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Short review

RIFM fragrance ingredient safety assessment, 2-(*p*-menth-1-ene-10-yl) cyclopentanone, CAS Registry Number 95962-14-4

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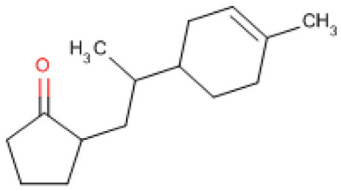
Version: 032918. This version replaces any previous versions.

Name: 2-(*p*-Menth-1-ene-10-yl)cyclopentanone

CAS Registry Number: 95962-14-41. Human Health Endpoint Summaries:



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., 2015, 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

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DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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
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 under the limits described in this safety assessment.

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

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

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

Summary: The use of this material under current conditions is supported by existing information.

2-(*p*-Menth-1-ene-10-yl)cyclopentanone 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 there are no safety concerns for 2-(*p*-Menth-1-ene-10-yl)cyclopentanone for skin sensitization under the current declared levels of use. The developmental and reproductive as well as the local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 2-(*p*-menth-1-ene-10-yl)cyclopentanone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2015b; RIFM, 1989c)
Repeated Dose Toxicity: NOAEL = 82 mg/kg/day (ECHA Dossier, 2-(*p*-Menth-1-ene-10-yl) cyclopentanone; 2017
Developmental and Reproductive Toxicity: NOAEL = 720 mg/kg/day (RIFM, 2015a)
Skin Sensitization: No safety concerns at current, declared use levels. (RIFM, 1989f)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 90% OECD 302C (RIFM, 2000c)
Bioaccumulation: Screening-level: 1004 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 72-h Algae NOEC: 0.07 mg/L (RIFM, 2001)
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: 72-h Algae NOEC: 0.07 mg/L (RIFM, 2001)
RIFM PNEC is: 7.0 µg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1 **Chemical Name:** 2-(*p*-Menth-1-ene-10-yl)cyclopentanone
2 **CAS Registry Number:** 95962-14-4
3 **Synonyms:** Cyclopentanone, 2-[2-(4-methyl-3-cyclohexen-1-yl) propyl]-; 2-[2-(4-Methylcyclohex-3-en-1-yl)propyl]cyclopentanone; Nectaryl; 2-(*p*-Menth-1-ene-10-yl)cyclopentanone
4 **Molecular Formula:** $C_{15}H_{24}O$
5 **Molecular Weight:** 220.56
6 **RIFM Number:** 5488
7 **Stereochemistry:** Isomer not specified. Three stereocenters and 8 total stereoisomers possible.

2. Physical data

1 **Boiling Point:** 308.22 °C (EPI Suite)
2 **Flash Point:** 324 °F TCC (162.22 °C)*
3 **Log K_{ow}:** Log Pow = 5.3 1. (RIFM, 2000b), log Pow = 4.8 (RIFM, 2010), 5.05 (EPI Suite)
4 **Melting Point**: 68.37 °C (EPI Suite)
5 **Water Solubility:** 1.655 mg/L (EPI Suite)
6 **Specific Gravity:** Not Available
7 **Vapor Pressure:** 0.000923 mm Hg @ 25 °C (EPI Suite), 0.000498 mm Hg @ 20 °C (EPI Suite v4.0)
8 **UV Spectra**: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol · cm^{-1})
9 **Appearance/Organoleptic:** A colorless clear liquid with a medium fruity, ketonic, peach, apricot, lactonic odor.*

*http://www.thegoodscentscompany.com/data/rw1052381.html#toorgano, retrieved 9/11/2017.

3. Exposure

1 **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2 **95th Percentile Concentration in Hydroalcoholics:** 0.050% (RIFM, 2015)
3 **Inhalation Exposure*:** 0.00029 mg/kg/day or 0.022 mg/day (RIFM, 2015)
4 **Total Systemic Exposure**:** 0.0027 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., 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:** 100%
2 **Oral:** Assumed 100%
3 **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
II*	II	I

*See Appendix below for explanation.

