8. UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**8. UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**8. UV Spectra:** Not available	**8. UV Spectra:** Not available	**8. UV Spectra:** Not available
9. Appearance/Organoleptic: Colorless liquid	**9. Appearance/Organoleptic:** Not available	**9. Appearance/ Organoleptic:** Not available	**9. Appearance/ Organoleptic:** Not available	**9. Appearance/ Organoleptic:** Not available

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 1.5% (RIFM, 2021)
2. **Inhalation Exposure**:** 0.0016 mg/kg/day or 0.11 mg/day (RIFM, 2021)
3. **Total Systemic Exposure***:** 0.028 mg/kg/day (RIFM, 2021)

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

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. *Cramer classification*

Class I, Low (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I*	I	III

*See the Appendix below for further details.

6.2. *Analogs selected*

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification:** None

7. Metabolism

Not considered for this risk assessment and therefore not reviewed

except where it may pertain in specific endpoint sections as discussed below.

Additional References: None.

8. Natural occurrence

Oxacyclohexadecen-2-one, oxacyclohexadec-12-en-2-one, (12E)-, oxacyclohexadec-13-en-2-one, (13E)-, oxacyclohexadec-12-en-2-one, (12Z)-, and oxacyclohexadec-13-en-2-one, (13Z)- are not reported to occur in foods by the VCF*.

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

9. REACH dossier

Available for all materials; accessed 11/04/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for oxacyclohexadecen-2-one are detailed below.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, oxacyclohexadecen-2-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity oxacyclohexadecen-2-one was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were exposed to oxacyclohexadecen-2-one in dimethyl sulfoxide (DMSO) at the concentrations of 0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1500, and 5000 μg/plate in the presence and absence of metabolic activation mix (S9). No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2005a). The lack of mutagenic potential of the test material was confirmed in the mammalian system in an *in vitro* mammalian cell gene mutation test conducted in accordance with OECD TG 476 (RIFM, 2001a). Under the conditions of the study, oxacyclohexadecen-2-one was considered not mutagenic.

Table 1
Data Summary for oxacyclohexadecen-2-one.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
8750 [1]	Weak	7559	NA	NA	7500

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

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

The clastogenic potential of oxacyclohexadecen-2-one was assessed in an *in vitro* chromosome aberration study conducted *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OCED TG 473. Human peripheral blood lymphocytes were treated with oxacyclohexadecen-2-one in ethanol at concentrations up to 2650 μg/mL in the presence and absence of exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test material, either with or without S9 metabolic activation (RIFM, 2005c). Under the conditions of the study, oxacyclohexadecen-2-one was considered to be non-clastogenic to human cells.

Based on the available data, oxacyclohexadecen-2-one does not represent a concern for genotoxic potential.

Additional References: RIFM, 1992c; RIFM, 2001a.

Literature Search and Risk Assessment Completed On: 02/11/21.

