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Short Review

# Update to RIFM fragrance ingredient safety assessment, *l*-carvone, CAS Registry Number 6485-40-1

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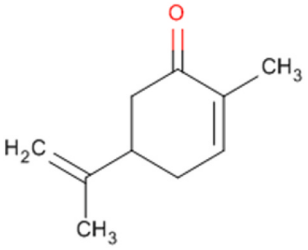
Version: 011024. This safety assessment is an updated version and replaces the previous version at https://doi.org/10.1016/j.fct.2022.112975 (RIFM, 2022a). All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: **fragrancematerialsafetyresource.elsevier.com**.




Name: *l*-Carvone
CAS Registry Number: 6485-40-1
Additional CAS Numbers*:
2244-16-8 *d*-Carvone
99-49-0 Carvone
*These materials are included in this assessment because they 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
**CAESAR** - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
**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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
**ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**HESS** - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
**IFRA** - The International Fragrance Association
**ISS** - Instituto Superiore di Sanita (Italian National Institute of Health)
**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
**OASIS** - OASIS Laboratory of Mathematical Chemistry (LMC)
**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

(*continued on next column*)

(*continued*)

**Toxtree** - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
**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 clarification. 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.**

*l*-Carvone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that *l*-carvone is not genotoxic and provided a No Expected Sensitization Induction Level (NESIL) of 2600 μg/cm$^2$ for the skin sensitization endpoint. Data on *l*-carvone provided a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The photoirritation/photoallergenicity endpoint was completed based on data and ultraviolet/visible (UV/Vis) spectra; *l*-carvone is not photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class II material (0.47 mg/day); the exposure to *l*-carvone is below the TTC. The environmental endpoints were evaluated; *l*-carvone 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 (2013) |
| **Repeated Dose Toxicity:** NOAEL = 30 mg/kg/day. | EFSA (2014) |
| **Reproductive Toxicity:** Developmental toxicity NOAEL = 250 mg/kg/day. Fertility NOAEL = 90 mg/kg/day. | (ECHA, 2013; EFSA, 2014) |
| **Skin Sensitization:** NESIL = 2600 μg/cm$^2$. | RIFM (2007a) |
| **Photoirritation/Photoallergenicity:** Not photoirritating/photoallergenic. | (UV/Vis Spectra, RIFM Database; RIFM, 1986a; RIFM, 1986b) |

**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**

| | |
|---|---|
| **Persistence:** Critical Measured Value: 90% (OECD 301F) | RIFM (1997a) |
| **Bioaccumulation**: Screening-level: 24.13 L/kg | US EPA (2012a) |
| **Ecotoxicity:** Screening-level: 96-h algae EC50: 8.17 mg/L | US EPA (2012b) |

**Conclusion**: Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**

| | |
|---|---|
| **Screening-level:** PEC/PNEC (North America and Europe) > 1 | (Salvito et al., 2002) |
| **Critical Ecotoxicity Endpoint:** 96-h algae EC50: 8.17 mg/L | US EPA (2012b) |

**RIFM PNEC is:** 0.817 μg/L

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

## 1. Identification

| | | |
|---|---|---|
| **1. Chemical Name**: *l*-Carvone<br>**2. CAS Registry Number:** 6485-40-1<br>**3. Synonyms:** *laevo*-Carvone; 2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-, (R)-; *l*-*p*-Mentha-6,8(9)-dien-2-one; *l*-*p*-Mentha-1(6),8-dien-2-one; *l*-1-Methyl-4-isopropenyl-6-cyclohexen-2-one; Carvone Laevo DQ; 1,8(9)-p-ﾒﾝﾀｼﾞｴﾝ-6-ｵﾝ; 5-Isopropenyl-2-methyl-cyclohex-2-en-1-one; Carvone; *l*-Carvone<br>**4. Molecular Formula:** $C_{10}H_{14}O$<br>**5. Molecular Weight:** 150.22 g/mol<br>**6. RIFM Number:** 195<br>**7. Stereochemistry:** *l* isomer specified. One stereocenters and 2 total stereoisomers possible. | **1. Chemical Name**: Carvone<br>**2. CAS Registry Number:** 99-49-0<br>**3. Synonyms:** *p*-Mentha-6,8-dien-2-one; 1-Methyl-4-isopropenyl-6-cyclohexen-2-one; 2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-; 5-Isopropenyl-2-methylcyclohex-2-en-1-one; 6,8(9)-*p*-Menthadien-2-one; Carvone<br>**4. Molecular Formula:** $C_{10}H_{14}O$<br>**5. Molecular Weight:** 150.22 g/mol<br>**6. RIFM Number:** 1460<br>**7. Stereochemistry:** No isomer specified. One stereocenters and 2 total stereoisomers possible. | **1. Chemical Name**: *d*-Carvone<br>**2. CAS Registry Number:** 2244-16-8<br>**3. Synonyms:** (S)-2-Methyl-5-(1-methylvinyl) cyclohex-2-en-1-one; *d*-*p*-Mentha-6,8(9)-dien-2-one; *d*-1-Methyl-4-isopropenyl-6-cyclohexen-2-one; *d*-Carvone; 1,8(9)-p-ﾒﾝﾀｼﾞｴﾝ-6-ｵﾝ; 2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-, (S)-; 5-Isopropenyl-2-methylcyclohex-2-en-1-one<br>**4. Molecular Formula:** $C_{10}H_{14}O$<br>**5. Molecular Weight:** 150.22 g/mol<br>**6. RIFM Number:** 251<br>**7. Stereochemistry:** *d* isomer specified. One stereocenters and 2 total stereoisomers possible. |

