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Short Review

RIFM fragrance ingredient safety assessment, camphene, CAS Registry Number 79-92-5

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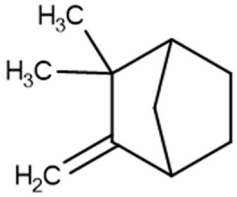

Name: Camphene
CAS Registry Number: 79-92-5
Additional CAS Numbers: 5794-04-7* (No reported use)
*Included because the materials are isomers

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., 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 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

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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.

Camphene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that camphene is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and developmental toxicity endpoints. The fertility and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to camphene is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across analog β-pinene (CAS # 127-91-3) provided camphene a No Expected Sensitization Induction Level (NESIL) of 7200 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; camphene is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; camphene 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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Camphene; ECHA, 2011a)
Repeated Dose Toxicity: NOAEL = 3.33 mg/kg/day.	(ECHA REACH Dossier: Camphene; ECHA, 2011a)
Reproductive Toxicity: Developmental toxicity: NOAEL = 1000 mg/kg/day. Fertility: No fertility NOAEL available. Exposure is below the TTC.	(ECHA REACH Dossier: Camphene; ECHA, 2011a)
Skin Sensitization: NESIL = 7200 μg/cm^2.	RIFM (2021a)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/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: 78% (OECD 301F)	(RIFM, 2010b)
Bioaccumulation:	
Critical Measured Value: BCF: 922–1290 (OECD 305C)	(ECHA REACH Dossier: Camphene; ECHA, 2011a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 0.615 mg/L	(ECOSAR v2.0; 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: 0.615 mg/L	(ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 0.0615 μg/L	

- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe: <1

1. Identification

Chemical Name: Camphene	Chemical Name: *l*-camphene
CAS Registry Number: 79-92-5	**CAS Registry Number:** 5794-04-7
Synonyms: Bicyclo[2.2.1]heptane, 2,2-dimethyl-3-methylene-; 2,2-Dimethyl-3-methylenenorbornane; 3,3-Dimethyl-2-methylenenorcamphane; dl-Camphene; (+-)-2,2-Dimethyl-3-methylenebicyclo [2.2.1]heptane; 3,3-Dimethyl-2-methylenenorbornane; カンフエン; 2,2-Dimethyl-3-	**Synonyms:** (1S)-2,2-Dimethyl-3-methylenebicyclo[2.2.1]heptane; *l*-camphene; 2,2-Dimethyl-3-methylenebicyclo[2.2.1]heptane; Bicyclo [2.2.1]heptane, 2,2-dimethyl-3-methylene

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(*continued*)

Chemical Name: Camphene	Chemical Name: *l*-camphene
methylenebicyclo[2.2.1]heptane; Camphene	
Molecular Formula: $C_{10}H_{16}$	**Molecular Formula:** $C_{10}H_{16}$
Molecular Weight: 136.23 g/mol	**Molecular Weight:** 136.23 g/mol
RIFM Number: 532	**RIFM Number:** None
Stereochemistry: Isomer unspecified. Two stereocenters and 4 total stereoisomers are possible.	**Stereochemistry:** Isomer unspecified. Two stereocenters and 4 total stereoisomers are possible.

2. Physical data

CAS # 79-92-5	CAS # 5794-04-7
Boiling Point: 160 °C (Fragrance Materials Association [FMA]), 150.8 °C (EPI Suite)	**Boiling Point:** 150.8 °C (EPI Suite)
Flash Point: 105 °F; closed cup (FMA), 30 °C (Globally Harmonized System)	**Flash Point:** Not available
Log K_{OW}: 4.35 (EPI Suite)	**Log K_{OW}:** 4.35 (EPI Suite)
Melting Point: 15.3 °C (EPI Suite)	**Melting Point:** 15.3 °C (EPI Suite)
Water Solubility: 6.275 mg/L (EPI Suite)	**Water Solubility:** 6.275 mg/L (EPI Suite)
Specific Gravity: 0.866 (FMA)	**Specific Gravity:** Not available
Vapor Pressure: 1.14 mm Hg at 20 °C (EPI Suite v4.0), 2.2 mm Hg at 20 °C (FMA), 1.78 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 1.14 mm Hg at 20 °C (EPI Suite v4.0), 1.78 mm Hg at 25 °C (EPI Suite)
UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** Not available
Appearance/Organoleptic: A colorless, granular-crystalline, tenacious mass	**Appearance/Organoleptic:** A colorless, granular-crystalline, tenacious mass

3. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient* (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0091% (RIFM, 2021b)
2. **Inhalation Exposure**:** 0.00012 mg/kg/day or 0.0094 mg/day (RIFM, 2021b)
3. **Total Systemic Exposure***:** 0.00046 mg/kg/day (RIFM, 2021b)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

**95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford, 2015; Safford, 2017; Comiskey, 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; Safford, 2015; Safford, 2017; Comiskey, 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 v4.5
I	I	I

2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** β-pinene (CAS # 127-91-3)
e. **Photoirritation/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.
Additional References: None.