2 **Analogs Selected:**
a **Genotoxicity:** None
b **Repeated Dose Toxicity:** None
c **Developmental and 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)

2-(*p*-Menth-1-ene-10-yl)cyclopentanone 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 that contains 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 on 10/07/14.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-(*p*-menth-1-ene-10-yl)cyclopentanone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 2-(*p*-Menth-1-ene-10-yl)cyclopentanone was tested using the BlueScreen assay and found to be not genotoxic with

and without S9 metabolic activation (RIFM, 2013). The mutagenic activity of 2-(*p*-menth-1-ene-10-yl)cyclopentanone 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, and *Escherichia coli* strain WP2uvrA were treated with 2-(*p*-menth-1-ene-10-yl)cyclopentanone 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 dose in the presence or absence of S9 (RIFM, 2015b). Under the conditions of the study, 2-(*p*-menth-1-ene-10-yl)cyclopentanone was not mutagenic in the Ames test.

The clastogenicity of 2-(*p*-menth-1-ene-10-yl)cyclopentanone was assessed in an *in vivo* mouse micronucleus study conducted in compliance with GLP regulations and guideline equivalent with OECD TG 474. Male and female OF1 mice were treated with a daily oral dose of 2-(*p*-menth-1-ene-10-yl)cyclopentanone in Codex liquid paraffin at the concentration of 4800 mg/kg body weight. Animals were euthanized at 24, 48, and 72 h, at which time femora were removed and samples prepared. No significant increase in the ratio of normochromatic/polychromatic erythrocytes was observed (RIFM, 1989c). Under the conditions of the study, 2-(*p*-menth-1-ene-10-yl)cyclopentanone was considered not mutagenic in mice.

Based on the available data, 2-(*p*-menth-1-ene-10-yl)cyclopentanone does not present a concern for genotoxic potential.

Additional References: RIFM, 2014; RIFM, 1989a; RIFM, 2006.

Literature Search and Risk Assessment Completed On: 08/30/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 2-(*p*-menth-1-ene-10-yl)cyclopentanone 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 2-(*p*-menth-1-ene-10-yl) cyclopentanone. An OECD TG 407 and GLP-compliant repeated dose 28-day oral dietary toxicity study was conducted in Wistar rats (SPF-bred, 30 animals/sex/dose) administered 2-(*p*-menth-1-ene-10-yl) cyclopentanone daily for 28 days at concentrations of 0, 1000, 3000, and 10000 ppm in the diet followed by a 14-day recovery period. At the end of treatment, rats showed increased liver weights (approximately 45% and 33% for high-dose males and females and 17% at 3000 ppm in males [relative to body weight]). Furthermore, there was an increase in the relative thyroid weights in males at 10000 ppm, while higher absolute and relative kidney weights were observed in males at 3000 and 10000 ppm. No observations were reported at necropsy during macroscopic examination. Microscopic examination revealed increased incidence of follicular cell hypertrophy/hyperplasia in thyroid glands in high-dose males and dose-dependent increases in the incidence and severity of hyaline droplet accumulation in kidneys at all dose levels among treated males. Microscopic alterations in the thyroid gland were considered as adaptive, non-adverse effects, since thyroid cell hypertrophy may be related to hepatocyte hypertrophy due to the induction of hepatocyte drug metabolizing enzymes. This induction increases the turnover of T4 that results in secondary thyroid hypertrophy/hyperplasia due to stimulation of the hypothalamus-pituitary-thyroid axis (Hall, 2012). Hyaline droplets represent α-2μ-globulin, a normal protein that undergoes reabsorption in proximal cortical tubules in male rats causing secondary injury (proximal cortical tubule cell injury); however, appropriate confirmatory staining for α-2μ-globulin was not reported. Additionally, this protein is specific to male rats, and it is neither present in female rats nor in higher mammals including humans, and hence it is not considered a hazard to human health. Based on the liver weights recorded at 10000 ppm in both sexes, the NOAEL for 2-(*p*-menth-1-ene-10-yl) cyclopentanone was considered to be 3000 ppm, corresponding to 285 and 274 mg 2-(*p*-menth-1-ene-10-yl) cyclopentanone/kg body weight/day, for males and females, respectively (ECHA Dossier, 2-(*p*-Menth-1-ene-10-yl) cyclopentanone; 2017).

