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RIFM fragrance ingredient safety assessment, dihydrocarvyl acetate, CAS Registry Number 20777-49-5

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ABSTRACT

The existing information supports the use of this material as described in this safety assessment. Dihydrocarvyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs dihydrocarveol (isomer unspecified) (CAS # 619-01-2) and acetic acid (CAS # 64-19-7) show that dihydrocarvyl acetate is not expected to be genotoxic. Data on read-across analogs isopulegol (CAS # 89-79-2) and acetic acid (CAS # 64-19-7 provide a calculated MOE >100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to dihydrocarvyl acetate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across analog 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate (CAS # 122,760-85-4) provided dihydrocarvyl acetate a NESIL of 2500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; dihydrocarvyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; dihydrocarvyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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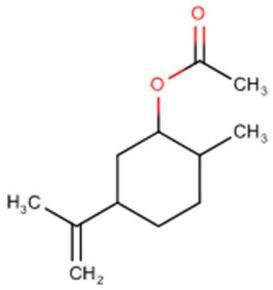
Conflicts of interest

The authors declare that they have no conflicts of interest.

Version: 031,121. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available.
Name: Dihydrocarvyl acetate
CAS Registry Number: 20,777-49-5



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., 2020)
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
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
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,

(*continued on next column*)

(*continued*)

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.

Dihydrocarvyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs dihydrocarveol (isomer unspecified) (CAS # 619-01-2) and acetic acid (CAS # 64-19-7) show that dihydrocarvyl acetate is not expected to be genotoxic. Data on read-across analogs isopulegol (CAS # 89-79-2) and acetic acid (CAS # 64-19-7 provide a calculated MOE >100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to dihydrocarvyl acetate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across analog 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate (CAS # 122,760-85-4) provided dihydrocarvyl acetate a NESIL of 2500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; dihydrocarvyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; dihydrocarvyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2016a; RIFM, 2016b; ECHA REACH Dossier: Acetic acid; ECHA, 2011)

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: NESIL = 2500 μg/cm^2. (RIFM, 1996a; RIFM, 1996b)

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: 2.9 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 360.5 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 2.25 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: 2.25 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.00225 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Dihydrocarvyl acetate
2. **CAS Registry Number:** 20,777-49-5
3. **Synonyms:** Carhydrine; Cyclohexanol, 2-methyl-5-(1-methylethenyl)-, acetate; *p*-Menth-8 (9)-en-2-yl acetate; 8-*p*-Menthen-2-yl acetate; 1-Methyl-4-isopropenylcyclohexan-2-yl acetate; 6-Methyl-3-isopropenylcyclohexyl acetate; (1a,2 b, 5a)-2-Methyl-5-(1-methylvinyl)cyclohexyl acetate; Tuberyl acetate; 1,2-ｼﾞﾋﾄﾞﾛｶﾙﾍﾞｵｰﾙｱﾙｶﾝ酸(C = 1 ~ 3)ｴｽﾃﾙ; 5-Isopropenyl-2-methylcyclohexyl acetate; Dihydrocarvyl acetate
4. **Molecular Formula:** $C_{12}H_{20}O_2$
5. **Molecular Weight:** 196.29
6. **RIFM Number:** 1110
7. **Stereochemistry:** Isomer not specified. Three stereocenters and 1 geometric center present. Sixteen isomers are possible.

2. Physical data

1. **Boiling Point:** 238 °C (Fragrance Materials Association [FMA]), 239.13 °C (EPI Suite)
2. **Flash Point:** 88 °C (Globally Harmonized System), 190 °F; CC (FMA)
3. **Log K_{OW}:** 4.38 (EPI Suite)
4. **Melting Point**: 1.66 °C (EPI Suite)
5. **Water Solubility:** 8.307 mg/L (EPI Suite)
6. **Specific Gravity:** 0.954 (FMA)
7. **Vapor Pressure:** 0.0311 mm Hg at 20 °C (EPI Suite v4.0), 0.0485 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid that has a sweet, slightly minty, floral, rosy odor with a herbal undertone

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0012 % (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0000082 mg/kg/day or 0.00059 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2018)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I*, Low (Expert Judgment)

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

*See the Appendix for details.

