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RIFM fragrance ingredient safety assessment, cadinene, CAS Registry Number 29350-73-0

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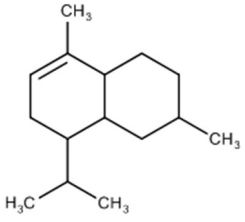
Name: Cadinene
CAS Registry Number: 29350-73-0



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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)

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

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

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

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

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

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

Cadinene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cadinene is not genotoxic. Data on read-across analog camphene (CAS # 79-92-5) 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 I material, and the exposure to cadinene is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; cadinene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cadinene 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2013a; RIFM, 2016; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 83.33 mg/kg/day.	(ECHA REACH Dossier: Camphene; ECHA, 2011)

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
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:	
Screening-level: 2.74 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 6392 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 0.021 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: 48-h *Daphnia magna* LC50: 0.021 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0021 μg/L

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

1. Identification

1. **Chemical Name:** Cadinene
2. **CAS Registry Number:** 29350-73-0
3. **Synonyms:** (1S-(1a,4a,4aa,6a,8 ab))-Decahydro-4-isopropyl-1,6-dimethylnaphthalene, didehydro derivative; 3,4,5,8,9,10-Hexahydro-4-isopropyl-1,6-dimethylnaphthalene; 1-Isopropyl-4,7-dimethyl-1,2,4a,5,8,8a-hexahydronaphthalene; Cadinene
4. **Molecular Formula:** $C_{15}H_{26}$
5. **Molecular Weight:** 206.37 g/mol
6. **RIFM Number:** 289
7. **Stereochemistry:** Four stereocenters and 16 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 124 °C at 9 mm Hg (Fragrance Materials Association [FMA]), 253.22 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 6.27 (EPI Suite)
4. **Melting Point**: 15.72 °C (EPI Suite)
5. **Water Solubility:** 0.05181 mg/L (EPI Suite)
6. **Specific Gravity:** 0.923 (FMA)
7. **Vapor Pressure:** 0.0241 mm Hg at 20 °C (EPI Suite v4.0), 0.003 mm Hg 20 °C (FMA), 0.0374 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm under neutral and basic conditions. Minor absorbance under acidic conditions; the molar absorption coefficient (320 L mol^{-1} • cm^{-1}) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless slightly viscous oil generally carrying the odor of the oil from which it is derived

3. Volume of use (Worldwide Band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.022% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000024 mg/kg/day or 0.0017 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00030 mg/kg/day (RIFM, 2018)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

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

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** Camphene (CAS # 79-92-5)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

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

8. Natural occurrence

Cadinene is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Pre-registered for 2010; no dossier available as of 09/16/21.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, cadinene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Cadinene was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013b). 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 cadinene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with cadinene in acetone at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2013a). Under the conditions of the study, cadinene was not mutagenic in the Ames test.

The clastogenic activity of cadinene was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with cadinene in dimethyl formamide (DMF) at concentrations up to 1000 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of metabolic activation. Cadinene did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system in the 3-h treatments but did induce binucleated cells with micronuclei in the 24-h treatment with questionable biological relevance (RIFM, 2016). Under the conditions of the study, cadinene was considered to be clastogenic in the *in vitro* micronucleus test.

To verify the results of the *in vitro* micronucleus test in a more biologically relevant system, a GLP-compliant 3D reconstructed skin micronucleus (RSMN) assay was conducted to evaluate the genotoxic potential of cadinene (CAS # 29350-73-0) in EpiDerm. Acetone was used as the vehicle. EpiDerm tissues were treated with cadinene at 24-h intervals for 48 and 72 h, at concentrations up to 100 mg/mL (highest tested dose). Cadinene did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration (RIFM, 2017). Under the conditions of the study, cadinene was concluded to be negative for the induction of micronuclei in the RSMN in EpiDerm.

Based on the data available, cadinene does not present a concern for genotoxic potential.

Additional References: Zeiger (1988); Galloway (1987).
Literature Search and Risk Assessment Completed On: 10/02/20

11.1.2. Repeated dose toxicity

The MOE for camphene is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on cadinene. Read-across material camphene (CAS # 79-92-5) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 407 and GLP-compliant study, camphene was administered orally (via gavage) to 5 SPF Wistar rats/sex/group at doses of 0, 62.5, 250, and 1000 mg/kg/day. During the study, no alterations in general behavior and overall health were observed. However, animals in the 1000 mg/kg/day dose group demonstrated increased salivation. Although hematological tests revealed no evidence of compound-related toxicity, male animals receiving the 1000 mg/kg/day dose showed increased blood urea nitrogen and decreased phosphorus levels. Animals in the highest-dose group demonstrated increased absolute and relative liver weights, as well as increased vacuolization in hepatocytes. In males, macroscopic evaluation showed spotted kidneys in 2/5 animals at 62.5 mg/kg/day, whereas pale kidneys were observed in 3/5 males in the 250 mg/kg/day group and all males in the 1000 mg/kg/day group. Additionally, male rats receiving 62.5–1000 mg/kg/day doses exhibited test substance accumulation in the renal epithelium of proximal tubules along with single-cell necrosis, an effect not seen in females. These toxic renal effects that were observed in male rats are not considered to be a human health concern. Therefore, the NOAEL for repeated dose toxicity was considered to be 250 mg/kg/day, based on the hepatotoxic effects observed at the highest dose (ECHA, 2011).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day or OECD 407 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 250/3 or 83.33 mg/kg/day.