Another OECD TG 410, GLP-compliant repeated dose 4-week dermal toxicity study on 2-(*p*-menth-1-ene-10-yl) cyclopentanone (LRG 1371) was conducted in rats. Groups comprised of 5 rats/sex/group (Sprague Dawley, 9 weeks old) were treated once daily for 4 weeks at dose levels of 0, 50, 200, and 1000 mg/kg/day at dose volumes of 0.05, 0.2, and 1 mL/kg for the low-, mid-, and high-dose groups, respectively. Erythema and desquamation were observed at all dose levels more markedly in females than in males. Microscopically, minimal to moderate acanthosis with hyperkeratosis and hyperplasia of the sebaceous gland in all treated skin was observed in high-dose animals, but no inflammation or necrosis accompanied these findings. These findings were not attributed to treatment-related adverse effects but considered as a local reaction of epidermis after application of viscous substance. Based on the results, the NOAEL was established at 1000 mg/kg/day, the highest dose tested, since no systemic toxicity was reported among treated animals (RIFM, 1989b).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day or OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The dietary study provides the more conservative NOAEL and was considered for the repeated dose toxicity endpoint.

Thus, the derived NOAEL for the repeated dose toxicity data is 274/3 or 82 mg/kg/day.

Therefore, the 2-(*p*-menth-1-ene-10-yl) cyclopentanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-(*p*-menth-1-ene-10-yl) cyclopentanone NOAEL in mg/kg/day by the total systemic exposure to 2-(*p*-menth-1-ene-10-yl) cyclopentanone, 82/0.0027 or 30370.

In addition, the total systemic exposure to 2-(*p*-menth-1-ene-10-yl) cyclopentanone (2.7 μg/kg bw/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use. bib_RIFM_2015a.

*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: RIFM, 2012; Belsito, 2012.

Literature Search and Risk Assessment Completed On: 09/11/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2-(*p*-menth-1-ene-10-yl)cyclopentanone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on 2-(*p*-menth-1-ene-10-yl) cyclopentanone.

An OECD TG 421, GLP-compliant oral toxicity study was conducted on 2-(*p*-menth-1-ene-10-yl) cyclopentanone to evaluate the reproductive performance and developmental toxicity in treated rats. Four dose groups, 10 rats/sex/dose, were treated daily at 0, 1000, 3000, and 10000 ppm by the oral route via diet. Males were treated for 29 days while females were exposed for 40–55 days. The NOAEL for reproductive and developmental toxicity was considered to be 10000 ppm (corresponds to 743–750 mg/kg/day for males and 720–1226 mg/kg/day for females), the highest dose tested. At 10000 ppm, the findings were limited to parental toxicity characterized by increased liver and thyroid weights (correlated with hepatocellular hypertrophy and follicular cell hypertrophy microscopically) and hyaline droplet accumulation in kidneys. The most conservative oral NOAEL of 720 mg/kg/day was considered for the risk assessment of 2-(*p*-menth-1-ene-10-yl) cyclopentanone for the developmental and reproductive toxicity endpoints (RIFM, 2015a; cited in ECHA Dossier, 2017).

Therefore, the 2-(*p*-menth-1-ene-10-yl) cyclopentanone MOE for the

developmental and reproductive toxicity endpoints can be calculated by dividing the 2-(*p*-menth-1-ene-10-yl) cyclopentanone NOAEL in mg/kg/day by the total systemic exposure to 2-(*p*-menth-1-ene-10-yl) cyclopentanone, 720/0.0027 or 266667.

In addition, the total systemic exposure to 2-(*p*-menth-1-ene-10-yl) cyclopentanone (2.7 μg/kg bw/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: RIFM, 2012; Belsito, 2012.

Literature Search and Risk Assessment Completed On: 03/18/15.