11.1.2. Repeated dose toxicity

The MOE for oxacyclohexadecen-2-one 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 oxacyclohexadecen-2-one for the repeated dose toxicity endpoint. An OECD 408 gavage 90-day subchronic toxicity study was conducted in rats. Groups of 15 Sprague Dawley Crl:CD BR strain rats/sex/dose were administered oxacyclohexadecen-2-one via gavage at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose for 90 days. Two recovery groups of 10 rats/sex were gavaged with 0 or 1000 mg/kg/day for 90 days and then maintained without treatment for a further 28 days. There were no treatment-related mortalities or toxicologically significant changes in any of the parameters measured during the study. Two males treated with 1000 mg/kg/day were found dead on days 34 and 85, and the cause of death was considered to be due to mal-dosing. However, there were no signs of mal-dosing during histopathology. The NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 1998b). In a 4-week gavage toxicity study followed by a 2-week recovery period conducted in rats, groups of 6 Crl:CD(SD)BR strain (VAF plus) rats/sex/dose were administered oxacyclohexadecen-2-one via gavage at doses of 0, 500, 750, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose. Two recovery groups of 6 rats/sex were added to the control and highest-dose groups and then maintained without treatment for 2-weeks. There were no treatment-related effects up to the highest dose tested; the NOEL for systemic toxicity was considered to be 1000 mg/kg/day (RIFM, 1996a). In another OECD/GLP 407 gavage 28-day toxicity study followed by a 2-week recovery period conducted in rats, groups of 5 Crl:CD rats/-sex/dose were administered oxacyclohexadecen-2-one (Globalide) via gavage at doses of 0, 100, 300, or 1000 mg/kg/day in 0.8% aqueous hydroxypropylmethylcellulose gel for 28 days. Two recovery groups of 5 rats/sex were added to the control and highest-dose groups and then maintained without treatment for 2-weeks. Salivation was observed in males and females treated at 1000 mg/kg/day, which began 3 min after test material administration and lasted for 30 min. Apart from salivation, no other effects on functional, hematological, clinical, and pathological parameters were observed. The NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2005b). A NOAEL of 1000 mg/kg/day from the OECD 408 study was considered for this safety assessment. **Therefore, the oxacyclohexadecen-2-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to oxacyclohexadecen-2-one, 1000/0.028 or 35714.**

In addition, the total systemic exposure to oxacyclohexadecen-2-one (28.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.58
2	Products applied to the axillae	0.17
3	Products applied to the face/body using fingertips	3.5
4	Products related to fine fragrances	3.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.82
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.82
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.82
5D	Baby cream, oil, talc	0.27
6	Products with oral and lip exposure	0.76
7	Products applied to the hair with some hand contact	6.6
8	Products with significant ano-genital exposure (tampon)	0.27
9	Products with body and hand exposure, primarily rinse-off (bar soap)	6.3
10A	Household care products with mostly hand contact (hand dishwashing detergent)	19
10B	Aerosol air freshener	23
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.27
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For oxacyclohexadecen-2-one, the basis was the reference dose of 10 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 7500 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; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.07193			1000000	7.19E-05	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.663	1.012	0.273	10000	0.027	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.507	0.376	0.841			Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.803		0.027	10	2.7	
Daphnia		0.48	0.039			
Algae		0.4	0.26			

repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic reference dose (RfD) of 10 mg/kg/day.

11.1.2.2. Derivation of subchronic RfD. The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for oxacyclohexadecen-2-one was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 1000 mg/kg/day by the uncertainty factor, 100 = 10 mg/kg/day.

Additional References: RIFM, 2011b; RIFM, 2011a; RIFM, 1995b.

Literature Search and Risk Assessment Completed On: 02/08/21.

11.1.3. Reproductive toxicity

The MOE for oxacyclohexadecen-2-one is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on oxacyclohexadecen-2-one for the developmental toxicity endpoint. An OECD 414/GLP gavage developmental toxicity study was conducted in rats. Groups of 24 mated Sprague Dawley CD strain female rats/dose were administered oxacyclohexadecen-2-one via gavage at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose from days 5–19 of gestation. There were no significant treatment-related effects on fetal viability, growth, and development up to the highest dose tested. The NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003c). **Therefore, the oxacyclohexadecen-2-one MOE for the developmental toxicity endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to oxacyclohexadecen-2-one, 1000/0.028, or 35714.**

There are sufficient fertility data on oxacyclohexadecen-2-one for the fertility endpoint. An OECD 415/GLP gavage 1-generation reproductive toxicity study was conducted in rats. Groups of 28 Sprague Dawley Crl: CD(SD) IGS BR strain rats/sex/dose were administered oxacyclohexadecen-2-one at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose daily, throughout pre-mating, mating, gestation, and lactation. The males were dosed for 72 days, and females were dosed for 16 days prior to mating. There were no effects on the reproductive organs, fertility, or mating performance up to the highest dose tested. The NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003b). **Therefore, the oxacyclohexadecen-2-one MOE for the reproductive toxicity endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to oxacyclohexadecen-2-one, 1000/0.028, or 35714.**

In addition, the total systemic exposure to oxacyclohexadecen-2-one (28.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2011b; RIFM, 2011a; RIFM, 1995b.