## 2. Physical data

| | | |
|---|---|---|
| **1. Boiling Point**: 230 °C (Fragrance Materials Association [FMA]), 224.23 °C (EPI Suite)<br>**2. Flash Point:** 200 °F (closed cup [CC]) (FMA), 98 °C (Globally Harmonized System [GHS])<br>**3. Log $K_{OW}$:** log Pow = 2.6 (RIFM, 1997b), 3.07 (EPI Suite)<br>**4. Melting Point**: 9.86 °C (EPI Suite)<br>**5. Water Solubility:** 367.1 mg/L (EPI Suite)<br>**6. Specific Gravity:** 0.956–0.960 (FMA Database), 0.958–0.962 (FMA Database)<br>**7. Vapor Pressure:** 0.0863 mm Hg at 20 °C (EPI Suite v4.0), 0.1 mm Hg 20 °C (FMA), 0.13 mm Hg at 25 °C (EPI Suite)<br>**8. UV Spectra:** No absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L • $mol^{-1}$ • $cm^{-1}$)<br>**9. Appearance/ Organoleptic:** A clear, colorless to pale straw-colored liquid having a spearmint odor | **1. Boiling Point**: 231 °C (FMA), 224.23 °C (EPI Suite)<br>**2. Flash Point:** 89 °C (GHS)<br>**3. Log $K_{OW}$:** 3.07 (EPI Suite)<br>**4. Melting Point**: 9.86 °C (EPI Suite)<br>**5. Water Solubility:** 367.1 mg/L (EPI Suite)<br>**6. Specific Gravity:** 0.960 (FMA)<br>**7. Vapor Pressure:** 0.13 mm Hg at 25 °C (EPI Suite)<br>**8. UV Spectra:** Not available<br>**9. Appearance/ Organoleptic:** Not available | **1. Boiling Point**: 230 °C (FMA), 224.23 °C (EPI Suite)<br>**2. Flash Point:** 93 °C (GHS); 199 °F (CC) (FMA)<br>**3. Log $K_{OW}$:** 3.07 (EPI Suite)<br>**4. Melting Point**: 9.86 °C (EPI Suite)<br>**5. Water Solubility:** 367.1 mg/L (EPI Suite)<br>**6. Specific Gravity:** 0.965<br>**7. Vapor Pressure:** 0.0863 mm Hg at 20 °C (EPI Suite v4.0), 0.07 mm Hg 20 °C (FMA), 0.13 mm Hg at 25 °C (EPI Suite)<br>**8. UV Spectra:** No absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L • $mol^{-1}$ • $cm^{-1}$)<br>**9. Appearance/ Organoleptic:** Colorless or pale straw-colored, mobile liquid with bread-like, spicy, slightly floral odor |

## 3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2019)

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.2.9)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.015% (RIFM, 2022b)
2. **Inhalation Exposure****: 0.00024 mg/kg/day or 0.018 mg/day (RIFM, 2022b)
3. **Total Systemic Exposure*****: 0.0089 mg/kg/day (RIFM, 2022b)

*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 et al., 2015; Safford et al., 2015; Safford et al., 2024; Safford et al., 2017; and 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 et al., 2015; Safford et al., 2015; Safford et al., 2024; Safford et al., 2017; and 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 II, Intermediate

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.6 (OECD, 2023) |
|---|---|---|
| II | II | II |

2. **Analogs Selected**:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

## 7. Metabolism

**Mascher et al., 2001:** The pharmacokinetic profile of carvone was determined in 15 healthy human volunteers. Essential oil, caraway oil consisting of 50%–65% *d*-carvone, was administered either as enteric-coated (50 mg) or non-enteric-coated (20 mg) capsules. The volunteers were part of an open, randomized, 2-period cross-over study with a washout period of 1 week before administration of the second formulation. The volunteers first received the 2 enteric-coated capsules equivalent to 100 mg/person dose of caraway oil (50%–65% *d*-carvone). The capsules were administered after a 10-h fast and with 250 mL of

water. Blood was withdrawn between 0- to 15-h time intervals. The plasma samples were examined by GC/MS to determine the following pharmacokinetic parameters: $C_{max}$, $T_{max}$, AUC, and $t_{1/2}$. The same protocol was followed for the non-enteric-coated capsules following a 1-week washout period, wherein the volunteers received 5 capsules (100 mg/person) of caraway oil followed by plasma sampling as described above. The pharmacokinetic parameters determined are summarized in the table below. The parameters indicated that *d*-carvone has a plasma half-life of 2.4 h and is more readily absorbed from non-enteric-coated capsules.

