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RIFM fragrance ingredient safety assessment, sabinene, CAS Registry Number 3387-41-5

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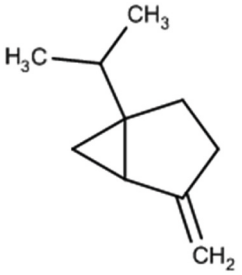
Name: Sabinene
CAS Registry Number: 3387-41-5



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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., 2021)
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.,

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

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

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

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

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is 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.

Sabinene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that sabinene 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 and developmental toxicity endpoints. The fertility and local respiratory toxicity endpoints were evaluated using the threshold for toxicological concern (TTC) for a Cramer Class I material, and the exposure to sabinene 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; sabinene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; sabinene 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, 2014; RIFM, 2021; Xie, 2021)
Repeated Dose Toxicity: NOAEL = 83.33 mg/kg/day.	(ECHA REACH Dossier: Camphene; ECHA, 2011)
Reproductive Toxicity: Developmental toxicity NOAEL: 250 mg/kg/day. Fertility: Exposure is below the TTC.	(ECHA REACH Dossier: Camphene; ECHA, 2011)
Skin Sensitization: No safety concerns at current, 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: Critical Measured Value: 81% after 61 days (OECD 301F)	RIFM (2010b)
Bioaccumulation: Screening-level: 576.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1.005 mg/L	(RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 1.005 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.001005 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe (No VoU): Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Sabinene
2. **CAS Registry Number:** 3387-41-5
3. **Synonyms:** Bicyclo[3.1.0]hexane, 4-methylene-1-(1-methylethyl)-; 1-Isopropyl-4-methylenebicyclo[3.1.0]hexane; Sabinene
4. **Molecular Formula:** $C_{10}H_{16}$
5. **Molecular Weight:** 136.24 g/mol
6. **RIFM Number:** 6750
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 141.81 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** Log P_{ow} = 4.6 (RIFM, 2010a), 4.69 (EPI Suite)
4. **Melting Point**: 21.55 °C (EPI Suite)
5. **Water Solubility:** 2.494 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 5.44 mm Hg at 20 °C (EPI Suite 4.0), 7.36 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Arctander, Volume II, 1969: Colorless mobile liquid Insoluble in water, soluble in alcohol and oils. Warm, oily-peppery, woody-herbaceous, and spicy odor of moderate to poor tenacity.

3. Volume of use (worldwidew band)

1. **Volume of Use (Worldwide Band):** <0.1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.027% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000031 mg/kg/day or 0.0023 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00050 mg/kg/day (RIFM, 2018)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Camphene (CAS # 79-92-5)
   c. **Reproductive Toxicity:** Camphene (CAS # 79-92-5)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

Sabinene is reported to occur in the following foods by the VCF:

Cardamom (Ellettaria cardamomum Maton.)	Laurel (Laurus nobilis L.)
	Mastic (Pistacia lentiscus)
Citrus fruits	Mentha oils
Coriander seed (Coriandrum sativum L.)	Pepper (Piper nigrum L.)
Fennel (Foeniculum vulg., Ssp. capillaceum; Var.)	Salvia species
	Wormwood oil (Artemisia absinthium L.)

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*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. This is a partial list.

9. REACH dossier

Available; accessed 01/02/21 (ECHA, 2018).

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, sabinene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Sabinene was assessed in the BlueScreen assay and found negative for genotoxicity and positive for cytotoxicity (positive: <80% relative cell density) with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of sabinene 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 sabinene in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2021). Under the conditions of the study, sabinene was not mutagenic in the Ames test.

The clastogenic activity of sabinene 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 sabinene in ethanol at concentrations up to 1360 μg/mL in the dose range finding (DRF) study, and micronuclei analysis was conducted up to 200 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Sabinene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels concentration in either the presence or absence of an S9 activation system (Xie, 2021). Under the conditions of the study, sabinene was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/19/21.

11.1.2. Repeated dose toxicity

The MOE for sabinene is sufficient 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 sabinene. Read-across material camphene (CAS # 79-92-5; see Section VI) has sufficient repeated dose toxicity data.

In an OECD 407 and GLP-compliant study, camphene was administered via gavage to 5 SPF Wistar rats/sex/group at doses of 0, 62.5, 250, and 1000 mg/kg/day for 28 days. 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 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 in all males treated with 1000 mg/kg/day. Additionally, male rats receiving 62.5–1000 mg/kg/day doses exhibited eosinophilic globule accumulation in the renal epithelium of proximal tubules along with single-cell necrosis, an effect not seen in females. These renal effects that were observed in male rats are consistent with α2u-globulin nephropathy and, thus, 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*. Thus, the derived NOAEL for the repeated dose toxicity data is 250/3 or 83.33 mg/kg/day.

Therefore, the sabinene 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 sabinene, 83.33/0.0005 or 166660.

Additionally, the total systemic exposure to sabinene (0.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 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: None.

Literature Search and Risk Assessment Completed On: 10/13/21.

11.1.3. Reproductive Toxicity

The MOE for sabinene is sufficient for the developmental toxicity endpoint at the current level of use. There are insufficient fertility data on sabinene nor any read-across materials. The total systemic exposure to sabinene is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on sabinene. Read-across material camphene (CAS # 79-92-5; see Section VI) has sufficient developmental toxicity data.