Literature Search and Risk Assessment Completed On: 02/08/21.

11.1.4. Skin sensitization

Based on the existing data, oxacyclohexadecen-2-one is considered a skin sensitizer with a defined NESIL of 7500 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, oxacyclohexadecen-2-one is a skin sensitizer. The chemical structure of oxacyclohexadecen-2-one indicates that the material would not be expected to react with skin proteins directly (Roberts, 2007; OECD Toolbox v4.2; Toxtree v3.1.0). In a murine local lymph node assay (LLNA), oxacyclohexadecen-2-one was found to be sensitizing with an EC3 value of 35% (8750 μg/cm^2) (RIFM, 2010). In a guinea pig maximization test, the material did not result in reactions classifiable as sensitization (RIFM, 1992b; RIFM, 1997b; RIFM, 2004a). In a Confirmation of No Induction in Humans test (CNIH), no sensitization reactions were observed to oxacyclohexadecen-2-one when 6.4% or 7559 μg/cm^2 oxacyclohexadecen-2-one in 1:3 ethanol:diethyl phthalate (EtOH:DEP) (RIFM, 2016). Similarly, no reactions were observed in another CNIH when 15% or 7500 μg/cm^2 oxacyclohexadecen-2-one in DEP was used for induction and challenge (RIFM, 1997a).

Based on the available data, summarized in Table 1, oxacyclohexadecen-2-one is considered to be a skin sensitizer with a defined NESIL of 7500 μg/cm^2. 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 subchronic RfD of 10 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/13/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, oxacyclohexadecen-2-one would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for oxacyclohexadecen-2-one in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, oxacyclohexadecen-2-one does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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: None.

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for oxacyclohexadecen-2-one is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on oxacyclohexadecen-2-one. Based on the Creme RIFM Model, the inhalation exposure is 0.11 mg/day. This exposure is 12.7 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of oxacyclohexadecen-2-one was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, oxacyclohexadecen-2-one was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified oxacyclohexadecen-2-one as not persistent but possibly 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 $\geq$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), oxacyclohexadecen-2-one presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation***

For CAS # 34902-57-3.

RIFM, 1996b: A biodegradation study was conducted following OECD 301F guidelines. 100 mg/L of the test material was incubated for 28 days. At the end of the study, 95% biodegradation was observed.

RIFM, 1995f: A biodegradation study was conducted following OECD 301B guidelines (modified strum test). 10 and 20 mg/L of the test material was incubated for 28 days. At the end of the study 86.1% (at 10 mg/L) and 87.1% (at 20 mg/L) biodegradation was observed.

RIFM, 1998a: A study was conducted following the OECD 301C guideline. 100 mg/L of the test material was incubated for 28 days. At the end of 28 days, 92% biodegradation was observed.

RIFM, 1995g: A semi-continuous activated sludge removability test was performed at 20 mg/L test material concentration. 95% removal was observed.

RIFM, 2005d: A biodegradation of the test material was evaluated according to the OECD 301F method. Under the conditions of the study, biodegradation of 97% was observed after 28 days.

Ecotoxicity

For CAS # 34902-57-3.

RIFM, 1995d: A 48-h *Daphnia magna* immobilization study was conducted under static test conditions according to the OECD 202 method. The 48-h EC50 value based on measured test concentration was reported to be 0.48 mg/L (95% CI: 0.42–0.54 mg/L).

RIFM, 1995c: A 96-h acute fish (*Oncorhynchus mykiss*) study according to the OECD 203 method was conducted under continuous flow conditions. The 96-h LC50 value based on measured test concentration was reported to be 2.0 mg/L (95% CI: 1.3–3.0 mg/L).