2. Analogs Selected:
   a. **Genotoxicity:** Dihydrocarveol (isomer unspecified) (CAS # 619-01-2) and acetic acid (CAS # 64-19-7)
   b. **Repeated Dose Toxicity:** Isopulegol (CAS # 89-79-2) and acetic acid (CAS # 64-19-7)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 4-Methyl-8-methylenetricyclo [3.3.1.(3,7)] decan-2-yl acetate (CAS # 122,760-85-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Dihydrocarvyl acetate is reported to occur in food by the VCF*:
Anise (*Pimpinella anisum* L.)
Celery (*Apium graveolens* L.)
Dill (*Anethum* species)
Olive (*Olea europaea*)
Origanum (Spanish) (*Coridothymus cap*. (L.) Rchb.)
*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

Pre-registered for 2010; no dossier available as of 03/11/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for dihydrocarvyl acetate 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)	0.19
2	Products applied to the axillae	0.057
3	Products applied to the face/body using fingertips	0.065
4	Products related to fine fragrances	1.1
5 A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.27
5 B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.087
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.11
5D	Baby cream, oil, talc	0.029
6	Products with oral and lip exposure	0.63
7	Products applied to the hair with some hand contact	0.022
8	Products with significant ano-genital exposure (tampon)	0.029
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.50
10 A	Household care products with mostly hand contact (hand dishwashing detergent)	1.1
10 B	Aerosol air freshener	3.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.029
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	99

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

dihydrocarvyl acetate, the basis was the reference dose of 0.38 mg/kg/day, a predicted skin absorption value of 40 %, and a skin sensitization NESIL of 2500 μg/cm^2.

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

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Dihydrocarvyl acetate 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, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic and clastogenic activity of dihydrocarvyl acetate; however, read-across can be made to hydrolysis products of the target ester, dihydrocarveol (isomer unspecified) (CAS # 619-01-2) and acetic acid (CAS # 64-19-7) (see Section VI).

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, and this can be extended to dihydrocarvyl acetate.

The mutagenic activity of acetic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 were treated with acetic acid in phosphate buffer at concentrations up to 10,000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, acetic acid was not mutagenic in the Ames test, and this can be extended to dihydrocarvyl acetate.

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 480 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h Dihydrocarveol (isomer unspecified) did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2016b). Under the conditions of the study, dihydrocarveol (isomer unspecified) was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to dihydrocarvyl acetate.

The clastogenicity of acetic acid was assessed in an *in vitro* chromosome aberration study conducted according to a protocol similar to OECD TG 473. Chinese hamster ovary or lung cells were treated with acetic acid in water at concentrations up to 10 mM 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 concentration of the test material, either with or without S9 metabolic activation (ECHA, 2011). Under the conditions of the study, acetic acid was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to dihydrocarvyl acetate.

Based on the available data, dihydrocarveol (isomer unspecified) and acetic acid do not present a concern for genotoxic potential, and this can be extended to dihydrocarvyl acetate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/17/20.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for dihydrocarvyl acetate 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 dihydrocarvyl acetate. Read-across materials isopulegol (CAS # 89-79-2; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI) have sufficient data to support the repeated dose toxicity endpoint. Isopulegyl acetate was assessed by EFSA as part of the Scientific Opinion on Flavouring Group Evaluation 57, 2017 (EFSA, 2017) along with isopulegone and isopulegol. Isopulegyl acetate is expected to hydrolyze to isopulegol (CAS # 89-79-2) and acetic acid (CAS # 64-19-7). There are sufficient repeated dose toxicity data available on isopulegol. **Based on the available data (**NICNAS, 2013; EFSA, 2012; JECFA, 2006**), acetic acid does not show specific reproductive or developmental toxicity. Thus, as such acetic acid does not pose any systemic (repeated dose) toxicity to human health when used in fragrances.** 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 dietary levels of 0, 3000, 25,000, or 50,000 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. However, due to the lack of statistical significance in changes in food efficiency, the bodyweight changes were not considered to be of 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. Microscopic alteration included increased incidence and severity of chronic progressive nephropathy and tubular hyaline droplets in mid- and high-dose 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. 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. **Since diet contained only 20 % isopulegol from the total dose the equivalent NOAEL was calculated to be 38 mg/kg/day.**

Therefore, the dihydrocarvyl acetate MOE for repeated dose toxicity can be calculated by dividing the isopulegol NOAEL in mg/kg/day by

the total systemic exposure to dihydrocarvyl acetate (mg/kg/day), 38/0.00014 or 271,429.