| Carvone | Enteric-coated mean ± SD (geometric mean) | Non-enteric-coated mean ± SD (geometric mean) |
|---|---|---|
| **AUC (0-∞) (ng/mL × h)** | 40.8 ± 74.6 (24.28) | 28.9 ± 20 (25.12) |
| **$C_{max}$ (ng/mL)** | 14.9 ± 23.2 (9.92) | 14.8 ± 10.4 (12.57) |
| **$T_{max}$ (h)** | 2.5 ± 0.7 (2.41) | 1.3 ± 0.6(1.24) |
| **$t_{1/2}$ (h)** | 2.5 ± 0.7 (2.4) | 2.4 ± 1.2 (2.0) |

**Engel (2001):** Metabolism of *d*- and *l*-carvone was investigated in 6 (3/sex) healthy human volunteers. Carvone was administered at doses of 1 mg/kg body weight, and urine was collected 24 h before and after administration. The metabolites were identified by MS using synthetic standards and NMR analysis. The urine samples were treated with sulphatase and glucuronidase. The metabolites identified included 3 side-chain oxidation products as the main primary unconjugated metabolites of *d*- and *l*-carvone: dihydrocarvonic acid, carvonic acid, and uroterpenolone, with 10-hydroxycarvone as the proposed intermediate metabolic step (see Fig. 1). However, 10-hydroxycarvone was not detected in humans, and the authors suggested this was due to efficient oxidation of it to produce carvonic acid. The authors also identified minor metabolites in the form of reduction products of carvone: carveol and dihydrocarveol. The authors concluded there were no differences observed between the metabolisms of *l*- and *d*-carvone.

**Jager et al., 2000:** *In vitro* metabolism of R-(−)- and S-(+)-carvone (*l*- and *d*-carvone, respectively) was studied in liver microsomes from the rat (Sprague Dawley males) and humans (undergoing liver resection; 1 female, 2 males) using chiral gas chromatography. The results indicated the sole metabolite formed from *l*-carvone was 4R, 6S-(−)-carveol, whereas the sole metabolite from *d*-carvone was 4S, 6S-(+)-carveol. In both rat and human microsomes, a significantly lower apparent Michaelis-Menten Constant (Km) was observed for 4R, 6S-(−)-carveol compared to 4S, 6S-(+)-carveol. The maximal formation rate (Vmax) was almost twice as high with human liver microsomes when compared to rat microsomes. When the rat and human liver microsomes were incubated in the presence of UDPGA (uridine 5′-diphosphoglucuronic acid), only the glucuronidation of 4R, 6S-(−)-carveol was observed, and the Vmax for glucuronide formation was more than 4-fold higher in the rat liver compared with human liver preparations (no species-related differences were observed for Km values). This *in vitro* study demonstrated stereoselective phase-I and phase-II metabolism for *l*- and *d*-carvone.

**Shimada et al., 2002:** *In vitro* metabolism of *d*-carvone ((+)-carvone), *d*-carveol ((+)-carveol), and other structurally related terpenoids

