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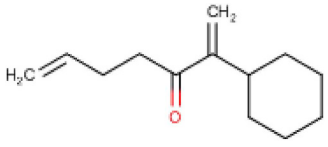
Short Review

RIFM fragrance ingredient safety assessment, 1,6-heptadien-3-one, 2-cyclohexyl-, CAS Registry Number 313973-37-4

A.M. Api[a], D. Belsito[b], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], L. Jones[a], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, 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 RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, 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 RIFM Expert Panel, 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 RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, 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*

Version: 112018. This version replaces any previous versions.
Name: 1,6-Heptadien-3-one, 2-cyclohexyl-
CAS Registry Number: 313973-37-4



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; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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

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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
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

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

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

Summary: The existing information supports the use of this material as described in this safety assessment.
This material was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that this material is not genotoxic and provided an MOE >100 for the repeated dose toxicity endpoint. Data show that the material does not have skin sensitization potential. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on data on the target material. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2001a; RIFM, 2005)
Repeated Dose Toxicity: NOAEL = 66.7 mg/kg/day.	RIFM (2004b)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: Not sensitizing.	(RIFM, 2001c; RIFM, 2003)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB; RIFM, 2002f)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 70% (OECD 302C)	RIFM (2002d)
Bioaccumulation: Screening-level: 475 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia manga* LC50: 0.568 mg/L	(EPI Suite v4.1; US EPA, 2012a)
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: 0.568 mg/L	(EPI Suite v4.1; US EPA, 2012a)
RIFM PNEC is: 0.0568 µg/L	
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe: < 1	

1. Identification

1. **Chemical Name:** 1,6-Heptadien-3-one, 2-cyclohexyl-
2. **CAS Registry Number:** 313973-37-4
3. **Synonyms:** 2-Cyclohexyl-1,6-heptadien-3-one; Pharaone; Cyclohexyl heptadienone; 1,6-Heptadien-3-one, 2-cyclohexyl-
4. **Molecular Formula:** $C_{13}H_{20}O$
5. **Molecular Weight:** 192.3
6. **RIFM Number:** 6961

2. Physical data

1. **Boiling Point:** 284.45 °C @ 760.00 mm Hg (estimated*)
2. **Flash Point:** 234.00 °F. TCC (112.22 °C)*
3. **Log K_{OW}**: Log Pow = 4.9 (RIFM, 2001b)
4. Melting Point: Not Available
5. Water Solubility: Not Available
6. Specific Gravity: Not Available
7. **Vapor Pressure:** 0.0167 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar

absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Estimated to be a colorless to pale yellow clear liquid with an odor described as green galbanum, fruity, pineapple and metallic when in a 10% solution in dipropylene glycol.

*http://www.thegoodscentscompany.com/data/rw1584171.html, retrieved 02/07/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1 to 1 metric ton per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.028% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000039 mg/kg/day or 0.0028 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00052 mg/kg/day (RIFM, 2017)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I*	I	II

*See Appendix below for explanation.

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

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. Natural occurrence (discrete chemical) or Composition (NCS)

1,6-Heptadien-3-one, 2-cyclohexyl- 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.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 11/20/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1,6-heptadien-3-one, 2-cyclohexyl- does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 1,6-heptadien-3-one, 2-cyclohexyl- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the both standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 1,6-heptadien-3-one, 2-cyclohexyl- in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2001a). Under the conditions of the study, 1,6-heptadien-3-one, 2-cyclohexyl-was not mutagenic in the Ames test.

The clastogenic activity of 1,6-heptadien-3-one, 2-cyclohexyl- 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 NMRI mice (5/sex/dose). Doses of 500, 1000, or 2000 mg/kg were administered. Mice from each dose level were euthanized 24 and 48 h after the treatment, 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, 2005). Under the conditions of the study, 1,6-heptadien-3-one, 2-cyclohexyl- was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 1,6-heptadien-3-one, 2-cyclohexyl- does not present a concern for genotoxic potential.

Additional References: RIFM, 2007; RIFM, 2004a.

Literature Search and Risk Assessment Completed On: 01/25/17.

10.1.2. Repeated dose toxicity

The margin of exposure for 1,6-heptadien-3-one, 2-cyclohexyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 1,6-heptadien-3-one, 2-cyclohexyl-. An OECD 407 GLP gavage 28-day subchronic toxicity study was conducted on rats. Groups of 5 rats/sex/dose were gavaged daily with 0, 50, 200, or 800 mg/kg/day of the test material 1,6-heptadien-3-one, 2-cyclohexyl- in a polyethylene

glycol 300 (PEG 300) vehicle for 28 days. Additional groups of 5 rats/sex/dose were gavaged daily with 0 or 800 mg/kg/day for 28 days followed by a 14-day treatment-free recovery period. The NOAEL was considered to be 200 mg/kg/day, based on mortality, clinical signs and reduced bodyweight gain in the 800 mg/kg/day treatment groups (RIFM, 2004b).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 study. The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 200/3 or 66.7 mg/kg/day.

