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RIFM fragrance ingredient safety assessment, cyclooct-4-en-1-yl methyl carbonate, CAS registry number 87731-18-8

A.M. Api [a], D. Belsito [b], 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], 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] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave, New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St, Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel for Fragrance Safety, 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] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel for Fragrance Safety, 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] *Member of Expert Panel for Fragrance Safety, 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] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel for Fragrance Safety, 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*

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Name: Cyclooct-4-en-1-yl methyl carbonate
CAS Registry Number: 87731-18-8
Additional CAS Numbers*:
84681-92-5
8-Ethyl-1,5-dimethylbicyclo[3.2.1]octan-8-ol

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

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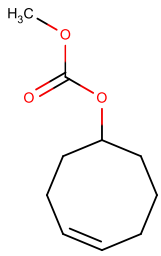
*This material is included in this assessment because they are a commercial mixture.



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; bib_Safford_et_al_2015Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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

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guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

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

Cyclooct-4-en-1-yl methyl carbonate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclooct-4-en-1-yl methyl carbonate is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to cyclooct-4-en-1-yl methyl carbonate is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). Data provided cyclooct-4-en-1-yl methyl carbonate 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; cyclooct-4-en-1-yl methyl carbonate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; Cyclooct-4-en-1-yl methyl carbonate 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, 1986a; RIFM, 1986b)
Repeated Dose Toxicity: NOAEL = 167 mg/kg/day. RIFM (1987b)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 7500 μg/cm^2. RIFM (2018a)
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: 73% (OECD 301F) for CAS # 87731-18-8 RIFM (2011b)

Bioaccumulation:
Screening-level: 66.8 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: 96-hour algae EC50: 2.818 mg/L (ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-hour algae EC50: 2.818 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.2818 μg/L

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

1. Identification

Chemical Name: Cyclooct-4-en-1-yl methyl carbonate	**Chemical Name**: 8-Ethyl-1,5-dimethylbicyclo[3.2.1]octan-8-ol
CAS Registry Number: 87731-18-8	**CAS Registry Number:** 84681-92-5
Synonyms: Carbonic acid, 4-cyclooctenyl-1-yl methyl ester; Violiff; Violet T; Cyclooct-4-en-1-yl methyl carbonate	**Synonyms:** Bicyclo[3.2.1]octan-8-ol, 8-ethyl-1,5-dimethyl-; Huminol
Molecular Formula: $C_{10}H_{16}O_3$	**Molecular Formula:** $C_{12}H_{22}O$
Molecular Weight: 184.23	**Molecular Weight:** 182.3
RIFM Number: 5481	**RIFM Number:** 6018
Stereochemistry: Isomer not specified. One chiral center and one geometric center present. Two stereoisomers and 2 enantiomers possible	**Stereochemistry:** Isomer not specified. One chiral center and one geometric center present. Two stereoisomers and 2 enantiomers possible

2. Physical data

Boiling Point: 231.9–244.9 °C (RIFM, 1986c), 257.63 °C (US EPA, 2012a)	**Boiling Point**: 236.09 °C (US EPA, 2012a)
Flash Point: 110 °C at 1016 mbar (RIFM, 1986c), 110 °C (Globally Harmonized System)	**Flash Point:** Not available
Log K_{OW}: Log P = 2.8994 at 21 C (RIFM, 1986c), 3.27 (US EPA, 2012a), log Pow = 3.1 and 3.2 (RIFM, 2011a)	**Log K_{OW}:** 3.87 (US EPA, 2012a)
Melting Point: 33.45 °C (US EPA, 2012a)	**Melting Point:** 45.38 °C (US EPA, 2012a)
Water Solubility: 84.57 mg/L (US EPA, 2012a)	**Water Solubility:** Not available
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.0181 mm Hg at 25 °C (US EPA, 2012a), 0.0113 mm Hg at 20 °C (US EPA, 2012a)	**Vapor Pressure:** 0.00486 mm Hg at 25 °C (US EPA, 2012a), 0.00258 mm Hg at 20 °C (US EPA, 2012a)
UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra**: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: Not available	**Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.08% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0079 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2020b)

*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).

***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 hydroalcoholics, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate* (Expert Judgment)

Cramer Class for CAS # 87731-18-8		
Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I**	III	II
Cramer Class for CAS # 84681-92-5		
Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II**	III	I

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* The most conservative Cramer Class was used for this commercial mixture.
**See the Appendix below for further detail.