Therefore, the cadinene MOE for the repeated dose toxicity endpoint can be calculated by dividing the camphene NOAEL in mg/kg/day by the total systemic exposure to cadinene, 83.33/0.0003, or 277767.

Additionally, the total systemic exposure to cadinene (0.30 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007) 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: US EPA, 2006; NIH, 2020; OECD, 1993

Literature Search and Risk Assessment Completed On: 09/08/20

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on cadinene or any read-across materials. The total systemic exposure to cadinene is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on cadinene or any of the read-across materials. The total systemic exposure to cadinene (0.30 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) 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: 10/01/20

11.1.4. Skin sensitization

Based on existing data and the application of DST, cadinene does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for cadinene. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1972). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for cadinene that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None

Literature Search and Risk Assessment Completed On: 09/02/20

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available

Table 1
Maximum acceptable concentrations for cadinene that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	4.0×10^{-4}%
2	Products applied to the axillae	0.021%	0.0024%
3	Products applied to the face using fingertips	0.41%	0.0025%
4	Fine fragrance products	0.39%	0.022%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0031%
6	Products with oral and lip exposure	0.23%	2.0×10^{-4}%
7	Products applied to the hair with some hand contact	0.79%	3.0×10^{-4}%
8	Products with significant ano-genital exposure	0.041%	No Data[b]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.015%
10	Household care products with mostly hand contact	2.7%	0.10%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[b]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.082%

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

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

for cadinene in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm under neutral and basic conditions and minor absorbance under acidic conditions. The corresponding molar absorption coefficient (320 L mol^{-1} • cm^{-1} under acidic conditions) is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of significant absorbance, cadinene does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm under neutral and basic conditions. There was minor absorbance under acidic conditions; the molar absorption coefficient (320 L mol^{-1} • cm^{-1}) 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: 09/01/20

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on cadinene. Based on the Creme RIFM Model, the inhalation exposure is 0.0017 mg/day. This exposure is 823.5 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None

Literature Search and Risk Assessment Completed On: 09/30/20

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cadinene 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, cadinene 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 cadinene as not possibly persistent but 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).

11.2.2. Risk assessment

Based on current VoU (2015), cadinene presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

Other available data: Cadinene has been pre-registered for REACH with no additional data at this time.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.27	6.27
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 additional assessment is necessary.

The RIFM PNEC is 0.0021 μg/L. The revised PEC/PNECs for EU and NA are <1 and 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: 10/04/20

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.054			1000000	5.34E-05	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.025	0.021	0.079	10000	0.0021	Neutral Organic

- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/16/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112860.

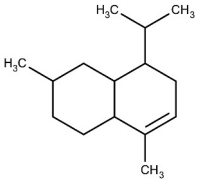
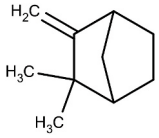
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of alert system.

	Target Material	Read-across Material
Principal Name	Cadinene	Camphene
CAS No.	29350-73-0	79-92-5
Structure		
Similarity (Tanimoto Score)		0.58
Endpoint		• Repeated dose toxicity
Molecular Formula	$C_{15}H_{26}$	$C_{10}H_{16}$
Molecular Weight	206.37	136.24
Melting Point (°C, EPI Suite)	15.72	52.00
Boiling Point (°C, EPI Suite)	253.22	159.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.99	333.31
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.05	4.60
Log K_{OW}	6.27	4.22
J_{max} (μg/cm^2/h, SAM)	0.01	0.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	44684.32	16313.33
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Aliphatic/Alicyclic hydrocarbons (Alpha 2u-globulin nephropathy) Rank C
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on cadinene (CAS # 29350-73-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, camphene (CAS # 79-92-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusion

- Camphene (CAS # 79-92-5) was used as a read-across analog for the target material cadinene (CAS # 29350-73-0) for the repeated dose toxicity endpoint.
  - o The target material and read-across analog belong to the class of aliphatic hydrocarbons.
  - o The key difference between the target substance and the read-across analog is that the target material is a bicyclic compound containing a vinylene double bond whereas the read-across analog is a bridged structure with an isolated vinyl group. Moreover, the target material has 1 isopropyl and 2 methyl substituents on the bicyclic ring whereas the read-across analog has 2 methyl substituents. These structural differences are predicted to make the read-across analog more reactive than the target material.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score presented in the above table. The Tanimoto score is mainly driven by the ester fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant for the skin sensitization endpoint.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the skin sensitization endpoint are consistent between the target substance and the read-across analog as seen in the table above.
  - o The target substance and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read-across analog and the target substance.

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