8. Natural occurrence

Camphene is reported to occur in the following foods by the VCF*:

Citrus fruits	Mastic (*Pistacia lentiscus*)
Thyme (*Thymus* species)	Pepper (*Piper nigrum* L.)
Fennel (*Foeniculum vulg.*, ssp. *Capillaceum*; Var.)	*Cinnamomum* species
Salvia species	Ginger (*Zingiber* species)
Mentha oils	*Ocimum* species

l-Camphene is reported to occur in the following foods by the VCF:

Citrus fruits	Pepper (*Piper nigrum* L.)
Mastic (*Pistacia lentiscus*)	Rosemary (*Rosmarinus officinalis* L.)
Nutmeg (*Myristica fragrans* Houttuyn)	

*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 for camphene; accessed on 04/20/23; *l*-camphene has been pre-registered for 2010; no dossier available as of 04/20/23.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for camphene are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.13
2	Products applied to the axillae	0.16

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
3	Products applied to the face/body using fingertips	0.25
4	Products related to fine fragrances	3.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.78
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.25
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.38
5D	Baby cream, oil, talc	0.085
6	Products with oral and lip exposure	0.76
7	Products applied to the hair with some hand contact	0.38
8	Products with significant ano-genital exposure (tampon)	0.085
9	Products with body and hand exposure, primarily rinse-off (bar soap)	6.0
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.9
10B	Aerosol air freshener	6.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.085
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For camphene, the basis was the subchronic reference dose of 0.83 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 7200 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.10.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, camphene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476. Mouse lymphoma L5178Y/TK ± cells were treated with camphene in ethanol at concentrations of 80 μg/mL for 3 h or 24 h in the absence of metabolic activation or 3 h in the presence of S9. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (ECHA, 2011a). Under the conditions of the study, camphene was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of camphene was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in sesame oil via oral gavage to groups of male and female NMRI mice. Doses of 0 and 4000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011a). Under the conditions of the study, camphene was considered to be not clastogenic in the *in vivo* micronucleus test.

Additional References: ECHA, 2011a.

Literature Search and Risk Assessment Completed On: 04/01/22.

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 sufficient repeated dose toxicity data on camphene. In an OECD 407 and GLP-compliant study, camphene was orally (via gavage) administered 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 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, a 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 test material 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, 2011a).

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 camphene 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 camphene, 83.33/0.00046, or 181152.

Additionally, the total systemic exposure to camphene (0.46 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.

11.1.3. Derivation of subchronic reference dose (RfD)

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 0.83 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for camphene was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 83 mg/kg/day by the uncertainty factor, 100 = 0.83 mg/kg/day.

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

Additional References: OECD SIDS, 1993.

Literature Search and Risk Assessment Completed On: 03/29/22.

11.1.4. Reproductive Toxicity

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

There are no fertility data on camphene or on any read-across materials. The total systemic exposure to camphene is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

11.1.4.1. Risk assessment. There are sufficient data on camphene that can be used to support the developmental toxicity endpoint. An OECD 414/GLP-compliant prenatal developmental toxicity study was conducted in pregnant female Sprague Dawley rats. Groups of 20 rats/dose were administered 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. At 1000 mg/kg/day, a statistically significant reduction in motor activity was observed, and salivation commenced within 5–20 min of dosing and lasted for up to 6 h in 6/20 dams after the first dosing. Two high-dose dams also exhibited salivation after the second dosing. Food consumption in high-dose group animals was impaired transiently on GDs 7, 8, and 9 by 6%, 22%, and 10%, respectively. 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, and omphalocele). This incident was not considered to be of toxicological concern since 1 fetus in the control group also demonstrated a stump tail. 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 considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2011a).

Therefore, the camphene MOE for the developmental toxicity endpoint can be calculated by dividing the camphene NOAEL in mg/kg/day by the total systemic exposure to camphene, 1000/0.00046 or 2173913.

Table 1
Summary of existing data on β-pinene as a read-across for camphene.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[4]	Buehler[4]
Weak	7205	8280	NA	7200	7250	Negative	NA
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	NA	NA	NA		No alert found	Michael addition	Michael addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available

[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[2]Data derived from CNIH or HMT

[3]WoE NESIL limited to 2 significant figures

[4]Studies conducted according to the OECD TG 406 are included in the table.

[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

In addition, the total systemic exposure to camphene (0.46 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 camphene or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to camphene (0.46 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: Hasegawa, 1978; OECD SIDS, 1993.

Literature Search and Risk Assessment Completed On: 03/29/22.

11.1.5. Skin sensitization

Based on the existing data and read-across material β-pinene (CAS # 127-91-3), camphene is considered a skin sensitizer with a defined NESIL of 7200 μg/cm^2.

