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Short review

RIFM fragrance ingredient safety assessment, Fenchone, CAS Registry Number 1195-79-5

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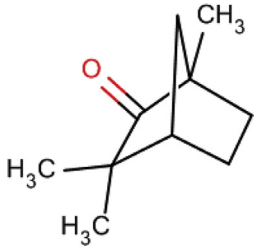
Version: 042618. This version replaces any previous versions.
Name: Fenchone CAS Registry Number: 1195-79-5
Additional CAS Numbers*:
4695-62-9 *d*-Fenchone
7787-20-4 *l*-Fenchone
*These materials are included in this assessment because the materialsare isomers.



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

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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; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api 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 use of this material under current conditions is supported by existing information.

Fenchone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that fenchone is not genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials. The reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). The repeated dose toxicity endpoint was completed using the read-across analog 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS# 76-22-2), which provided fenchone an MOE > 100. The developmental toxicity endpoint was completed using read-across analogs 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS# 76-22-2) and *d*-camphor (CAS# 464-49-3), which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Bornan-2-one)
Developmental and Reproductive Toxicity: Developmental NOAEL = 1000 mg/kg/day. No reproductive NOAEL, the exposure is below the TTC.	(Leuschner, 1997)
Skin Sensitization: Not a sensitization concern. Exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 85% (OECD 301F) (RIFM, 2010b)

Bioaccumulation: Screening-level: 97.61 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 61.73 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: 61.73 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.06173 µg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

Chemical Name: Fenchone	Chemical Name: d-Fenchone	Chemical Name: l-Fenchone
CAS Registry Number: 1195-79-5	**CAS Registry Number:** 4695-62-9	**CAS Registry Number:** 7787-20-4
Synonyms: Bicyclo [2.2.1]heptan-2-one, 1,3,3-trimethyl-; 3,3-Dimethyl-8,9-dinorbornan-2-one; 1,3,3,-Trimethyl-2-norbornane; 1,3,3-Trimethylbicyclo [2.2.1]heptan-2-one; Fenchone	**Synonyms:** Bicyclo [2.2.1]heptan-2-one, 1,3,3-trimethyl-, d-; d-2-Fenchanone; (1S)-1,3,3-Trimethylbicyclo (2.2.1)heptan-2-one; 1,3,3-Trimethylbicyclo (2.2.1)heptan-2-one; 1,3,3-Trimethylbicyclo [2.2.1]heptan-2-one; d-1,3,3-Trimethyl-2-norbornanone; d-1,3,3-Trimethyl-2-norcamphanone	**Synonyms:** Bicyclo [2.2.1]heptan-2-one, 1,3,3-trimethyl-, (1R)-; 1,3,3-Trimethylbicyclo [2.2.1]heptan-2-one; l-1,3,3-Trimethylbicyclo [2.2.1]heptan-2-one; 1,3,3-Trimethylnorbornane-2-one
Molecular Formula: $C_{10}H_{16}O$	**Molecular Formula:** $C_{10}H_{16}O$	**Molecular Formula:** $C_{10}H_{16}O$
Molecular Weight: 152.24	**Molecular Weight:** 152.24	**Molecular Weight:** 152.24
RIFM Number: 669	**RIFM Number:** 5370 5046	**RIFM Number:** 5370

2. Physical data*

1. **Boiling Point:** 193 °C (FMA), 203.89 °C (EPI Suite)
2. **Flash Point:** 64 °C (GHS), 147 °F;CC (FMA)
3. **Log K_{ow}:** 3.04 (EPI Suite), log Pow = 2.6 (RIFM, 2010a)
4. **Melting Point:** 28.07 °C (EPI Suite)
5. **Water Solubility:** 73.14 mg/L (EPI Suite)
6. **Specific Gravity:** 0.948 (FMA)
7. **Vapor Pressure:** 0.502 mm Hg @ 20 °C (EPI Suite v4.0), 0.2 mm Hg 20C (FMA), 0.721 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorbance below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not available

*Physical data are identical for all materials included in this assessment (see Table 1).