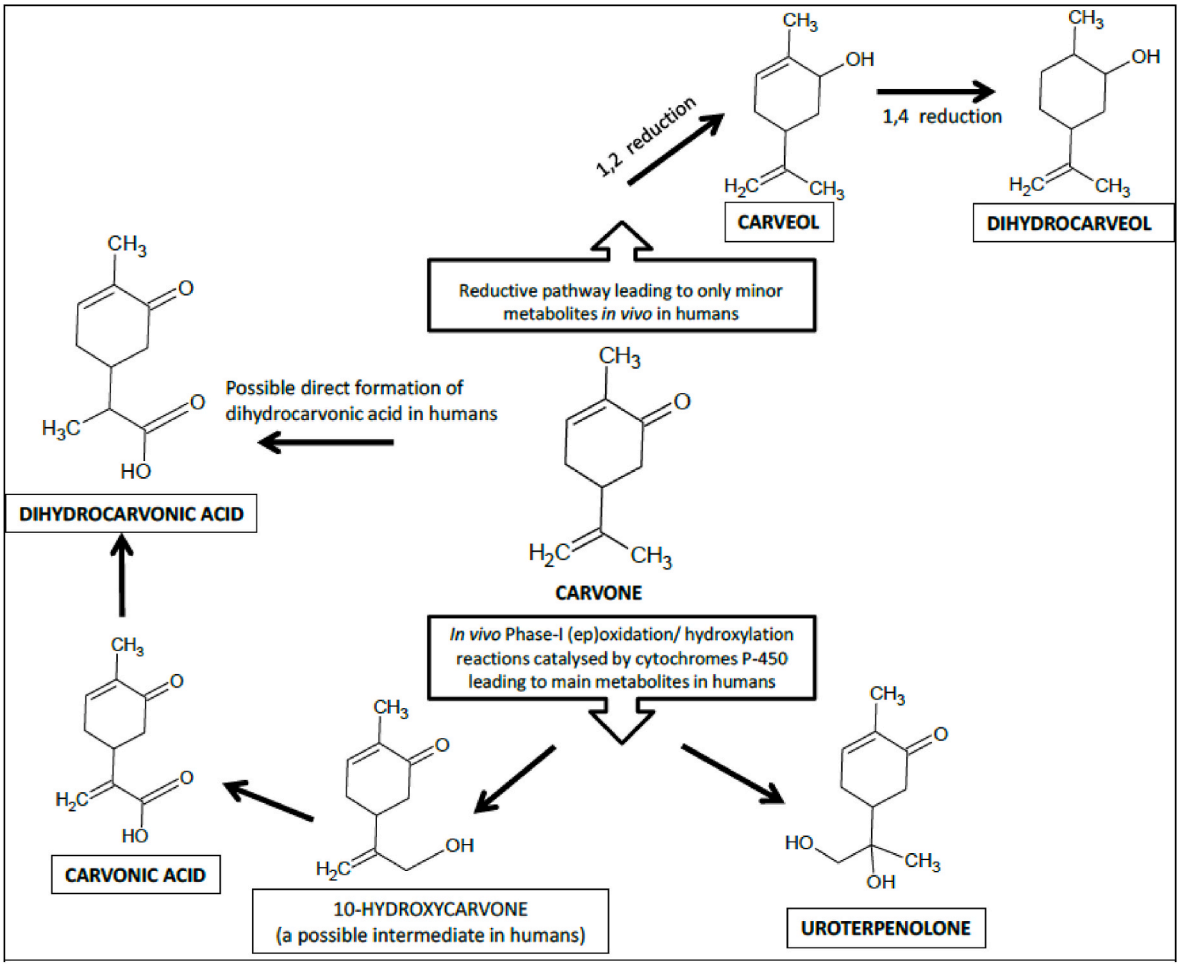



**Fig. 1.** (Adapted from EFSA report on carvone; EFSA, 2014).

were investigated using liver microsomes from mice, rats, guinea pigs, rabbits, dogs, monkeys, and humans. Microsomes were obtained from male liver samples for all species except for the rat, in which microsomal preparations of livers from both male and female Sprague Dawley rats were assessed. When *d*-carveol and *d*-carvone were used as substrates, dogs, rabbits, and guinea pigs metabolized them to *d*-carvone and *d*-carveol, respectively. In contrast, humans, monkeys, rats, and mice did not convert *d*-carveol to *d*-carvone but metabolized *d*-carvone to *d*-carveol, with liver microsomes from male rats having the highest rates. Hepatic CYP2C enzymes were suggested to play a major role in metabolizing *d*-carveol to *d*-carvone and *d*-carvone to *d*-carveol since the activities were inhibited significantly by anti-human CYP2C9 antibodies. Studies with recombinant P450 enzymes suggested that CYP2C9 and CYP2C19 in humans had the highest activities. CYP2C11 and CYP2B1 in male rats were the major enzymes in metabolizing (+)-carvone. Female-specific CYP2C12 had very low activity, suggesting that the metabolism of carvone by female rats may be slower than males. These results suggest that there are species-related differences in the metabolism of *d*-carvone, and for rats, potentially sex-related differences.

**Conclusions:** Human toxicokinetic studies on *d*-carvone suggest rapid clearance from plasma with a plasma half-life of 2.4 h. No such data are available on *l*-carvone (Mascher et al., 2001). Data from *in vitro* and *in vivo* metabolic studies indicate species differences (Shimada et al., 2002; Jager et al., 2000). Since rats have a tendency to undergo enterohepatic recirculation, and no such recirculation has been demonstrated via human *in vivo* studies, this makes rats more susceptible to liver effects from carvone or its metabolites.

