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# RIFM fragrance ingredient safety assessment, dihydrocarveol (isomer unspecified), CAS Registry Number 619-01-2

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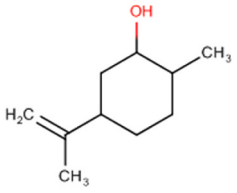


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Name: Dihydrocarveol (isomer unspecified)
CAS Registry Number: 619-01-2
Additional CAS Numbers*:
38049-26-2 Dihydrocarveol (R,R,R) (No Reported Use)
18675-34-8 Neodihydrocarveol (No Reported Use)

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*Included because the materials are isomers

**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts
**DRF** - Dose Range Finding
**DST** - Dermal Sensitization Threshold
**ECHA** - European Chemicals Agency
**ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**IFRA** - The International Fragrance Association
**LOEL** - Lowest Observable Effect Level
**MOE** - Margin of Exposure
**MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
**NA** - North America
**NESIL** - No Expected Sensitization Induction Level
**NOAEC** - No Observed Adverse Effect Concentration
**NOAEL** - No Observed Adverse Effect Level
**NOEC** - No Observed Effect Concentration
**NOEL** - No Observed Effect Level
**OECD** - Organisation for Economic Co-operation and Development
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
**PBT** - Persistent, Bioaccumulative, and Toxic
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
**Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use
**vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

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

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

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

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

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

Dihydrocarveol (isomer unspecified) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that dihydrocarveol (isomer unspecified) is not genotoxic. Data on read-across material isopulegol (CAS # 89-79-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; the exposure to dihydrocarveol (isomer unspecified) is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm$^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; dihydrocarveol (isomer unspecified) is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; dihydrocarveol (isomer unspecified) was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

**Human Health Safety Assessment**

**Genotoxicity:** Not genotoxic. (RIFM, 2016a; RIFM, 2016b)
**Repeated Dose Toxicity:** NOAEL = 38 mg/kg/day. (EFSA Scientific Opinion on Flavouring Group Evaluation 57; EFSA, 2017)
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
**Phototoxicity/Photoallergenicity:** Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:**
Screening-level: 3.02 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
**Bioaccumulation:**
Screening-level: 60.95 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:**
Critical Ecotoxicity Endpoint: Fish LC50: 13.4 mg/L (RIFM Framework; Salvito, 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, 2002)
**Critical Ecotoxicity Endpoint:** Fish LC50: 13.4 mg/L (RIFM Framework; Salvito, 2002)
**RIFM PNEC is:** 0.0134 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

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## 1. Identification

| | | |
|---|---|---|
| Chemical Name: Dihydrocarveol (isomer unspecified) | Chemical Name: Dihydrocarveol (R,R,R) | Chemical Name: Neodihydrocarveol |
| **CAS Registry Number:** 619-01-2 | **CAS Registry Number:** 38049-26-2 | **CAS Registry Number:** 18675-34-8 |
| **Synonyms:** Cyclohexanol, 2-methyl-5-(1-methylethenyl)-; 8-p-Menthen-2-ol; 6-Methyl-3-isopropenylcyclohexanol; メチルイソプロペニルシクロヘキサノール; メチルイソプロペニルシクロヘキサノール; 5-Isopropenyl-2-methylcyclohexanol; Dihydro carveol; Dihydrocarveol (isomer unspecified) | **Synonyms:** (1α,2β,5α)-2-Methyl-5-(1-methylvinyl) cyclohexan-1-ol; 5-Isopropenyl-2-methylcyclohexanol; Cyclohexanol, 2-methyl-5-(1-methylethenyl)-, (1α,2β,5α)-; Dihydrocarveol (R,R,R) | **Synonyms:** Cyclohexanol, 2-methyl-5-(1-methylethenyl)-, (1α,2α,5α)-; Neo-*p*-menth-8-en-2-ol; Neodihydrocarveol |
| **Molecular Formula:** $C_{10}H_{18}O$ | **Molecular Formula:** $C_{10}H_{18}O$ | **Molecular Formula:** $C_{10}H_{18}O$ |
| **Molecular Weight:** 154.25 g/mol | **Molecular Weight:** 154.25 g/mol | **Molecular Weight:** 154.25 g/mol |
| **RIFM Number:** 891 | **RIFM Number:** 891 | **RIFM Number:** None |