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

Cyclooct-4-en-1-yl methyl carbonate is not reported to occur in foods by the VCF*.

8-Ethyl-1,5-dimethylbicyclo[3.2.1]octan-8-ol is not reported to occur in food 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 cyclooct-4-en-1-yl methyl carbonate; accessed on 10/01/21 (ECHA, 2014); 8-ethyl-1,5-dimethylbicyclo[3.2.1]octan-8-ol has been pre-registered for 2010; no dossier available as of 10/01/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for cyclooct-4-en-1-yl methyl carbonate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.58
2	Products applied to the axillae	0.17
3	Products applied to the face/body using fingertips	1.2
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	1.2

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
7	Products applied to the hair with some hand contact	2.5
8	Products with significant ano-genital exposure (tampon)	0.27
9	Products with body and hand exposure, primarily rinse-off (bar soap)	5.0
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.0
10B	Aerosol air freshener	15
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 cyclooct-4-en-1-yl methyl carbonate, the basis was the reference dose of 1.67 mg/kg/day, a predicted skin absorption value of 80%, 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).

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, cyclooct-4-en-1-yl methyl carbonate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Cyclooct-4-en-1-yl methyl carbonate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). 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 cyclooct-4-en-1-yl methyl carbonate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with cyclooct-4-en-1-yl methyl carbonate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Slight increases in revertant colonies were observed in TA1537 in the presence of metabolic activation in one of 2 assays. Therefore, this condition was repeated, and no increases in revertant colony numbers were observed, suggesting that the initial results were not biologically relevant. No increases in the mean number of revertant colonies were observed in any other tester strains at any dose in the presence or absence of S9 (RIFM, 1986a). Under the conditions of the study, cyclooct-4-en-1-yl methyl carbonate was not mutagenic in the Ames test.

The clastogenic activity of cyclooct-4-en-1-yl methyl carbonate was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female CD-1 mice. Doses up to 2850 mg/kg were administered. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1986b). Under the conditions of the study, cyclooct-4-en-1-yl methyl carbonate was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, cyclooct-4-en-1-yl methyl carbonate does not present a concern for genotoxic potential.

Additional References: RIFM, 2005b.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.2. Repeated dose toxicity

The MOE for cyclooct-4-en-1-yl methyl carbonate 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 cyclooct-4-en-1-yl methyl carbonate for the repeated dose toxicity endpoint. A 28-day GLP oral gavage subchronic toxicity study was conducted in CD strain rats. Groups of 5 rats/sex/dose were administered daily via gavage with test material cyclooct-4-en-1-yl methyl carbonate at concentrations of 0%, 0.4%, 2%, or 10% (equivalent to doses of 0, 20, 100, or 500 mg/kg/day) in corn oil for 28 days. No treatment-related effects were observed; thus, the NOAEL for repeated dose toxicity was considered to be 500 mg/kg/day, the highest dose tested (RIFM, 1987b; data also found in ECHA, 2014).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 500/3 or 167 mg/kg/day.

Therefore, the cyclooct-4-en-1-yl methyl carbonate MOE can be calculated by dividing the cyclooct-4-en-1-yl methyl carbonate NOAEL by the total systemic exposure to cyclooct-4-en-1-yl methyl carbonate, 167/0.0016, or 104375.

In addition, the total systemic exposure to cyclooct-4-en-1-yl methyl carbonate (1.6 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020a) and a reference dose of 1.67 mg/kg/day.

11.1.2.1.1. Derivation of reference dose (RfD). The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for cyclooct-4-en-1-yl methyl carbonate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 167 mg/kg/day by the uncertainty factor, 100 = 1.67 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/10/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on cyclooct-4-en-1-yl methyl carbonate or any read-across materials. The total systemic exposure to cyclooct-4-en-1-yl methyl carbonate is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on

cyclooct-4-en-1-yl methyl carbonate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (1.6 μg/kg/day) is below the TTC for cyclooct-4-en-1-yl methyl carbonate (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/30/20.