In addition, the total systemic exposure to dihydrocarvyl acetate (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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. (RIFM, 2020) and a reference dose of 0.38 mg/kg/day.

Derivation of reference dose (RfD)

The RIFM Criteria Document (Api, 2015) calls for a default margin of exposure (MOE) of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for dihydrocarvyl acetate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 38 mg/kg/day by the uncertainty factor, 100 = 0.38 mg/kg/day.

Additional References: None.

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

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on dihydrocarvyl acetate or on any read-across materials. The total systemic exposure to dihydrocarvyl acetate 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 dihydrocarvyl acetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to dihydrocarvyl acetate (0.14 μg/kg/day) is below the TTC (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: 12/15/20.

11.1.4. Skin sensitization

Based on the existing data and read-across material 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate (CAS # 122,760-85-4), dihydrocarvyl acetate is considered a skin sensitizer with a defined NESIL of 2500 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for dihydrocarvyl acetate. Based on the existing data and read-across material 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate (CAS # 122,760-85-4; see Section VI), dihydrocarvyl acetate is considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate was found to be non-sensitizing up to 30 % (7500 μg/cm^2) (RIFM, 2004). However, in a Buehler test the read-across material 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate did present reactions indicative of sensitization (RIFM, 1989c; IFRA (International Fragrance Association), 2015). In a human maximization test, 4 % (2760 μg/cm^2) dihydrocarvyl acetate did not result in reactions indicative of sensitization (RIFM, 1980). In 2 Confirmation of No Induction in Humans tests (CNIHs) with a total of 101 human subjects using 5 % (2500 μg/cm^2) of read-across material 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate in ethanol-based vehicle, no sensitization reactions were observed (RIFM, 1996a; RIFM, 1996b). In additional CNIH tests with small numbers of subjects, no reactions were observed (RIFM, 1989a; RIFM, 1989b).

Based on the available data on read-across material 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate, summarized in Table 1, dihydrocarvyl acetate is considered to be a skin sensitizer with a defined NESIL of 2500 μg/cm^2. 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. (RIFM, 2020) and a reference dose of 0.38 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/18/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, dihydrocarvyl acetate 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 dihydrocarvyl acetate in experimental models. UV/Vis absorption spectra indicate minor absorbance 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 significant absorbance in the critical range, dihydrocarvyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for dihydrocarvyl acetate were obtained. The spectra indicate minor 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: 12/11/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for dihydrocarvyl acetate 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 dihydrocarvyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.00059 mg/day. This exposure is 2373 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.

Table 1
Data summary for 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate as read-across material for dihydrocarvyl acetate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
>7500 [1]	Weak	2500	n/a	n/a	2500

NOEL = No observed effect level; CNIH = Human Repeat Insult Patch test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of dihydrocarvyl acetate 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, dihydrocarvyl acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

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

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Dihydrocarvyl acetate has been pre-registered for REACH with no additional information at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.38	4.38
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	< **1**	lt; **1**

The RIFM PNEC is 0.00225 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 12/16/20.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.25			1000000	0.0025	

&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 03/11/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112458.