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| | | |
|---|---|---|
| **Stereochemistry:** Isomer not specified. Three chiral centers and a total of 8 enantiomers possible. | **Stereochemistry:** RRR isomer specified. | **Stereochemistry:** 1R2R5R isomer specified |

## 2. Physical data

| | | |
|---|---|---|
| CAS # 619-01-2 | CAS # 38049-26-2 | CAS # 18675-34-8 |
| **Boiling Point:** 225 °C (Fragrance Materials Association [FMA]), 223.77 °C (EPI Suite) | **Boiling Point:** 223.77 °C (EPI Suite) | **Boiling Point:** Not available |
| **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA) | **Flash Point:** Not available | **Flash Point:** Not available |
| **Log $K_{OW}$:** 3.37 (EPI Suite) | **Log $K_{OW}$:** 3.37 (EPI Suite) | **Log $K_{OW}$:** Not available |
| **Melting Point**: −4.85 °C (EPI Suite) | **Melting Point**: −4.85 °C (EPI Suite) | **Melting Point**: Not available |
| **Water Solubility:** 426.5 mg/L (EPI Suite) | **Water Solubility:** 426.5 mg/L (EPI Suite) | **Water Solubility:** Not available |
| **Specific Gravity:** 0.923 (FMA) | **Specific Gravity:** | **Specific Gravity:** Not available |
| **Vapor Pressure:** 0.00954 mm Hg at 20 °C (EPI Suite v4.0), 0.04 mm Hg at 20 °C (FMA), 0.0159 mm Hg at 25 °C (EPI Suite) | **Vapor Pressure:** 0.00954 mm Hg at 20 °C (EPI Suite v4.0), 0.04 mm Hg at 20 °C (FMA), 0.0159 mm Hg at 25 °C (EPI Suite) | **Vapor Pressure:** Not available |
| **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$) | **UV Spectra:** Not available | **UV Spectra:** Not available |
| **Appearance/ Organoleptic:** Colorless or pale straw-colored liquid with a woody, floral odor, somewhat sickeningly sweet | **Appearance/ Organoleptic:** Not available | **Appearance/ Organoleptic:** Not available |

## 3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00097% (RIFM, 2018)
2. **Inhalation Exposure**:** 0.0000074 mg/kg/day or 0.00055 mg/day (RIFM, 2018)
3. **Total Systemic Exposure***:** 0.000083 mg/kg/day (RIFM, 2018)

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

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

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

## 5. Derivation of systemic absorption

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

## 6. Computational toxicology evaluation

### 6.1. Cramer Classification

Class I, Low.

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

### 6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** Isopulegol (CAS # 89-79-22)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

### 6.3. Read-across justification

None.

## 7. Metabolism

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

## 8. Natural occurrence

Dihydrocarveol (isomer unspecified) is not reported to occur in foods by the VCF*.

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

## 9. REACH dossier

Dihydrocarveol has been pre-registered for 2010; no dossier available as of 03/02/22.

## 10. Conclusion

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

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current existing data, dihydrocarveol (isomer unspecified) does not present a concern for genotoxicity.

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

The mutagenic activity of dihydrocarveol (isomer unspecified) 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with dihydrocarveol (isomer unspecified) in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2016a). Under the conditions of the study, dihydrocarveol (isomer unspecified) was not mutagenic in the Ames test.

The clastogenic activity of dihydrocarveol (isomer unspecified) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with dihydrocarveol (isomer unspecified) in DMSO at concentrations up to 1542.5 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 768 μg/mL in the presence and absence of metabolic activation. Dihydrocarveol (isomer unspecified) did induce some very small increases in the frequency of binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system in all treatments (RIFM, 2016b). However, since the increases were very small, not dose related, and within the historical control range, they were not considered biologically relevant. Under the conditions of the study, dihydrocarveol (isomer unspecified) was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, dihydrocarveol (isomer unspecified) does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/11/20.