11.1.5.1. Risk assessment. Limited skin sensitization data are available for camphene. Therefore, read-across material β-pinene (CAS # 127-91-3; see Section VI) was used for the risk assessment of camphene. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, camphene is a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). In a murine local lymph node assay (LLNA), read-across material β-pinene was found to be not sensitizing up to the highest tested concentration of 100% (Wei et al., 2010). However, in another LLNA, read-across material *l*-β-pinene was found to be sensitizing with an EC3 value of 29% (7250 μg/cm^2) (ECHA, 2011b). In an open epicutaneous test, camphene showed no reactions indicative of sensitization at 4% (Klecak, 1985). Further, in guinea pig maximization and open epicutaneous tests, read-across material β-pinene did not present reactions indicative of sensitization (Wei et al., 2006; Klecak, 1985). In human maximization tests, no skin sensitization reactions were observed with camphene or read-across material β-pinene at 2760 μg/cm^2 or 8280 μg/cm^2, respectively (RIFM, 1974; RIFM, 1975). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 7205 μg/cm^2 of read-across material β-pinene in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 114 volunteers (RIFM, 2021a).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies on the read-across material and the target material, camphene is a sensitizer with a WoE NESIL of 7200 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 0.83 mg/kg/day.

Additional References: Ishihara et al., 1986; Hausen et al., 1999.

Literature Search and Risk Assessment Completed On: 04/03/22.

11.1.6. Photoirritation/photoallergenicity

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

11.1.6.1. Risk assessment. There are no photoirritation studies available for camphene 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 photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, camphene does not present a concern for photoirritation or photoallergenicity.

11.1.7. 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 photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/21/22.

11.1.8. Local Respiratory Toxicity

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

11.1.8.1. Risk assessment. There are insufficient inhalation data available on camphene. Based on the Creme RIFM Model, the inhalation exposure is 0.0094 mg/day. This exposure is 148.9 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: Kovar et al., 1987; Boyd, 1970; Helmig et al., 1999a; Helmig et al., 1999b.

Literature Search and Risk Assessment Completed On: 03/23/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of camphene 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, camphene was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify camphene 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, 2017a). 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.

11.2.1.1. Risk assessment. Based on the current VoU (2019), camphene presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 2010a:** The inherent biodegradability of the test material was determined by a manometric respiratory method according to the OECD 302C method. Under the conditions of this study, biodegradation of 76% was observed after 61 days.

RIFM, 2010b: The ready biodegradability of the test material was evaluated according to the OECD 301F method. After 28 days, biodegradation of 78% was observed.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Camphene has been registered under REACH, and the following data is available (ECHA, 2011a):

A fish (*Brachydanio rerio*) acute toxicity study was conducted according to the OECD 203 method under flow-through conditions. The 96-h LC50 was reported to be 0.72 mg/L.

A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 was reported to be 0.72 mg/L (mean measured concentration).

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50, based on the growth rate, was reported to be greater than 1000 mg/L.

11.2.1.3. Risk assessment refinement. Since camphene has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.3	4.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	10–100	10–100
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 0.0615 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/29/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 04/20/23.

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. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.830			1000000	0.00183	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.843	0.615	1.123	10000	0.0615	Neutral Organics

Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114212.

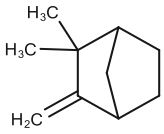
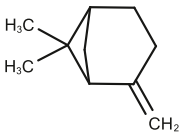
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 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, 2017b).

- 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 (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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Camphene	β-Pinene
CAS No.	79-92-5	127-91-3
Structure		
Similarity (Tanimoto Score)		0.92
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{10}H_{16}$	$C_{10}H_{16}$
Molecular Weight (g/mol)	136.24	136.24
Melting Point (°C, EPI Suite)	−15.30	−15.30
Boiling Point (°C, EPI Suite)	150.80	150.80
Vapor Pressure (Pa @ 25°C, EPI Suite)	237	334
Log Kow (KOWWIN v1.68 in EPI Suite)	4.22	4.16
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.6	7.061
J_{max} (μg/cm^2/h, SAM)	0.908	111.796
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.63E+004	1.63E+004
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)	• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on camphene (CAS # 79-92-5). 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, β-pinene (CAS # 127-91-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- β-Pinene (CAS # 127-91-3) was used as a read-across analog for the target material, camphene (CAS # 79-92-5), for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the class of bicyclic monoterpenes.
  - o The key difference between the target material and the read-across analog is that the read-across analog has [3.3.1] bicyclic rings while the target material has [2.2.1] bicyclic rings. The target material and the read-across analog are structural isomers. 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 a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, 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 an alert of moderately reactive by GSH rules from the OECD QSAR Toolbox protein binding potency model. The alert is due to the cycloalkane substructure and not because of the presence of the vinyl bond. Based on available data for β-pinene and α-pinene, β-pinene is considered a weak sensitizer. The data for the read-across material and the target are consistent with *in silico* alerts for the target material.
  - 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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