## 8. Natural occurrence

*l*-Carvone (CAS # 6485-40-1) is reported to occur in the following foods by the VCF*.

| | |
|---|---|
| Caraway (Carum carvi L.) | Dill (*Anethum graveolens* L.) |
| Citrus fruits | Rambutan (*Nephelium lappaceum* L.) |

*d*-Carvone (CAS # 2244-16-8) is reported to occur in the following foods by the VCF.

| | |
|---|---|
| Caraway (*Carum carvi* L.) | Dill (*Anethum graveolens* L.) |
| Chestnut (*Castanea* species) | Wine |
| *Cinnamomum* species | |

Carvone (CAS # 99-49-0) is reported to occur in the following foods by the VCF.

| | |
|---|---|
| Anise | Fennel (*Foeniculum vulg.*, ssp. *capillaceum*; var.) |
| Caraway (*Carum carvi* L.) | Mastic (*Pistacia lentiscus*) |
| Celery (*Apium graveolens* L.) | Mentha oils |
| Citrus fruits | Pistachio oil (*Pistachia vera*) |
| Dill (*Anethum graveolens* L.) | Turpentine oil (*Pistacia terebinthus*) |

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

## 9. REACH dossier

Available for *l*-carvone (CAS # 6485-40-1; ECHA, 2013) and *d*-carvone (CAS # 99-49-0; accessed 01/10/24; carvone has been pre-registered for 2010; no dossier available as of 01/10/24.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for *l*-carvone 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) | 0.20 |
| 2 | Products applied to the axillae | 0.060 |
| 3 | Products applied to the face/body using fingertips | 0.066 |
| 4 | Products related to fine fragrances | 0.20 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.17 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.033 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.066 |
| 5D | Baby cream, oil, talc | 0.011 |
| 6 | Products with oral and lip exposure | 0.66 |
| 7 | Products applied to the hair with some hand contact | 0.066 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.011 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.60 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 0.10 |
| 10B | Aerosol air freshener | 0.46 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.011 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | 19 |

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 *l*-carvone, the basis was the subchronic reference dose of 0.3 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 2600 μg/cm$^2$.
As a conservative approach, we assumed that 100% of the material exposed via the skin is bioavailable (see Section V), thereby deriving the most stringent MOE. Since the MOE is > 100 (see the repeated dose and reproductive toxicity sections), we then refined the exposure to 80% using an *in silico* Skin Absorption Model (SAM) to determine the Maximum Allowable Concentrations for each category listed in Section X.
[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 v3.3.1.

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current data, *l*-carvone does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* The mutagenic activity of *l*-carvone 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *l*-carvone in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, *l*-carvone was not mutagenic in the Ames test.

The clastogenicity of *l*-carvone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with *l*-carvone in DMSO at concentrations up to 1502.2 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test material, either with or without S9 (ECHA, 2013). Under the conditions of the study, *l*-carvone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, *l*-carvone does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 01/04/24.

*11.1.2. Repeated dose toxicity*

The MOE for *l*-carvone 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 stereoisomer *d*-carvone to support the repeated dose toxicity endpoint. In an NTP 90-day gavage study in Fischer 344 rats reported in 1982, groups of 10 rats/sex/group were administered *d*-carvone by gavage at 0, 93, 187, 375, 750, and 1500 mg/kg/day. Mortality was reported among animals of the 2 highest-dose groups (9/10 males and 10/10 females at 750 mg/kg/day, and 10/10 males and 10/10 females at 1500 mg/kg/day). Body weights were reduced among males only of the 187 and 575 mg/kg/day dose groups. Organ weight analysis showed an increase in relative liver weights among all treated animals and an increase in relative kidney weights among the 375 mg/kg/day group animals and the 187 mg/kg/day males. For males administered 375 mg/kg/day, depressed sperm motility and a mild decrease in sperm concentration were observed only at the end of the study (sperm analysis was conducted at weeks 2, 4, 6, and 8 of the study). For animals at 750 mg/kg/day, testicular degeneration and relative aspermia were observed. Similar effects were not observed among animals in the 93 and 187 mg/kg/day groups. The liver, kidney, and male reproductive organs were identified as the major organs affected by treatment with *d*-carvone. A NOAEL could not be derived from the study because there were no alterations in clinical pathology nor histopathology, although the relative liver weights were significantly increased. Microscopic alterations in the kidney were reported only among males of the 375 mg/kg/day dose groups, which could be related to male rat-specific alterations related to α2u-globulin accumulation; however, this was not confirmed by appropriate staining techniques (EFSA, 2014)*. Overall, the lack of appropriate study details and limitations in the study design precluded the derivation of a NOAEL.

In another study, groups of 10 Wistar Crl:(WI)BR rats/sex/dose were administered *d*-carvone in corn oil by gavage at doses of 0, 5, 30, and 180 mg/kg/day. The study was conducted according to OECD 408 and GLP guidelines. Hematological analysis showed significantly reduced prothrombin time among high-dose males and a dose-related increase in partial thromboplastin time (PTT) among mid- and high-dose females. Hematological alterations were not considered to be treatment-related adverse effects, because the increase in PTT was not accompanied by any other hematological change or any apparent hepatotoxicity. Organ weight analysis revealed a significant increase in relative liver weights among animals of the high-dose group and mid-dose females. The relative kidney weights were significantly increased among male and female animals of the high- and mid-dose groups in a dose-related manner. Microscopic examination revealed tubular necrosis of the kidney in males only and basophilic tubules in both males and females of the high-dose group. A follow-up study examining the kidney slides from all treated and control group animals confirmed the tubular necrosis in male rats to be due to renal accumulation of α2u-globulin (confirmed by highly positive staining of the treated high-dose group rats with an antibody against α2u-globulin), which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). The follow-up study did not report any histopathological alteration among female kidney slides. The kidney weight alterations were not considered to be an adverse effect in relation to treatment with carvone. The hematological alterations were not considered to be an adverse effect following treatment with carvone. The NOAEL was considered to be 30 mg/kg/day, based on a decrease in body weight and food consumption among high-dose males (EFSA, 2014)*.