3. Exposure***

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0060% (RIFM, 2014c)
4. **Inhalation Exposure*:** 0.000093 mg/kg/day or 0.0067 mg/day (RIFM, 2014c)
5. **Total Systemic Exposure **:** 0.00029 mg/kg/day (RIFM, 2014c)

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

***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 hydroalcoholics, inhalation exposure, and total exposure.

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

*See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS # 76-22-2)
   c. **Developmental and Reproductive Toxicity:** 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS # 76-22-2) and *d*-camphor (CAS # 464-49-3)
   d. **Skin Sensitization:** None

Table 1
Acceptable exposure limits for fenchone based on non-reactive DST.

IFRA Category[a]	Examples of Product Type	Calculated QRA
1	Lip Products	0.026%
2	Deodorant/Antiperspirant	0.033%
3	Hydroalc., Shaved Skin	0.136%
4	Hydroalc., Unshaved Skin	0.407%
5	Women Facial Cream	0.214%
6	Mouthwash	0.652%
7	Intimate Wipes	0.068%
8	Hair Styling Aids Non-Spray	0.91%
9	Conditioners, Rinse-off	4.50%
10	Hard Surface Cleaners	2.5%
11	Candle (Non-Skin/Incidental Skin)	Not Restricted

Note: [a]For a description of the categories, refer to the QRA Informational Booklet. (www.rifm.org/doc/QRAInfoJuly2011.pdf.

e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

6. Metabolism

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

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

Fenchone is reported to occur in the following foods* and in some natural complex substances (NCS):

Anise brandy.
Apricot (*Prunus armeniaca* L.).
Calamus (sweet flag) (*Acorus calamus* L.).
Caraway (*Carum carvi* L.).
Cheese, various types.
Cinnamomum species.
Citrus fruits.
Clam.
Cloves (*Eugenia caryophyllata* Thunberg).
Dill (Anethum species).
Fennel (*Foeniculum vulg.*, ssp. *Capillaceum*; var.).
Ginger (*Zingiber* species).
Grape brandy.
Lemon balm (*Melissa officinalis* L.).
Licorice (*Glycyrrhiza glabra* L.).
Lovage (*Levisticum officinale* Koch).
Mangifera species.
Mastic (*Pistacia lentiscus*).
Mentha oils.
Mountain papaya (*C. candamarcensis, C. pubescens*).
Ocimum species.
Origanum species (Spanish) (*Coridothymus cap*. (L.) Rchb.).
Pepper (*Piper nigrum* L.).
Salvia species.
Star anise.
Tapereba, caja fruit (*Spondias lutea* L.).
Tea.
Wormwood oil (*Artemisia absinthium* L.).

d-Fenchone is reported to occur is the following foods*:
Fennel (*Foeniculum vulg.*, ssp. *Capillaceum*; var.).

l-Fenchone is not reported to occur in food by the VCF*.

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

8. IFRA standard

None.

9. REACH dossier

A dossier is available for fenchone; accessed 04/26/2018. *D*-fenchone and *L*-fenchone are pre-registered for 2010; no dossier available as of 04/26/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Fenchone was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2015). The mutagenicity of fenchone was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2 uvrA were treated with fenchone in DMSO (dimethyl sulfoxide) at concentrations of 1.5, 5, 15, 50, 150, 500, 1500, or 5000 μg/plate in the presence and absence of metabolic activation. No significant increases in the number of revertant colonies was observed in the treated samples compared to vehicle control (RIFM, 2014a). Under the conditions of the study, fenchone was considered not mutagenic.

The clastogenicity of fenchone was assessed in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD 487. Human peripheral blood lymphocytes were treated with fenchone in DMSO at concentrations of 190–1520 μg/mL for both the 4- and 24-h treatment groups either in the presence and absence of S9. There were no toxicologically significant increases in the frequency of micronuclei observed with any dose of fenchone, either in the presence or absence of S9 metabolic activation (RIFM, 2014b). Under the conditions of the study, fenchone was considered negative for the induction of micronuclei in human cells.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/10/16.