*11.1.2. Repeated dose toxicity*

The MOE for dihydrocarveol (isomer unspecified) is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on dihydrocarveol (isomer unspecified). Read-across material isopulegol (CAS # 89-79-2; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In an OECD TG 408 and GLP compliant subchronic toxicity study, 10 CRL Sprague Dawley CD IGS rats/sex/group were administered the test material, isopulegol, at doses of 0, 300, 2500, or 50000 mg/kg in the feed. The diet contained microencapsulated isopulegol (20%) containing acacia gum (80%). The mean overall daily intakes were calculated to be 0, 190, 1750, and 3500 mg/kg/day for males and 0, 190, 1760, and 3530 mg/kg/day for females. Decreased body weight among males and bodyweight gains in both sexes were attributed to reduced food consumption; there was no statistically significant change in food efficiency, so the bodyweight changes were considered to be related to reduced food intake, and thus of no toxicological significance. Hematological alterations included a dose-related decrease in eosinophils, statistically significant only in males of the highest-dose group in comparison to the carrier control group. Lymphocyte population counts and total white blood cell counts were also decreased in males at the mid and high doses, but these changes were not statistically significant. Microscopic alterations included increased incidence and severity of chronic progressive nephropathy and tubular hyaline droplets in mid- and high-dose group males compared to basal and carrier control groups. These findings, along with the presence of granular casts in renal tubules of high-dose males, are characteristics of sex and species-specific α-2u-globulin nephropathy. Hence, this effect was not considered to be a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). Organ weight analysis revealed an increase in relative male kidney weights and increased relative liver weights in both sexes of the mid- and high-dose groups. Liver weight changes were not considered to be toxicologically relevant since they were not accompanied by correlating clinical chemistry parameters or microscopic changes. Due to a lack of evidence presented that kidney alterations were due to α-2u-globulin accumulation (no immunohistochemistry), the EFSA panel considered the kidney alterations along with decreased lymphocyte cell counts among mid- and high-dose groups to be treatment-related adverse events. Thus, the NOAEL for repeated dose toxicity was considered to be 190 mg/kg/day (EFSA, 2017). **Since the diet contained only 20% isopulegol from the total dose, the equivalent NOAEL was calculated to be 38 mg/kg/day.**

Therefore, the dihydrocarveol (isomer unspecified) MOE for repeated dose toxicity can be calculated by dividing the isopulegol NOAEL in mg/kg/day by the total systemic exposure to dihydrocarveol (isomer unspecified) (mg/kg/day), 38/0.000083, or 457831.

In addition, the total systemic exposure to dihydrocarvyl acetate (0.083 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/09/20.

*11.1.3. Reproductive toxicity*

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

*11.1.3.1. Risk assessment.* There are no reproductive toxicity data on dihydrocarveol (isomer unspecified) or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.083 μg/kg/day) is below the TTC for dihydrocarveol (isomer unspecified) (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/07/20.

*11.1.4. Skin sensitization*

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

*11.1.4.1. Risk assessment.* Limited skin sensitization data are available for dihydrocarveol (isomer unspecified). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2) In a human maximization test, no skin sensitization reactions were observed with 4% (2760 μg/cm$^2$) dihydrocarveol (isomer unspecified) in petrolatum (RIFM, 1977). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm$^2$ (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1

**Table 1**
Maximum acceptable concentrations for dihydrocarveol (isomer unspecified) that present no appreciable risk for skin sensitization based on reactive DST.

| IFRA Category[a] | Description of Product Type | Maximum Acceptable Concentrations in Finished Products Based on Reactive DST | Reported 95th Percentile Use Concentrations in Finished Products |
|---|---|---|---|
| 1 | Products applied to the lips | 0.0049% | $1.7 \times 10^{-5}$% |
| 2 | Products applied to the axillae | 0.0015% | $1.6 \times 10^{-4}$% |
| 3 | Products applied to the face using fingertips | 0.029% | $1.4 \times 10^{-5}$% |
| 4 | Fine fragrance products | 0.027% | $9.7 \times 10^{-4}$% |
| 5 | Products applied to the face and body using the hands (palms), primarily leave-on | 0.0070% | $1.4 \times 10^{-4}$% |
| 6 | Products with oral and lip exposure | 0.016% | 0.0018% |
| 7 | Products applied to the hair with some hand contact | 0.056% | $3.2 \times 10^{-5}$% |
| 8 | Products with significant ano-genital exposure | 0.0029% | No Data[b] |
| 9 | Products with body and hand exposure, primarily rinse-off | 0.054% | $5.6 \times 10^{-4}$% |
| 10 | Household care products with mostly hand contact | 0.19% | $4.3 \times 10^{-4}$% |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate | 0.11% | No Data[b] |
| 12 | Products not intended for direct skin contact, minimal or insignificant transfer to skin | Not restricted | 0.024% |

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

provides the maximum acceptable concentrations for dihydrocarveol (isomer unspecified) that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/15/20.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, dihydrocarveol (isomer unspecified) would not be expected to present a concern for phototoxicity or photoallergenicity.