Therefore, the 1,6-heptadien-3-one, 2-cyclohexyl-MOE can be calculated by dividing the 1,6-heptadien-3-one, 2-cyclohexyl- NOAEL in mg/kg/day by the total systemic exposure to 1,6-heptadien-3-one, 2-cyclohexyl-, 66.7/0.00052 or 128269.

In addition, the total systemic exposure to 1,6-heptadien-3-one, 2-cyclohexyl- (0.52 µg/kg/day) is below the TTC (30 µg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: 01/09/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1,6-heptadien-3-one, 2-cyclohexyl- or any read-across materials. The total systemic exposure to 1,6-heptadien-3-one, 2-cyclohexyl- is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or fertility toxicity data or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1,6-heptadien-3-one, 2-cyclohexyl- (0.52 µg/kg/day) is below the TTC (30 µg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/09/17.

10.1.4. Skin sensitization

Based on the existing data, 1,6-Heptadien-3-one, 2-cyclohexyl- does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data, 1,6-heptadien-3-one, 2-cyclohexyl does not present a concern for skin sensitization. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test no sensitization reactions were observed with 1,6-heptadien-3-one, 2-cyclohexyl- (RIFM, 2001c). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 1000 µg/cm^2 1,6-heptadien-3-one, 2-cyclohexyl- in unidentified vehicle, no reactions indicative of sensitization were observed in any of the 47 volunteers (RIFM, 2003).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/27/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and the available *in vivo* data, 1,6-heptadien-3-one, 2-cyclohexyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In *in vivo* phototoxicity and photoallergenicity studies conducted with guinea pigs (RIFM, 2002f), positive reactions were seen after application of 1,6-heptadien-3-one, 2-cyclohexyl-, but because the reactions were similar between irradiated and unirradiated sites, they were not considered phototoxic or photoallergenic in nature. Based on the available *in vivo* data, 1,6-heptadien-3-one, 2-cyclohexyl- would not be expected to present a concern for phototoxicity or photoallergenicity. UV/Vis absorption spectra for 1,6-heptadien-3-one, 2-cyclohexyl- are not available. In *in vivo* phototoxicity and photoallergenicity studies conducted with guinea pigs (RIFM, 2002f), positive reactions were seen after application of 1,6-heptadien-3-one, 2-cyclohexyl-, but because the reactions were similar between irradiated and unirradiated sites, they were not considered phototoxic or photoallergenic in nature. Based on UV/Vis absorption spectra and the available *in vivo* data, 1,6-heptadien-3-one, 2-cyclohexyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 1,6-heptadien-3-one, 2-cyclohexyl- were obtained. The spectra indicate minor 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: 04/06/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1,6-heptadien-3-one, 2-cyclohexyl- is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 1,6-heptadien-3-one, 2-cyclohexyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.0028 mg/day. This exposure is 500 times lower than the Cramer Class I TTC value of 1.4 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: 4/25/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1,6-heptadien-3-one, 2-cyclohexyl- 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, 1,6-heptadien-3-one, 2-cyclohexyl- 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 v4.1 did not identify 1,6-heptadien-3-one, 2-cyclohexyl- as being either 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 *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015; #68218). 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current VoU (IFRA, 2011), 1,6-heptadien-3-one, 2-cyclohexyl- presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. **RIFM, 2002d**: The inherent biodegradability of the test material was evaluated according to the OECD 302C method. Biodegradation of 70% was observed after 28 days.

RIFM, 2002e: The ready biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 61% was observed.

10.2.2.2. Ecotoxicity. **RIFM, 2002a**: A 96-h fish (Carp) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 was estimated to be 0.95 mg/L.

RIFM, 2002b: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 was reported to be1.1 mg/L.

RIFM, 2002c: An algae growth inhibition test was conducted according to the OECD 201 method. The 0–72 h EC50 based on cell growth and growth rate was reported to be 2.7 mg/L and 8.3 mg/L, respectively.

10.2.2.3. Other available data. 1,6-heptadien-3-one, 2-cyclohexyl- has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk Assessment Refinement. Since 1,6-heptadien-3-one, 2-cyclohexyl 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

.

	LC50 (Fish) mg/L	EC50 (*Daphnia*) mg/L	EC50 (Algae) mg/L	AF	PNEC µg/L	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>0.778</u>			1,000,000	0.000778	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.173	0.651	0.639			Vinnyl/Allyl Ketones
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.790	<u>0.568</u>	1.126	10,000	0.0568	Neutral Organic SAR (Baseline toxicity)

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002; #40315).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.9	4.9
Biodegradation Factor Used	1	1
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 further assessment is necessary.

The RIFM PNEC is 0.0568 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 02/07/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 11/20/18.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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. 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**
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? **No**
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open-chain? **No**
Q23. Aromatic? **No**
Q24. Monocarbocyclic with simple substituents? **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 Low (Class I)**

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