11.1.4. Skin sensitization

Based on the existing data, cyclooct-4-en-1-yl methyl carbonate 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, cyclooct-4-en-1-yl methyl carbonate is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree v3.0.1; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), cyclooct-4-en-1-yl methyl carbonate was found to be non-sensitizing up to 30% (7500 μg/cm^2) (RIFM, 2004). However, in a Buehler delayed contact hypersensitivity study, sensitization was observed in 3/19 animals at 24 h when 3% and 1% cyclooct-4-en-1-yl methyl carbonate was used for induction and challenge, respectively (RIFM, 1987a). In a Confirmation of No Induction in Humans test (CNIH) with 1000 μg/cm^2 and 7558 μg/cm^2 of cyclooct-4-en-1-yl methyl carbonate in alcohol SDA 39C and 1:3 EtOH:DEP, respectively, no reactions indicative of sensitization were observed in any of the 53 and 102 volunteers, respectively (RIFM, 1985; RIFM, 2018a).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, cyclooct-4-en-1-yl methyl carbonate is a weak sensitizer with a WoE NESIL of 7500 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020a) and a reference dose of 1.67 mg/kg/day.

Additional References: RIFM, 1982.

Literature Search and Risk Assessment Completed On: 10/21/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cyclooct-4-en-1-yl methyl carbonate 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 cyclooct-4-en-1-yl methyl carbonate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, cyclooct-4-en-1-yl methyl carbonate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/09/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for cyclooct-4-en-1-yl methyl carbonate 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 cyclooct-4-en-1-yl methyl carbonate. Based on the Creme RIFM Model, the inhalation exposure is 0.0079 mg/day. This exposure is 59.5 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cyclooct-4-en-1-yl methyl carbonate 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, cyclooct-4-en-1-yl methyl carbonate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify cyclooct-4-en-1-yl methyl carbonate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative

Table 1
Data Summary for cyclooct-4-en-1-yl methyl carbonate.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	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
>7500 [1]	Weak	7558	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.

and toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), cyclooct-4-en-1-yl methyl carbonate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation

11.2.3.1.1. For CAS # 87731-18-8. **RIFM, 2011b**: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 60% was observed after 28 days and 73% after 50 days.

RIFM, 2015: The ready biodegradability of the test material was evaluated according to the OECD 301C method. Biodegradation of 55% was observed after 28 days.

RIFM, 1986f: Biodegradation of the test material was evaluated according to the OECD 301D method. Under the conditions of the study, biodegradation of 67% was observed after 28 days.

11.2.3.2. Ecotoxicity

11.2.3.2.1. For CAS # 87731-18-8. **RIFM, 2005a:** An algal growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-hour EC50 values based on mean measured test concentration for growth rate and biomass were reported to be 8.18 mg/L (95% CI: 7.18–9.17 mg/L) and 3.49 mg/L (95% CI: 2.63–4.59 mg/L).

RIFM, 1986d: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method. The 48-hour EC50 value based on the nominal test was reported to be 26 mg/L (95% CI: 20–23 mg/L).

RIFM, 1986e: A semi-static fish (Rainbow trout) acute toxicity study was conducted according to the OECD 203 method, under semi-static conditions. Under the conditions of the study, the 96-hour LC50 value based on the mean measured concentration was reported to be 22 mg/L (95% CI: 17.35–29.05 mg/L).

RIFM, 2018b: An algal growth inhibition test was conducted according to the OECD 201 guideline. The 72-hour EC50 value based on nominal test concentration for growth rate was reported to be 13.4 mg/L (95% CI: 12.8–13.9 mg/L).

11.2.3.2.2. For CAS # 84681-92-5. **RIFM, 2001**: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-hour EC50 value based on nominal test concentration was reported to be 21 mg/L (95% CI: 20–23 mg/L).

11.2.4. Other available data

Cyclooct-4-en-1-yl methyl carbonate has been registered under REACH with the following additional data available at this time (ECHA, 2014):

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-hour EC50 value based on the mean measured concentration was reported to be 21 mg/L (95% CI: 15.1–29.2 mg/L).

11.2.5. Risk assessment refinement

Since cyclooct-4-en-1-yl methyl carbonate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.2	3.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume for both CAS #

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

The RIFM PNEC is 0.2818 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: 11/05/20.

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 10/01/21.

Declaration of competing interest

The authors declare that they have no known competing financial

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	22.5			1000000	0.0225	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.462	8.096	2.818	10000	0.2818	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	10.94	6.985	8.451			Neutral Organic SAR (Baseline toxicity)

interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix

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).

Explanation for CAS 87731-18-8.

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, divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see explanation in Cramer et al., 1978)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? Yes
Q18. One of the list (see Cramer et al., 1978 for a detailed explanation of list of categories)? No, Class I (Low Class)

Explanation for CAS 84681-92-5.

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? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? Yes, Class II (Intermediate Class)

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