In another study, a 2-generation reproductive toxicity study conducted according to OECD 416 and GLP guidelines, groups of 25 Wistar Crl:(WI)Br rats/sex/dose were administered *d*-carvone by gavage at doses of 0, 3, 10, or 30 mg/kg/day. For the F1 generation, the dose levels were changed to 0, 10, 30, and 90 mg/kg/day. Males of the F0 generation dosed at 30 mg/kg/day, and those of the 30 and 90 mg/kg/day dose groups in the F1 generation had increased relative kidney weights. Histopathological results showed the kidney weight increases to be related to well-documented changes of α2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). Statistically significant increases in the relative liver weights (up to approximately 15%) were observed in males of the F1 generation dosed at 30 and 90 mg/kg/day. Histopathological evaluation of these livers was not performed. No differences were seen in females, and no other histopathological changes were reported. Since there was no histopathological examination associated with the increased relative liver weights, a NOAEL for systemic toxicity was considered to be 90 mg/kg/day (EFSA, 2014)*.

In another study, groups of 40 B6C3F1 mice (30 males and 10 females) were administered *d*-carvone in corn oil at doses of 0, 93, 375, and 1500 mg/kg/day, 5 days per week, for 13 weeks. An additional group of 20 B6C3F1 mice (10 per sex) were administered 187 and 750 mg/kg/day. All 30 males and 9/10 females treated with 1500 mg/kg/day and 1/10 males treated with 93 mg/kg/day died before the end of the study. The final mean body weight of the only high-dose female survivor was 12% lower than that of the controls. The relative liver weights for the animals treated with 750 mg/kg/day were significantly greater than the controls, but no treatment-related lesions were observed during microscopy. The NOAEL for systemic toxicity was considered to be 375 mg/kg/day, based on mortality and an increase in relative liver weights among higher dose group animals (NTP, 1990). Subsequently, a 2-year carcinogenicity study was conducted on groups of 100 B6C3F1 mice/dose (50 per sex) administered 0, 375, or 750 mg/kg of *d*-carvone in corn oil by gavage, 5 days per week, for 103 weeks. The control group of 100 animals (50 per sex) was treated with the vehicle only. Under the conditions of this study, there was no evidence of carcinogenic activity of *d*-carvone for male or female mice (NTP, 1990).

As described in the metabolism section (see Section VII), rats are

suspected to be more sensitive to the effects of treatment with carvone as compared to humans due to enterohepatic recirculation of its metabolites among rats but not humans. This explains the liver weight increase in rats as seen during the 90-day rat studies; thus, the rats are a more sensitive species to the effects of carvone treatment. It is to be noted that the 2-year carcinogenicity study conducted in mice did not show any evidence of tumors up to doses of 750 mg/kg/day (NTP, 1990). However, the most conservative NOAEL of 30 mg/kg/day was considered for the repeated dose toxicity study based on a decrease in body weights among rats during the OECD 408 90-day gavage study (EFSA, 2014)*.

Therefore, the *l*-carvone MOE for the repeated dose toxicity endpoint can be calculated by dividing the *d*-carvone NOAEL in mg/kg/day by the total systemic exposure to *l*-carvone, 30/0.0089, or 3371.

In addition, the total systemic exposure to *l*-carvone (8.9 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

*11.1.2.1.1. 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 0.3 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 *l*-carvone was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 30 mg/kg/day by the uncertainty factor, 100 = 0.3 mg/kg/day.

*The original study reports were not available for review.

**Additional References:** CLH, 2012.

**Literature Search and Risk Assessment Completed On:** 01/08/24.

### *11.1.3. Reproductive toxicity*

The MOE for *l*-carvone is adequate for the reproductive toxicity endpoint at the current level of use.