10.1.2. Repeated dose toxicity

The margin of exposure for fenchone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on fenchone. Read-across material, 1,7,7-trimethylbicyclo [2.2.1] heptan-2-one (CAS # 76-22-2; see section V) has sufficient repeated

dose toxicity data. Dermal 13-week subchronic toxicity studies were conducted in rats and mice with 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one. Ten Fisher 344 rats/sex/dose were treated with 0, 16, 32, 64, 125, or 250 mg/kg/day 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one in an ethanol vehicle. Dermal treatment was 5 days per week for 13 weeks. Alterations in relative lung and kidney weights were reported at either 64 or 250 mg/kg/day. The NOAEL was determined to be 250 mg/kg/day, the highest dose tested. In another study, a group of 10 B6C3F1 mice/sex/dose were treated with 0, 200, 400, 600, 800, or 1000 mg/kg/day 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one in an ethanol vehicle. Dermal treatment was 5 days per week for 13 weeks. Minimal epidermal hyperplasia was observed at the application site at 1000 mg/kg/day. No other test material–related alteration was reported. Thus, the NOAEL was determined to be 1000 mg/kg/day, the highest dosage tested. Since the NOAELs identified in both mice and rats were the highest dose tested, the NOAEL for the repeated dose toxicity endpoint was determined to be 1000 mg/kg/day, the highest dose tested among rats (ECHA REACH Dossier: Bornan-2-one, accessed 09/23/13). **Therefore, the fenchone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 1,7,7-trimethylbicyclo [2.2.1] heptan-2-one NOAEL in mg/kg/day by the total systemic exposure to fenchone, 1000/0.00029 or 3448276.**

In addition, the total systemic exposure to fenchone (0.29 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for fenchone is adequate for the developmental toxicity endpoint at the current level of use.

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

10.1.3.1. Risk assessment. There are insufficient developmental toxicity data on fenchone or any of the combined materials. Read-across material, 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS # 76-22-2; see section V) has sufficient repeated dose toxicity data. Groups of 20 pregnant Sprague Dawley rats were administered 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one in propylene glycol by gavage at doses of 0, 216, 464, and 1000 mg/kg from gestation days (GDs) 6–17. Pronounced clinical signs such as clonic convulsion, piloerection, reduced motility and reduced bodyweight gain were observed with 1000 mg/kg. Ulcers in the cardiac region of the stomach were observed in 2 and 5 dams treated with 464 and 1000 mg/kg, respectively. A thickened rough cardiac epithelium was observed in 1 additional dam treated with 1000 mg/kg. No treatment-related effect on prenatal fetal development was observed. Thus, the NOAEL for developmental toxicity was determined to be 1000 mg/kg/day (Leuschner, 1997). In another study, groups of 12 pregnant Himalayan rabbits were administered 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS # 76-22-2) in propylene glycol by gavage at doses of 147, 316, and 681 mg/kg from GDs 6–18. No treatment-related effects on prenatal fetal development were observed up to the highest dose tested. Thus, the NOAEL was determined to be 618 mg/kg/day, the highest dose tested (Leuschner, 1997). In another study, the isomer, *d*-camphor (CAS # 464-49-3; see Section V) was administered to a group of 26–29 pregnant female Crl:CD VAF/Plus outbred Sprague Dawley–derived rats by gavage at doses of 0, 100, 400, and 800 mg/kg in corn oil from GDs 6–15. Maternal systemic toxicity was observed; however, no adverse effects on fetal growth, viability, or morphological development were observed when the uterine contents were examined in animals treated with 100–800 mg/kg/day. The NOAEL for developmental toxicity was determined to be greater than 800 mg/kg/day. In another study, isomer *d*-camphor (CAS # 464-49-3; see section V) was administered to a group of 26 pregnant New Zealand white rabbits daily by gavage at dose levels of 0, 50, 200, or 400 mg/kg in corn oil during major organogenesis (GDs 6–19). Maternal weight gain decreased with higher doses of *d*-camphor was reported in a dose-related manner. Examination of the uterine contents revealed that *d*-camphor had no effect on fetal growth, viability, or morphological development. Thus, the maternal and developmental NOELs of camphor are greater than 400 mg/kg/day (NTP, 1992). Since the NOAELs determined from all the studies were the highest dose tested, a NOAEL of 1000 mg/kg/day was determined for the developmental toxicity endpoint, the highest dose tested among all the materials combined with *d*-camphor. **Therefore, the fenchone MOE for the developmental toxicity endpoint can be calculated by dividing the *d*-camphor NOAEL in mg/kg/day by the total systemic exposure to fenchone, 1000/0.00029 or 3448276.**