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

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/04/20.

*11.1.6. Local Respiratory Toxicity*

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

*11.1.6.1. Risk assessment.* There are no inhalation data available on dihydrocarveol (isomer unspecified). Based on the Creme RIFM Model, the inhalation exposure is 0.00055 mg/day. This exposure is 2546 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/19/20.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of dihydrocarveol (isomer unspecified) was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log $K_{OW}$, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, dihydrocarveol (isomer unspecified) 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 is $< 1$).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify dihydrocarveol (isomer unspecified) 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, 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 $\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).

*11.2.1.1. Risk assessment.* Based on the current Volume of Use (2015), dihydrocarveol (isomer unspecified) does not present a risk to the aquatic compartment in the screening-level assessment.

*11.2.2. Key studies*

*11.2.2.1. Biodegradation.* No data available.

*11.2.2.2. Ecotoxicity.* No data available.

*11.2.2.3. Other available data.* Dihydrocarveol (isomer unspecified) has been pre-registered for REACH with no additional data at this time.

*11.2.2.4. Risk assessment refinement.* Endpoints used to calculate PNEC are underlined.

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 3.37 | 3.37 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band* | <1 | <1 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

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

*Combined Regional Volumes of Use for all CAS #s.

The RIFM PNEC is 0.0134 μg/L μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 12/02/20.

## 12. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 03/02/22.

## 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.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113241.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 13.4 | | | 1000000 | 0.0134 | |

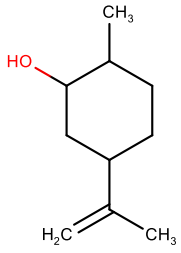
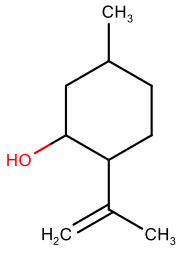
## Appendix

*Read-across Justification*

*Methods*

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

| | Target Material | Read-across Material |
|---|---|---|
| **Principal Name** | Dihydrocarveol (isomer unspecified) | Isopulegol |
| **CAS No.** | 619-01-2 | 89-79-2 |
| **Structure** |  |  |
| **Similarity (Tanimoto Score)** | | 0.87 |
| **Endpoint** | | • Repeated dose toxicity |
| **Molecular Formula** | $C_{10}H_{18}O$ | $C_{10}H_{18}O$ |
| **Molecular Weight (g/mol)** | 154.253 | 154.253 |
| **Melting Point (°C, EPI Suite)** | −4.85 | 78.00 |
| **Boiling Point (°C, EPI Suite)** | 225.00 | 223.77 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 2.12E+00 | 6.61E-01 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 4.27E+02 | 3.09E+02 |
| **Log $K_{OW}$** | 3.21 | 3.37 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 41.53 | 34.56 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 1.36E+00 | 1.36E+00 |
| ***Repeated Dose Toxicity*** | | |
| **Repeated Dose (HESS)** | Not categorized | Not categorized |
| ***Metabolism*** | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)** | See Supplemental Data 1 | See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on dihydrocarveol (isomer unspecified) (CAS # 619-01-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, isopulegol (CAS # 89-79-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

*Conclusion*

- Isopulegol (CAS # 89-79-2) was used as a read-across analog for the target material dihydrocarveol (isomer unspecified) (CAS # 619-01-2) for the repeated dose endpoint.
  - o The target material and the read-across analog are structurally similar and belong to monocyclic monoterpenoid alcohol.
  - o The target material and the read-across analog share a cyclohexanol structure.

- The key difference between the target material and the read-across analog is that the target material has an isopropylidene group at the 5 position. In comparison, the read-across analog has the same group at the 2 position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- There are no alerts for the target material and the read-across analog for the repeated dose toxicity endpoint. *In silico* alerts are consistent with the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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