*11.1.3.1. Risk assessment.* There are sufficient developmental toxicity data on *l*-carvone to support the developmental toxicity endpoint. An OECD 414 prenatal developmental toxicity study was conducted with *l*-carvone administered to 24 females pregnant Wistar Crl rats per dose by gavage at doses of 125, 250, and 500 mg/kg/day from gestation days 6–20. A statistically significant decrease in body weight in correlation to a statistically significant decrease in food consumption was observed at 500 mg/kg/day. A statistically significant decrease in the absolute weight of the uterus was observed at 500 mg/kg/day. Furthermore, incomplete ossification of the supraoccipital bone was increased in females at the highest-dose level compared to the control group. A statistically significant decrease in the mean body weights was observed for fetuses at the highest dose. Incomplete ossification of the supraoccipital bone, which could be associated with lower fetal body weight, was observed at 500 mg/kg/day. Bipartite ossification of the supraoccipital bone and unossified supraoccipital bone, which could be associated with maternal toxicity, was seen at the highest dose only. Increased incidence of transitional findings, such as a hole in the supraoccipital bone, asymmetric ossification of sternebra, and bipartite and dumbbell ossification of vertebrae, were observed in all the treatment groups as compared to the control. It has been shown that mineralization of osseous tissue may develop later in gestation. Furthermore, reduced or delayed ossification are transient and develop more during lactation period. Hence, these effects are not considered malformations, but may only indicate delayed schedule of events (DeSesso and Scialli, 2018, Ellis-Hutchings, 2010). The absence of ribs was observed in all treated groups (3/135 for low dose, 3/170 for mid dose, and 3/135 for high dose), and there was no dose response seen with respect to absent ribs (the absent ribs incidence was 3 at each dose: 125 mg/kg/day [2.2%], 250 mg/kg/day [1.7%], and 500 mg/kg/day [2.4%]). In addition, euthanasia of dams at day 20 instead of 21 could also affect the development of the fetuses. Hence, the skeletal alterations were considered transient changes that may develop at a later stage of development.

Thus, in this study, the developmental toxicity NOAEL was considered to be is 250 mg/kg/day, based on significant decrease in mean body weights of fetuses at 500 mg/kg/day (ECHA, 2013). **Therefore, the *l*-carvone MOE for the developmental toxicity endpoint can be calculated by dividing the *d*-carvone NOAEL in mg/kg/day by the total systemic exposure to *l*-carvone, 250/0.0089, or 28090.**

There are sufficient fertility data on stereoisomer *d*-carvone to support the reproductive toxicity endpoint. In an OECD 416- and GLP-compliant 2-generation reproductive toxicity study conducted in Wistar Crl:(WI)Br rats, groups of 25 rats/sex/dose were administered *d*-carvone by gavage at doses of 0, 3, 10, or 30 mg/kg/day for 10 weeks prior to mating until termination. For the F1 generation, the dose levels were changed to 0, 10, 30, and 90 mg/kg/day. There were no differences between the control and treatment group animals in any of the reproductive performance parameters, sperm morphology and motility, and estrous cycle. The reproductive toxicity NOAEL was considered to be 90 mg/kg/day, the highest dose tested (EFSA, 2014)*. **Therefore, the *l*-carvone MOE for the fertility endpoint can be calculated by dividing the *d*-carvone NOAEL in mg/kg/day by the total systemic exposure to *l*-carvone, 90/0.0089, or 10112.**

In addition, the total systemic exposure to *l*-carvone (8.9 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

*The original study reports were not available for review.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 01/08/24.

### *11.1.4. Skin sensitization*

Based on the existing data, *l*-carvone is considered a skin sensitizer with a defined NESIL of 2600 μg/cm$^2$, and the maximum acceptable concentrations in finished products are provided in Section X.

*11.1.4.1. Risk assessment.* Based on the existing data, *l*-carvone is considered a skin sensitizer (Table 1). This material is predicted *in silico* to be reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.6). *l*-Carvone and isomer carvone were found to be positive in 2 separate direct peptide reactivity assays (DPRA), 2 separate KeratinoSens, human Cell Line Activation Test (h-CLAT), and U-SENS test (Urbisch et al., 2015; RIFM, 2018; RIFM, 2015a; RIFM, 2015b). The results were evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021), and based on the 2 out of 3 Defined Approach, *l*-carvone is considered a sensitizer. In 3 separate murine local lymph node assays (LLNA), *l*-carvone was found to be sensitizing with an EC3 value of 10.7% (2675 μg/cm$^2$), 12.9% (3225 μg/cm$^2$), and 5.7% (1425 μg/cm$^2$) (RIFM, 2007b; ECHA, 2013; Nilsson et al., 2005; RIFM, 2006). In 2 separate guinea pig maximization tests, *l*-carvone did not lead to skin sensitization reactions (RIFM, 1986c; RIFM, 1983). In 2 separate human maximization tests, no skin sensitization reactions were observed when *l*-carvone and isomer *d*-carvone were tested at 690 μg/cm$^2$ and 1380 μg/cm$^2$, respectively (RIFM, 1971; RIFM, 1976). In a Confirmation of No Induction in Humans (CNIH) test with 18898 μg/cm$^2$ of *l*-carvone in 1:3 ethanol: diethyl phthalate (EtOH:DEP), reactions indicative of sensitization were

**Table 1**
Summary of existing data on *l*-carvone.

| 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[4] Weighted Mean EC3 Value µg/cm² | GPMT[5] | Buehler |
| Weak | 2657 | 1380 | 18898 | 2600 | 2441 (9.77%) | Negative [2] | N/A |
| | *In vitro* Data[6] | | | | *In silico* protein binding alerts (OECD Toolbox v4.6) | | |
| | KE 1 | KE 2 | KE 3 | | Target Material | Autoxidation simulator | Metabolism simulator |
| | Positive [2] | Positive [2] | Positive [h-CLAT & U-SENS] | | Michael addition | Michael addition; Radical reactions | No alert found |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = 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]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
[5]Studies conducted according to the OECD TG 406 are included in the table.
[6]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

observed in 3 of the 93 volunteers (RIFM, 2008). Additionally, in a CNIH test with 2657 µg/cm$^2$ of *l*-carvone in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 99 volunteers (RIFM, 2007a).

