Food and Chemical Toxicology 149 (2021) 111983

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole, CAS Registry Number 38303-23-0

A.M. Api [a], D. Belsito [b], S. Biserta [a], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], S. Gadhia [a], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA
[b] Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave, New York, NY, 10032, USA
[c] Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden
[d] School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA
[e] Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany
[f] University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil
[g] University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany
[h] Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA
[i] Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA
[j] University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA
[k] The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA
[l] Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA
[m] The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

ARTICLE INFO

Handling editor: Aristides Tsatsakis

Keywords:
Genotoxicity
Repeated dose
Developmental
And reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

ABSTRACT

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

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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.

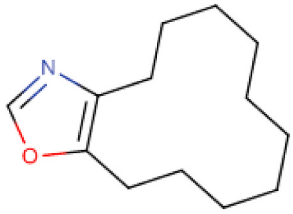
* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2021.111983
Received 6 October 2020; Received in revised form 1 December 2020; Accepted 10 January 2021
Available online 16 January 2021

Version: 100620. This version replaces any previous versions.

Name: 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole

CAS Registry Number: 38303-23-0



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
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api 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

(*continued on next column*)

(*continued*)

comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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, 2017; RIFM, 2016)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: No safety concerns at current, declared use levels; the exposure is below the DST.
Phototoxicity/Photoallergenicity: (UV Spectra; RIFM Database)
Not expected to be phototoxic/photoallergenic.
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 0% (OECD 301F) RIFM (2004b)
Bioaccumulation:
Screening-level: 1119 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 48-h *Daphnia magna* LC50: 0.201 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: 0.201 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0201 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole
2. **CAS Registry Number:** 38303-23-0
3. **Synonyms:** Cyclododecoxazole, 4,5,6,7,8,9,10,11,12,13-decahydro-; 4,5-Decamethyleneoxazole; Sclarene; 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododeca[d][1,3]oxazole; 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole
4. **Molecular Formula:** $C_{13}H_{21}NO$
5. **Molecular Weight:** 207.31
6. **RIFM Number:** 5687
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 293.95 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 5.13 (EPI Suite), Log Pow = 5.1 (RIFM, 2004c)

4. **Melting Point**: 72.14 °C (EPI Suite)
5. **Water Solubility:** 1.683 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000516 mm Hg at 20 °C (EPI Suite v4.0), 0.000965 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics**: 0.085% (RIFM, 2015)
2. **Inhalation Exposure***: 0.00017 mg/kg/day or 0.011 mg/day (RIFM, 2015)
3. **Total Systemic Exposure****: 0.0010 mg/kg/day (RIFM, 2015)

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

5. Derivation of systemic absorption

1. **Dermal**: 40%
2. **Oral**: Assumed 100%
3. **Inhalation**: Assumed 100%

Name	4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole
J_{max} (mg/cm^2/h)	0.27[1]
Skin Absorption Class	40%

[1] J_{max} was calculated based on estimated log K_{OW} = 5.13 (consensus model) and Solubility = 1.68 mg/L (consensus model).

6. Computational toxicology evaluation

1. Cramer Classification: Class III, High

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v3.2
III	III	III

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

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

8. Natural occurrence (discrete chemical) or composition (NCS)

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole 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

Pre-registered for 2010; no dossier available as of 10/06/20.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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 were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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 pre-incubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017). Under the conditions of the study, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole was not mutagenic in the Ames test.

The clastogenic activity of 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole in DMSO at concentrations up to 2000 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 320 μg/mL in the presence and absence of metabolic activation. 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation

system (RIFM, 2016). Under the conditions of the study, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/19/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole or any read-across materials. The total systemic exposure to 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole (1.0 μg/kg/day) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material (1.5 μg/kg/day; Kroes et al., 2007) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/26/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole or any read-across materials. The total systemic exposure to 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole (1.0 μg/kg/day) is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/26/20.

11.1.4. Skin sensitization

Based on the existing data and application of DST, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole does not present a concern for skin sensitization under current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, no skin sensitization reactions were observed (RIFM, 1999). Additionally, in a guinea pig open epicutaneous test (OET), no skin sensitization reactions were observed (RIFM, 1998). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/31/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole in experimental models. UV/Vis absorption spectra indicate no significant

Table 1
Maximum acceptable concentrations for 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	0.012%
3	Products applied to the face using fingertips	0.41%	0.0012%
4	Fine fragrance products	0.39%	0.85%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.013%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	0.0022%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0060%
10	Household care products with mostly hand contact	2.7%	0.033%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	3.3%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.

[b] No reported use.

[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

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, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole. Based on the Creme RIFM Model, the inhalation exposure is 0.011 mg/day. This exposure is 42.7 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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, 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole 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 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole as possibly persistent but not 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), 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 2004a**:** The inherent biodegradability of the test material was determined by the manometric respirometry test according to the OECD 302C method. Under the conditions of the study, no biodegradation was observed after 32 days.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.530			1000000	0.000530	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.266	0.201	0.494	10000	0.0201	Neutral Organics

RIFM, 2004b: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. No biodegradation was observed after 28 days.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole has been pre-registered under REACH with no additional data at this time.

11.2.5. Risk assessment refinement

Risk 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 et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.1	5.1
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0201 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 VoU.

Literature Search and Risk Assessment Completed On: 03/18/20.

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 09/30/20.

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.

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.

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.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

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.

RIFM (Research Institute for Fragrance Materials, Inc), 1998. 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole (Sclarene): Study of Skin Sensitization in the guinea Pig; Open Epicutaneous Test. Unpublished Report from Givaudan-Roure. RIFM Report Number 34614. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1999. 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole (Sclarene): Study of Skin Sensitization in Albino guinea Pigs; Maximization-Test. Unpublished Report from Givaudan-Roure. RIFM Report Number 34616. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, 2004a RIFM (Research Institute for Fragrance Materials, Inc), 2004a. Inherent Biodegradability of 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole (Sclarene). Unpublished Report from Givaudan. RIFM Report Number 57902. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, 2004b RIFM (Research Institute for Fragrance Materials, Inc), 2004b. Ready Biodegradability of 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole (Sclarene). Unpublished Report from Givaudan. RIFM Report Number 57903. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, 2004c RIFM (Research Institute for Fragrance Materials, Inc), 2004c. Partition Coefficient N-Octanol/water of 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole (Sclarene). Unpublished Report from Givaudan. RIFM Report Number 57904. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, 2014 RIFM (Research Institute for Fragrance Materials, Inc), 2014. Report on the Testing of 4,5,6,7,8,9,10,11,12,13-decahydrocyclododecaoxazole in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 67259. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2015. Exposure Survey 08. October 2015.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole: Micronucleus Test in Human Lymphocytes in Vitro. RIFM Report Number 71130. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017. 4,5,6,7,8,9,10,11,12,13-Decahydrocyclododecaoxazole: Reverse Mutation Assay 'Ames Test' Using Salmonella typhimurium and Escherichia coli. RIFM Report Number 71588. RIFM, Woodcliff Lake, NJ, USA.

Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.

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., 2015b. 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.
Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
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, v1.11. United States Environmental Protection Agency, Washington, DC, USA.