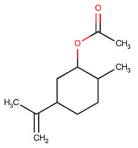
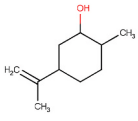
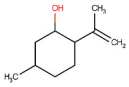
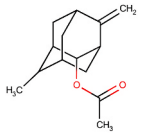
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Dihydrocarvyl acetate	Dihydrocarveol (isomer unspecified)	Acetic acid	Isopulegol	4-Methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate
CAS No.	20,777-49-5	619-01-2	64-19-7	89-79-2	122,760-85-4
Structure					
Similarity (Tanimoto Score)		0.59	0.11	0.56	0.77
Read-across Endpoint		• Genotoxicity	• Genotoxicity • Repeated Dose Toxicity	• Repeated Dose Toxicity	• Skin Sensitization
Molecular Formula	$C_{12}H_{20}O_2$	$C_{10}H_{18}O$	$C_2H_4O_2$	$C_{10}H_{18}O$	$C_{14}H_{20}O_2$
Molecular Weight	196.29	154.25	60.05	154.25	220.31
Melting Point (°C, EPI Suite)	1.66	−4.85	16.64	78	56.82
Boiling Point (°C, EPI Suite)	239.13	225	117.90	223.77	272.86
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.46	2.12	2.09 E+003	0.662	0.551
	4.38	3.21	−0.17	3.37	4.23

(continued on next page)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Log K_{OW} (KOWWIN v1.68 in EPI Suite)					
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	8.307	426.5	1e+006	308.6	8.327
J_{max} (μg/cm^2/h, SAM)	46.092	184.848	6283.04	110.111	34.158
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.82 E+001	1.36 E+000	1.45E-002	1.36 E+000	3.02 E+001
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2|AN2 ≫ Schiff base formation after aldehyde release|AN2 ≫ Schiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	• No alert found	• No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found		
Carcinogenicity (ISS)	• No alert found	• No alert found	• No alert found		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	• No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS**	• No alert found	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified	• Not classified		
Repeated Dose Toxicity					
Repeated Dose (HESS)	• Not categorized		• Carboxylic acids (Hepatotoxicity) No rank	• Not categorized	
Skin Sensitization					
Protein Binding (OASIS v1.1)	• No alert found				• No alert found
Protein Binding (OECD)	• No alert found				• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)				• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found				• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found				• No alert found
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• No metabolites	• See Supplemental Data 3	• See Supplemental Data 4

Summary

There are insufficient toxicity data on dihydrocarvyl acetate (CAS # 20,777-49-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, dihydrocarveol (isomer unspecified) (CAS # 619-01-2), acetic acid (CAS # 64-19-7), isopulegol (CAS # 89-79-2), and 4-methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate (CAS # 122,760-85-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Read-across alcohol dihydrocarveol (isomer unspecified) (CAS # 619-01-2) and read-across acid acetic acid (CAS # 64-19-7) were used as read-across analogs for the target ester dihydrocarvyl acetate (CAS # 20,777-49-5) for the genotoxicity endpoint.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target material.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.

- According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Read-across alcohol isopulegol (CAS # 89-79-2) and read-across acid, acetic acid (CAS # 64-19-7) were used as read-across analogs for the target ester dihydrocarvyl acetate (CAS # 20,777-49-5) for the repeated dose toxicity endpoint.
  - The products of ester hydrolysis are dihydrocarveol and acetic acid (see above). However, isopulegol, an isomer of dihydrocarveol, has been used as the read-across alcohol.
  - The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
  - The read-across carboxylic acid is predicted to have a hepatotoxicity alert for repeated dose toxicity by the HESS categorization scheme. It has been shown by numerous studies that carboxylic acids are excreted out from the human body relatively quickly with no toxic effects. The data described in the repeated dose section above shows that the MOE of the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by the availability of the data.
- 4-Methyl-8-methylenetricyclo [3.3.1.(3,7)]decan-2-yl acetate (CAS # 122,760-85-4) was used as a read-across analog for the target material dihydrocarvyl acetate (CAS # 20,777-49-5) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of esters.
  - The target material and the read-across analog share an acetic acid branch.
  - The key differences between the target material and the read-across analog are in the cyclic alcohol structure. Despite these differences in the cyclic hydrocarbon fragment, the target material and read-across analog share the same physical and chemical properties and key functional groups. These structural differences are toxicologically insignificant.
  - 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 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.
  - 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.

Explanation of Cramer Classification

Due to potential discrepancies between 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.

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and 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 (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? Yes
Q18. One of the list (see Cramer et al., 1978 for a detailed explanation on the list of categories)? No, Low (Class I)

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