Based on weight of evidence (WoE) from structural analysis, *in vitro* studies, animal studies, and human studies, *l*-carvone is a sensitizer with a WoE NESIL of 2600 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. ((Api et al., 2020)) and a subchronic RfD of 0.3 mg/kg/day.

**Additional References:** RIFM, 2014; Kern et al., 2010; Klecak (1979); Karlberg et al., 1992; Nilsson et al., 2001; Karlberg et al., 2001; Klecak (1985); Kozuka et al., 1996.

**Literature Search and Risk Assessment Completed On:** 12/05/23.

### *11.1.5. Photoirritation/photoallergenicity*

Based on the UV/Vis absorption spectra and available *in vivo* study data, *l*-carvone would not be expected to present a concern for photoirritation or photoallergenicity.

*11.1.5.1. Risk assessment.* 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). In a rat photoirritation study,

10% *l*-carvone in ethanol did not result in photoirritant reactions (RIFM, 1986b). In a guinea pig photoallergy study, 10% *l*-carvone did not induce photoallergenic reactions (RIFM, 1986a). Based on the *in vivo* study data and the lack of absorbance, *l*-carvone does not present a concern for photoirritation 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 photoirritant or photoallergenic effects, 1000 L $mol^{-1}$ • $cm^{-1}$ (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/17/23.

*11.1.6. Local respiratory toxicity*

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *l*-carvone is below the Cramer Class III* TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are insufficient inhalation data available on *l*-carvone. Based on the Creme RIFM Model, the inhalation exposure is 0.018 mg/day. This exposure is 26.1 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 for the local respiratory toxicity endpoint.

**Additional References:** Duchamp (1982); Revial et al., 1982; Silver (1992); Rice and Coats, 1994; Heuberger et al., 2001; Buchbauer et al., 2005; Buchbauer et al., 1993.

**Literature Search and Risk Assessment Completed On:** 01/04/24.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of *l*-carvone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log $K_{ow}$ and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor, as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class-specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, *l*-carvone 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 *l*-carvone 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, 2017). 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 $\geq$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), *l*-carvone presents a risk to the aquatic compartment in the screening-level assessment.

*11.2.1.2. Key studies.* ***Biodegradation***:

**For CAS # 6485–40–1.**

**RIFM, 1997a:** Ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Inoculated mineral medium containing 100 mg/L test material was stirred in a closed flask for 28 days. Biodegradation of 90% was observed.

**RIFM, 1994:** A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test following the OECD 301B guideline. Biodegradation of 89.3% was observed after 28 days.

**RIFM, 2001a:** In a closed bottle test according to the OECD 301D method, ready biodegradability was determined from municipal activated sewage sludge and soil. No biodegradation was observed after 28 days.

***Ecotoxicity***:

**For CAS # 6485–40–1.**

**RIFM, 2001b:** A 48-h *Daphnia magna* acute toxicity test was conducted according to OECD TG 202 under static conditions. Under the conditions of the study, the 48-h EC50 was 38 mg/L.

*11.2.1.3. Other available data.* *l*-Carvone (CAS # 6485-40-1) and *d*-carvone (CAS # 2244-16-8) has been registered under REACH, and the following additional data is available (ECHA, 2013):

A 96-h fish (*Oncorhynchus mykiss*) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. The LC50 based on 0-h measured test concentration was reported to be 6.1 mg/L.

An algae inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 for growth rate was reported to be 19 mg/L.

*11.2.2. Risk assessment refinement*

Since *l*-carvone has passed the screening criteria, measured data, including REACH data, are included in this document 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.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 60.91 | | | 1000000 | 0.0609 | |
| ECOSAR Acute Endpoints **(Tier 2)** v2.0 | 23.47 | 11.21 | 8.170 | 10000 | 0.8170 | Vinyl/Allyl Ketones |
| ECOSAR Acute Endpoints **(Tier 2)** v2.0 | 13.60 | 8.522 | 9.538 | | | Neutral Organic SAR (Baseline toxicity) |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 2.6 | 2.6 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 100–1000* | 10–100* |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

*Combined Regional Volume of Use for all CAS #

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

The RIFM PNEC is 0.817 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:** 11/21/23.

## 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 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 01/10/24.

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

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