In addition, the total systemic exposure to fenchone (0.29 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are insufficient reproductive toxicity data on fenchone or its combined materials. Read-across analog 1,7,7-trimethylbicyclo [2.2.1] heptan-2-one (CAS # 76-22-2; see section V) has some reproductive toxicity data. In a dermal 13-week subchronic toxicity in rats at doses of 0, 16, 32, 64, 125, or 250 mg/kg/day 1,7,7-trimethylbicyclo [2.2.1] heptan-2-one in an ethanol vehicle, there were no adverse effects reported in the male or female reproductive organs. One (out of 10) male rats in the high-dose group (250 mg/kg/day) had mild testicular degeneration (ECHA REACH Dossier: Bornan-2-one, accessed 09/23/13). In another study, the effects of 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one on the reproductive system were studied in male Sprague Dawley rats. The rats were treated intraperitoneally with 5, 10, or 20 mg/kg of 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (vehicle not reported) for 30 days. At all dose levels, a decrease in body weight and testes size and weight was observed and testicular sperm number and motility were also decreased. At 10 and 20 mg/kg, morphological changes and a toxic effect on sperm and sperm motility were also observed. No conclusion was derived from the reported study since details on procedure and results could not be obtained. No such effects were reported in a dermal 13-week NTP study in rats (Jamshidzadeh and Sajedianfard, 2006). In another study, the effect of camphor on histopathological changes of the reproductive system in young male mice of balb/c racial type was investigated. Thirty-six premature male balb/c mice were divided into 3 paired groups of experimental, control, and sham (n = 6). Experimental groups 1 and 2 received 30 mg/kg/day camphor (no CAS # or supplier details provided) dissolved in olive oil via gavage for 10 and 20 days, respectively. The control groups received the same volume of olive oil during the same periods of time, and no intervention was done in sham groups. All groups were kept in the same environmental condition. Comparing to the control groups, less vascularization in testes tissue of the experimental groups was seen. Furthermore, stereological methods demonstrated that internal diameters of seminiferous tubules in the experimental groups were significantly smaller than those in the control groups. Also, the number of released sexual cells was significantly lower in experimental groups (Nikravesh and Jalali, 2004). No conclusion could be derived from the study regarding the effects of camphor on the male reproductive system. Since there is no conclusive data to obtain an appropriate NOAEL for the male and female reproductive toxicity effects, the NAOEL for the reproductive toxicity endpoint was not determined. The total systemic exposure to fenchone (0.29 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.4. Skin sensitization

Based on the existing data and DST, fenchone does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and application of DST fenchone does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In a human maximization study no sensitization reactions were observed with 2760 μg/cm2 fenchone (RIFM, 1975). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 $\mu g/cm^2$. The current 95th percentile dermal exposure is below the DST for non-reactive materials when evaluated in all QRA categories. Fenchone does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/06/15.

10.1.5. Phototoxicity/photoallergenicity

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

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

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, of concern for phototoxic effects, 1000 $L\,mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/13/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for fenchone is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are limited inhalation data available on fenchone. Based on the Creme RIFM Model, the inhalation exposure is 0.0067 mg/day. This exposure is 70 times lower than the Cramer Class III* TTC value of 0.47 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.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Additional References: Perrucci, 1995; Helmig et al., 1999a; Helmig et al., 1999b.

Literature Search and Risk Assessment Completed On: 10/01/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of fenchone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers 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, fenchone 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 v4.1 (US EPA, 2012a) identified fenchone as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2011), fenchone does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2010b: The test material's biodegradability was evaluated using the manometric respirometry test according to the OECD 301F method. Under the conditions of the test, biodegradation of 85% was observed after 28 days.

10.2.2.2. Ecotoxicity. No data available.

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

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	61.73			1,000,000	0.06173	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.6	2.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1*	< 1[a]
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

[a]Combined volume for all isomers: fenchone (CAS# 1195-79-5); D-fenchone (CAS# 4695-62-9); and L-fenchone (CAS# 7787-20-4).

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

The RIFM PNEC is 0.06173 μg/L. The revised PEC/PNECs for EU and NA are: 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: 7/28/15.

11. Literature search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.052.

Appendix

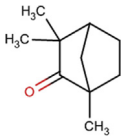
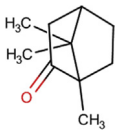
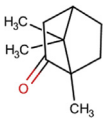
Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also 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, 2012).