10.1.4. Skin sensitization

Based on existing data, 2-(*p*-menth-1-ene-10-yl)cyclopentanone does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins. In guinea pigs, maximization tests did not present reactions indicative of sensitization (RIFM, 1989f). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 2500 μg/cm^2 of 2-(*p*-menth-1-ene-10-yl)cyclopentanone in dimethyl phthalate, no reactions indicative of sensitization was observed in any of the 53 volunteers (RIFM, 1996). Based on weight of evidence from structural analysis and animal and human data, 2-(*p*-menth-1-ene-10-yl)cyclopentanone does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/30/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-(*p*-menth-1-ene-10-yl)cyclopentanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-(*p*-menth-1-ene-10-yl)cyclopentanone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on lack of absorbance, 2-(*p*-menth-1-ene-10-yl)cyclopentanone does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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: 08/02/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-(*p*-menth-1-ene-10-yl)cyclopentanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-(*p*-menth-1-ene-10-yl)cyclopentanone. Based on the Creme RIFM model, the inhalation exposure is 0.022 mg/day. This exposure is 21.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/11/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-(*p*-menth-1-ene-10-yl)cyclopentanone 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, 2-(*p*-menth-1-ene-10-yl)cyclopentanone 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 2-(*p*-menth-1-ene-10-yl)cyclopentanone 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, 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.

10.2.2. Risk assessment

Based on current Volume of Use (2015), 2-(*p*-menth-1-ene-10-yl) cyclopentanone presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. RIFM, 2000a: The inherent biodegradability of the test material was determined by the manometric respirometry test according to the OECD 302C method.

30 mg/L of the test material was sealed in a vessel with culture medium for 28 days. 2-(*p*-Menth-1-ene-10-yl)cyclopentanone underwent 91% biodegradation in 28 days.

RIFM, 2000c: The ready biodegradability of the test material was determined by the manometric respirometry test. 100 mg/L of the test material was sealed in a vessel with culture medium for 28 days. 2-(*p*-Menth-1-ene-10-yl)cyclopentanone underwent 41% biodegradation in 39 days (28% in 28 days).

10.2.2.1.2. Ecotoxicity. RIFM, 1989e: A study was conducted to evaluate the acute toxicity of the test material over a 96-h period in freshwater fish (*Brachydanio rerio*) using a semi-static method following the OECD 203 guidelines. The 96-h LC50 was reported to be 5.47 mg/L.

RIFM, 2005a: A fish (*Danio rerio*) early life toxicity test was conducted according to the OECD 203 method under semi-static conditions. The 30-day LC50 was reported to be 0.34 mg/L with the overall NOEC of 0.14 mg/L.

RIFM, 2005b: Short-term chronic static renewal effluent toxicity tests with immature fathead minnows (*Pimephales promelas*) were conducted according to the EPA/600/4–90/027 and ASTM E729 methods. The 7-day NOECs were reported to be 0.62 mg/L and 1.24 mg/L for growth and survival, respectively.

RIFM, 2001: An algae inhibition test was conducted according to OECD 201 guidelines. The EC50 for growth inhibition was 0.46 mg/L and for growth rate reduction was 2.9 mg/L. The NOEC for growth inhibition and growth rate reduction were both 0.07 mg/L.

RIFM, 1989d: A study was conducted to evaluate inhibition of mobility in *Daphnia magna* by the test material according to the OECD 202 guidelines under static conditions. The 48-h EC50 for 2-(*p*-Menth-1-ene-10-yl)cyclopentanone was 0.49 mg/L.

RIFM, 2004: A *Daphnia magna* reproductive test was conducted following the OECD 211 guidelines under static conditions. The 21-day NOEC for the test material was reported to be 0.22 mg/L (nominal concentration) or 0.17 mg/L (average exposure concentration).

RIFM, 2005b: A *Daphnia magna* reproductive test was conducted according to EPA/600/4–90/027 and ASTM E729 method. The animals were exposed to 5 concentrations of 2-(*p*-menth-1-ene-10-yl)cyclopentanone for a period of 7 days. The LC50 was reported to be 4.97 mg/L, and the NOEC was 1.24 mg/L.

10.2.2.1.3. Other available data. 2-(p-Menth-1-ene-10-yl) cyclopentanone has been registered with REACH with no additional data.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	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>1.09</u>			1,000,000	0.00109	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.327	<u>0.246</u>	0.589	10,000	0.0246	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	5.47		0.14			
Daphnia		0.49	0.17			
Algae		0.46	<u>0.07</u>	10	7.0	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.8	4.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	10–100
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 7.0 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/16/17.

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.

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
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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