RIFM, 2002: A 21-day *Daphnia* magna reproduction study following OECD guidelines 211 was reported. The 21 day EC50 for immobilization and reproduction was reported as 0.27 mg/L (nominal concentration) or 0.079 mg/L (time-weighted mean measured test concentration). The reported NOEC and LOEC were 0.15 mg/L (nominal) or 0.039 mg/L (time-weighted mean measured test concentration) and 0.48 mg/L (nominal) or 0.16 mg/L (time-weighted mean measured test concentration), respectively.

RIFM, 2003a: A 33-day fish (*Pimephales promelas*) early-life stage study according to the OECD 210 method was conducted. The reported NOEC (mean measured concentration) was 0.027 mg/L (nominal concentration: 0.16 mg/L).

RIFM, 1995e: An algae inhibition test (*Scenedesmus subspicatus*) under static conditions in sealed containers was conducted according to the OECD 201 method. The 72-h NOEC for biomass and growth rate reduction was 0.625 mg/L. The 72-h EC50 for reduction of biomass was 2.4 mg/L. All endpoints are reported as nominal concentrations; no measurable material was reported after 72 h.

RIFM, 2005f: A 96-h toxicity study with rainbow trout was conducted according to the OECD 203 method under flow-through conditions. The 96-h LC50 based on nominal test concentration was reported to be greater than 0.803 mg/L.

RIFM, 2005g: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 based on geometric mean measured concentration was reported to be greater than 0.96 mg/L.

RIFM, 2005h: A static algal growth inhibition test was conducted according to the OECD 201 method. Under the test conditions and based on geometric mean measured concentrations, the 72-h EC50 values for biomass growth inhibition (ECb50) and rate-related inhibition (ECr50) were 1.07 mg/L and 5.17 mg/L, respectively. The NOEC values based on geometric mean measured concentration for biomass and growth rate were reported to be 0.47 mg/L and 0.74 mg/L, respectively.

RIFM, 2005i: In a semi-static algal growth inhibition test, according to the OECD 201 method. Under the test conditions, after 72 h, and based on nominal concentrations, the ECr50 (growth rate) was 41.5

mg/L, the NOEC was 3.13 mg/L. In consideration of the extremely low water solubility of the test material, it was concluded that the EC50, as well as the LOEC and NOEC values, are far above the maximum water solubility.

Other available data

Oxacyclohexadecen-2-one has been registered under REACH with the following additional data available at this time (ECHA, 2014):

The *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day LOEC and NOEC values, based on the arithmetic mean measured concentration, were reported to be 0.127 mg/L and 0.068 mg/L, respectively.

The algal inhibition test was conducted according to the Eu Method C.3 guidelines under static conditions. The 72-h EC50 value, based on the mean measured concentration for biomass and growth rate, was reported to be 0.4 mg/L and >0.47 mg/L, respectively. The NOEC and LOEC values, based on the mean measured concentration for cell growth, were reported to be 0.26 mg/L and 0.37 mg/L, respectively.

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	6.2	6.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000*	100–1000*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use for all CAS #

Based on available data, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 2.7 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 02/08/21.

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 02/03/22.

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

Explanation of Cramer Classification

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

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? Yes
Q8. Lactone or cyclic diester? Yes
Q9. Lactone, fused to another ring, or 5- or 6-membered α,β-unsaturated lactone? No
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) No, Class I (Low Class)

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2014. A mixture of: (E)-oxacyclohexadec-12-en-2-one; (E)-oxacyclohexadec-13-en-2-one; a) (Z)-oxacyclohexadec-(12)-en-2-one and b) (Z)-oxacyclohexadec-(13)-en-2-one Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/5971/1.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey. February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1992a. Determination of Physico-Chemical Parameters of Oxacyclohexadecen-2-One. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31500.

RIFM (Research Institute for Fragrance Materials, Inc), 1992b. Skin Sensitization Study of Oxacyclohexadecen-2-One in the guinea Pig - Magnusson & Kligman Maximization. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31509.

RIFM (Research Institute for Fragrance Materials, Inc), 1992c. Bacterial Reverse Mutation Assay of Oxacyclohexadecen-2-One. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31513.