- 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.

- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read-across material	
Principal Name	Fenchone	1,7,7-Trimethylbicyclo [2.2.1] heptan-2-one	*d*-Camphor
CAS No.	**1195–79–5**, 4695-62-9, 7787-20-4	76-22-2	464-49-3
Structure			
Similarity (Tanimoto score)[1]		0.609	0.609
Read-across endpoint		• Developmental and Reproductive • Repeated dose	• Developmental and Reproductive
Molecular Formula	$C_{10}H_{16}O$	$C_{10}H_{16}O$	$C_{10}H_{16}O$
Molecular Weight	152.24	152.37	152.24
Melting Point (°C, EPI Suite)	28.07	28.07	28.07
Boiling Point (°C, EPI Suite)	203.89	203.89	204
Vapor Pressure(Pa @ 25°C, EPI Suite)	96.1	1.42	1.42
Log Kow (KOWWIN v1.68 in EPI Suite)	3.52	2.74	2.74
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2150	1600	1600
J_{max} (mg/cm^2/h, SAM)	276.67	92.75	96.56
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.00E-005	7.00E-005	7.00E-005
Repeated dose toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, without OH or NH_2 group	• Non-binder, without OH or NH_2 group	• Non-binder, without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• toxicant (low reliability)	• toxicant (Experimental value)	• toxicant (Experimental value)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on fenchone (CAS # 1195-79-5). Hence *in silico* evaluation was conducted by determining suitable read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, materials 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS # 76-22-2) and *d*-camphor (CAS # 464-49-3) were identified as read-across analogs with data for their respective toxicity endpoints.

Conclusions

- The following materials could be used as structurally similar read-across analogs for the target material fenchone (CAS # 1195-79-5): 1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (CAS # 76-22-2) for the reproductive and developmental toxicity and repeated dose toxicity endpoints and *d*-camphor (CAS # 464-49-3) for the reproductive and developmental toxicity endpoints.
  - o The target substance and the read-across analogs are structurally similar and belong to a class of monoterpene cyclic ketones. The read-across analogs are stereoisomers of each other. The target substance and the read-across analogs have a 1-methylbicyclo [2.2.1]heptan-2-one fragment common among them.
  - o The key difference between the target substance and the read-across analogs is on the placement of dimethyl substitution. The target substance has a dimethyl substitution on the cyclohexane ring on the adjacent carbon from the ketone group while both of the read-across analogs have a dimethyl substitution on the spiro bridge head.
  - o The target substance and the read-across analogs have Tanimoto scores as mentioned in the above table. The Tanimoto score is mainly driven by the 1-methylbicyclo [2.2.1]heptan-2-one fragment. The differences in the structure that are responsible for the Tanimoto score < 1 are not relevent from a toxicological endpoint perspective.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analogs are estimated to be toxicologically insignificant for the reproductive and developmental toxicity and repeated dose toxicity endpoints.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the reproductive and developmental toxicity and repeated dose toxicity endpoints are consistent between the target substance and the read-across analog. The CAESAR model v.2.1.6 predicts the target and the read-

across analog to be sensitizers. Other protein binding alerts for both of the substances are negative. The data described in the skin sensitization section above show that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, this alert will be superseded by the availability of data. In addition, the target and read-across analog are predicted to be toxicants for the developmental endpoint by the CAESAR model v.2.1.6. The data described in the developmental and reproductive section supports the read-across material as safe to use within the given margin of exposure and level of use for the developmental toxicity endpoint, so this *in silico* prediction will be superseded.

- o The target substance and the read-across analogs are expected to be metabolized similarly as shown by metabolism simulator.
- o The structural differences between the target substance and the read-across analogs are deemed to be toxicologically insignificant for the reproductive and developmental toxicity and repeated dose toxicity endpoints.

Explanation of cramer class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O,N, divalent S? **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **No**
Q23. Aromatic? **No**
Q24. Monocarbocyclic with simple substituents? **No**
Q25. Cyclopropane, cyclobutane with substituents in Q24 or a mono or bicyclic sulfide or mercaptan?? **No**
Q26. Monocycloalkanone or a bicyclocompound? **Yes,** Class **Intermediate (Class II)**

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