There are sufficient data on camphene that can be used to support the developmental toxicity endpoint. An OECD 414/GLP prenatal developmental toxicity study was conducted in pregnant female Sprague Dawley rats. Groups of 20 rats/dose were administered with camphene via oral gavage at doses of 0, 250, or 1000 mg/kg/day in sesame oil from GDs 6–15. All animals were euthanized on GD 20 and submitted to gross necropsy. Slight but not statistically significant increases in resorption rate, and consequently, in post-implantation loss (11.5% vs. 5.2% in controls) were observed in the high-dose group animals. There was 1 malformed fetus from the high-dose group (shifted and fused dorsal, lumbar, and coccygeal vertebrae, bilateral crossed legs, stump tail, omphalocele). Under the conditions of the study, the NOAEL for maternal toxicity was considered to be 250 mg/kg/day. The NOAEL for developmental toxicity was also considered to be 250 mg/kg/day, based on the slight increase in resorption rate at 1000 mg/kg/day and malformation observed in 1 fetus at the highest dose (ECHA, 2011).

Therefore, the sabinene MOE for the developmental toxicity endpoint can be calculated by dividing the camphene NOAEL in mg/kg/day by the total systemic exposure to sabinene, 1000/0.0005, or 2000000.

In addition, the total systemic exposure to camphene (0.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on sabinene nor any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to sabinene (0.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/28/21.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a direct peptide reactivity assay (DPRA), sabinene demonstrated minimal reactivity, confirming this prediction (ECHA, 2018). Acting conservatively due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for sabinene 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: 10/21/21.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for sabinene in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, sabinene 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. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al.,

Table 1
Maximum acceptable concentrations for sabinene 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%	0.0015%
2	Products applied to the axillae	0.021%	0.0032%
3	Products applied to the face using fingertips	0.41%	3.7×10^{-4}%
4	Fine fragrance products	0.39%	0.027%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0035%
6	Products with oral and lip exposure	0.23%	0.0033%
7	Products applied to the hair with some hand contact	0.79%	4.1×10^{-4}%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0015%
10	Household care products with mostly hand contact	2.7%	0.0031%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.12%

Note: [a]For a description of the categories, refer to the IFRA/RIFM Information Booklet.
bNo reported use.
cFragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/13/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on sabinene. Based on the Creme RIFM Model, the inhalation exposure is 0.0023 mg/day. This exposure is 608.7 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: Helmig et al., 1999a; Helmig et al., 1999b.

Literature Search and Risk Assessment Completed On: 11/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of sabinene was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers of screening-level 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 (EPI Suite v4.11), 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, sabinene was identified as a fragrance material with no 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 did not identify sabinene as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WOE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), sabinene presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2010b**: The ready biodegradability of the test material was evaluated using the Manometric Respirometry Test according to the OECD 301F. Biodegradation of 81% was observed after 61 days (76% after 28 days).

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Sabinene has been registered for REACH with no additional information available 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

Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.6	4.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	No VoU	<1
Risk Characterization: PEC/PNEC	**NA**	**<1**

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

The RIFM PNEC is 0.001005 μg/L. The revised PEC/PNECs for EU (No VoU) and NA: not applicable; the material was cleared at screening-level 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: 11/15/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/27/22.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113066.

Appendix

Read-across Justification

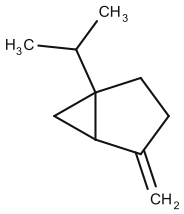
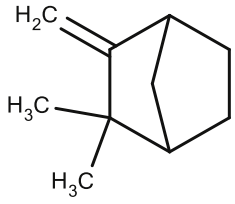
Methods

The read-across analog was 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 material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.005			1000000	0.001005	

- 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization 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).

	Target Material	Read-across Material
Principal Name	Sabinene	Camphene
CAS No.	3387-41-5	79-92-5
Structure		
Similarity (Tanimoto Score)		0.91
Endpoint		• Repeated dose toxicity • Developmental toxicity
Molecular Formula	$C_{10}H_{16}$	$C_{10}H_{16}$
Molecular Weight (g/mol)	136.238	136.238
Melting Point (°C, EPI Suite)	−21.55	52.00
Boiling Point (°C, EPI Suite)	141.81	159.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	9.81E+02	3.33E+02
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2.49E+00	4.60E+00
Log KOW	4.69	4.22
J_{max} (mg/cm^2/h, SAM)	0.53	0.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.63E+04	1.63E+04
Repeated Dose Toxicity		
Repeated Dose (HESS)	Aliphatic/alicyclic hydrocarbons (α2u-globulin nephropathy) Rank C	Aliphatic/alicyclic hydrocarbons (α2u-globulin nephropathy) Rank C
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Metabolism		
Metabolites	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on sabinene (CAS # 3387-41-5). 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.

- Camphene (CAS # 79-92-5) was used as a read-across analog for the target material, sabinene (CAS # 3387-41-5), for the repeated dose toxicity and developmental toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of bicyclic monoterpenes.
  - o The target material and the read-across analog share an unsaturated multicyclic ring structure.
  - o The key difference between the target material and the read-across analog is that the target material has a 5-membered and 3-membered ring fused, whereas the read-across analog has 2 5-membered rings in a bridge structure. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have been classified by the repeated dose HESS categorization as Aliphatic/Alicyclic hydrocarbons (α2u-globulin nephropathy), Rank C. This alert was given because the molecules possess an isopropyl substructure and their Log K_{OW}s are each greater than 3.5. The data described in the repeated dose section confirms that the MOE of the target material is adequate at the current level of use. Therefore, the alert is superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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