RIFM (Research Institute for Fragrance Materials, Inc), 1994. Determination of Partition Coefficient of Oxacyclohexadecen-2-One. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31503.

RIFM (Research Institute for Fragrance Materials, Inc), 1995a. Determination of Vapour Pressure of Oxacyclohexadecen-2-One. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31502.

RIFM (Research Institute for Fragrance Materials, Inc), 1995b. 7-Day Oral (Gavage) Dose Rangefinding Study of Oxacyclohexadecen-2-One in the Rat. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31511.

RIFM (Research Institute for Fragrance Materials, Inc), 1995c. Acute Toxicity of Oxacyclohexadecen-2-One to Rainbow Trout (Oncorhynchys Mykiss). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31515.

RIFM (Research Institute for Fragrance Materials, Inc), 1995d. Acute Toxicity of Oxacyclohexadecen-2-One to Daphnia Magna. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31516.

RIFM (Research Institute for Fragrance Materials, Inc), 1995e. Algal Inhibition Test of Oxacyclohexadecen-2-One. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31517.

RIFM (Research Institute for Fragrance Materials, Inc), 1995f. CO2 Production Test of Oxacyclohexadecen-2-One. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31519.

RIFM (Research Institute for Fragrance Materials, Inc), 1995g. Semi-continuous Activated Sludge (SCAS) Removability Test of Oxacyclohexadecen-2-One. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31520.

RIFM (Research Institute for Fragrance Materials, Inc), 1996a. 4-Week Oral (Gavage) Toxicity Study of Oxacyclohexadecen-2-One in the Rat Followed by a 2 Week Treatment-free Period. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31512.

RIFM (Research Institute for Fragrance Materials, Inc), 1996b. Assessment of Ready Biodegradability of Oxacyclohexadecen-2-One: Manometric Respirometry Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31518.

RIFM (Research Institute for Fragrance Materials, Inc), 1997a. Repeated Insult Patch Study of Oxacyclohexadecen-2-One (Habanolide). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 31510.

RIFM (Research Institute for Fragrance Materials, Inc), 1997b. Oxacyclohexadecen-2-one (Globalide): Test for Delayed Contact Hyper-Sensitivity Using the Guinea Pig Maximization Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 67622.

RIFM (Research Institute for Fragrance Materials, Inc), 1998a. Report on Biodegradability of Oxacyclohexadecen-2-One by Microorganisms. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich Incorporated. RIFM report number 30369.

RIFM (Research Institute for Fragrance Materials, Inc), 1998b. 90-Day Oral (Gavage) Toxicity Study of Oxacyclohexadecen-2-One (Habanolide) in the Rat. RIFM, Woodcliff Lake, NJ, USA [Addendum Attached]. Unpublished report from Firmenich Incorporated. RIFM report number 32224.

RIFM (Research Institute for Fragrance Materials, Inc), 2000. Oxacyclohexadecen-2-one (Habanolide): Determination of Partition Coefficient. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 40996.

RIFM (Research Institute for Fragrance Materials, Inc), 2001a. Oxacyclohexadecen-2-one (Habanolide): L5178Y TK +/- Mouse Lymphoma Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 40992.

RIFM (Research Institute for Fragrance Materials, Inc), 2001b. Oxacyclohexadecen-2-one (Habanolide): Determination of Water Solubility. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 40997.

RIFM (Research Institute for Fragrance Materials, Inc), 2002. Oxacyclohexadecen-2-one: Daphnia Magna Reproduction Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 43025.

RIFM (Research Institute for Fragrance Materials, Inc), 2003a. Oxacyclohexadecen-2-one: Fish, Early-Life Stage Toxicity Test. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 43024.

RIFM (Research Institute for Fragrance Materials, Inc), 2003b. Oxacyclohexadecen-2-one: Oral Gavage One Generation Reproduction Study in the Rat. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 44313.

RIFM (Research Institute for Fragrance Materials, Inc), 2003c. Oxacyclohexadecen-2-one: Oral Gavage Teratology Study in the Rat. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 44314.

RIFM (Research Institute for Fragrance Materials, Inc), 2004a. Oxacyclohexadecen-2-one (Globalide): Skin Sensitisation Test in guinea Pigs (Maximisation Test). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68026.

RIFM (Research Institute for Fragrance Materials, Inc), 2004b. Oxacyclohexadecen-2-one (Globalide): Determination of Flash Point. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68032.

RIFM (Research Institute for Fragrance Materials, Inc), 2004c. Oxacyclohexadecen-2-one (Globalide): Determination of the Melting Point. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68033.

RIFM (Research Institute for Fragrance Materials, Inc), 2004d. Oxacyclohexadecen-2-one (Globalide): Determination of Boiling Point. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68034.

RIFM (Research Institute for Fragrance Materials, Inc), 2004e. Oxacyclohexadecen-2-one (Globalide): Determination of Vapour Pressure. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68040.

RIFM (Research Institute for Fragrance Materials, Inc), 2005a. Oxacyclohexadecen-2-one (Habanolide): Reverse Mutation Assay "Ames Test" Using Slamonella Typhimurium and Escherichai Coli. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 58644.

RIFM (Research Institute for Fragrance Materials, Inc), 2005b. Oxacyclohexadecen-2-one (Globalide): 28-Day Repeated Dose Oral Toxicity Study in Rats. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68029.

RIFM (Research Institute for Fragrance Materials, Inc), 2005c. Oxacyclohexadecen-2-one (Globalide): in Vitro Chromosome Aberration Test in Human Lymphocytes. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68036.

RIFM (Research Institute for Fragrance Materials, Inc), 2005d. Oxacyclohexadecen-2-one (Globalide): Ready Biodegradability. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68037.

RIFM (Research Institute for Fragrance Materials, Inc), 2005e. Oxacyclohexadecen-2-one (Globalide): Determination of Hydrolysis as a Function of pH. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68039.

RIFM (Research Institute for Fragrance Materials, Inc), 2005f. Oxacyclohexadecen-2-one (Globalide): Acute Toxicity in Rainbow Trout (Oncorhynchus mykiss). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68042.

RIFM (Research Institute for Fragrance Materials, Inc), 2005g. Oxacyclohexadecen-2-one (Globalide): 48 Hour Acute Immobilization Test on Daphnia Magna. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68043.

RIFM (Research Institute for Fragrance Materials, Inc), 2005h. Oxacyclohexadecen-2-one (Globalide): 72 Hour Alga Growth Inhibition Test with Desmodesmus Subspicatus. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68044.

RIFM (Research Institute for Fragrance Materials, Inc), 2005i. Oxacyclohexadecen-2-one (Globalide): Acute Toxicity on the Single Cell Green Alga Desmodesmus Subspicatus. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 68045.

RIFM (Research Institute for Fragrance Materials, Inc), 2010. Oxacyclohexadecen-2-one: Local Lymph Node Assay (LLNA) in Mice to Identify Contact Allergens. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 63168.

RIFM (Research Institute for Fragrance Materials, Inc), 2011a. A Toxicological and Dermatological Assessment of Macrocyclic Lactone and Lactide Derivatives when Used as Fragrance Ingredients. The RIFM Expert Panel. RIFM Report Number 63118. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2011b. Fragrance Material Review on Oxacyclohexadecen-2-One(E- and Z-Oxacyclohexadec-12(+13)-En-2-One). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 63139.

RIFM (Research Institute for Fragrance Materials, Inc), 2012. Oxacyclohexadecen-2-one (Habanolide): Water Solubility (Slow-stir Method). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Firmenich SA. RIFM report number 64212.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Human Repeat Insult Patch Test Oxacyclohexadecen-2-One (Habanolide). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 71110.

RIFM (Research Institute for Fragrance Materials, Inc), 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76775.

RIFM (Research Institute for Fragrance Materials, Inc), 2021. Exposure Survey 31. March 2021.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.