



RIFM fragrance ingredient safety assessment, carvyl acetate, CAS registry number 97-42-7

A.M. Api^a, D. Belsito^b, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, J. Buschmann^e, M. A. Cancellieri^a, M.L. Dagli^f, M. Date^a, W. Dekant^g, C. Deodhar^a, A.D. Fryer^h, L. Jones^a, K. Joshi^a, M. Kumar^a, A. Lapczynski^a, M. Lavelle^a, I. Lee^a, D.C. Lieblerⁱ, H. Moustakas^a, M. Na^a, T.M. Penning^j, G. Ritacco^a, J. Romine^a, N. Sadekar^a, T.W. Schultz^k, D. Selechnik^a, F. Siddiqi^a, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

^b Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Member Expert Panel, Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmö, SE, 20502, Sweden

^d Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, USA

^e Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

^f Member Expert Panel, University of São Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, São Paulo, CEP 05508-900, Brazil

^g Member Expert Panel, University of Würzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

^h Member Expert Panel, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

ⁱ Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

^j Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

^k Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^l Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

^m Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

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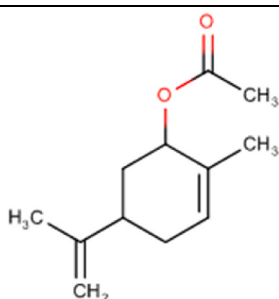
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Name: Carvyl acetate

CAS Registry Number: 97-42-7

Additional CAS Numbers*:

1205-42-1 laevo-Carvyl acetate (No



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Reported Use)

*Included because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)

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* Corresponding author.

E-mail address: gsullivan@rifm.org (G. Sullivan).

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Creame RIFM Model - The Creame 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

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.

Carvyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that carvyl acetate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to carvyl acetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from the target material and read-across analog pinocarvyl acetate (CAS # 1078-95-1) provided carvyl acetate a No Expected Sensitization Induction Level (NESIL) of 550 $\mu\text{g}/\text{cm}^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; carvyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; carvyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the

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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. (Mortelmans, 1986; RIFM, 2017)

Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: NESIL = 550 $\mu\text{g}/\text{cm}^2$. RIFM (2013)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.91 (BIOWIN 3) (EPI Suite v.4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 316.6 L/kg (EPI Suite v.4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 2.67 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: 2.67 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.00267 $\mu\text{g}/\text{L}$

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

1. Identification

Chemical Name: Carvyl acetate	Chemical Name: <i>laevo</i> -Carvyl acetate
CAS Registry Number: 97-42-7	CAS Registry Number: 1205-42-1
Synonyms: 2-Cyclohexen-1-ol, 2-methyl-5-(1-methylethenyl)-, acetate; <i>p</i> -Mentha-6,8-dien-2-yl acetate; 加片 [®] オル酢酸エステル; 5-Isopropenyl-2-methylcyclohex-2-en-1-yl acetate; Carvyl acetate	Synonyms: <i>cis</i> -Carvyl acetate; 2-Cyclohexen-1-ol, 2-methyl-5-(1-methylethenyl)-, acetate, <i>cis</i> -; 1- <i>p</i> -Mentha-6,8 (9)-dien-2-yl acetate; <i>cis</i> -2-Methyl-5-(1-methylvinyl)cyclohex-2-en-1-yl acetate; 5-Isopropenyl-2-methylcyclohex-2-en-1-yl acetate; 1-Carvyl acetate; <i>laevo</i> -Carvyl acetate
Molecular Formula: $\text{C}_{12}\text{H}_{18}\text{O}_2$	Molecular Formula: $\text{C}_{12}\text{H}_{18}\text{O}_2$
Molecular Weight: 194.27	Molecular Weight: 194.27
RIFM Number: 6269	RIFM Number: 736
Stereochemistry: Isomer not specified. Two stereocenters and 3 total stereoisomers possible.	Stereochemistry: <i>Cis</i> isomer specified. Two stereocenters and 3 total stereoisomers possible.

2. Physical data

CAS # 97-42-7	CAS # 1205-42-1
Boiling Point: 245.13 °C (EPI Suite)	Boiling Point: 78 °C at 0.1 mm Hg (FMA), 245.13 °C (EPI Suite)
Flash Point: >93 °C (Globally Harmonized System [GHS]), >200 °F; CC (Fragrance Materials Association [FMA])	Flash Point: >93 °C (GHS), >200 °F; CC (FMA)
Log K_{ow} : 4.29 (EPI Suite)	Log K_{ow} : 4.29 (EPI Suite)
Melting Point: 12.17 °C (EPI Suite)	Melting Point: 12.17 °C (EPI Suite)
Water Solubility: 10.06 mg/L (EPI Suite)	Water Solubility: 10.06 mg/L (EPI Suite)
Specific Gravity: Not Available	Specific Gravity: 0.976 (FMA)
Vapor Pressure: 0.0255 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.0353 mm Hg at 25 °C (EPI Suite)	Vapor Pressure: 0.0255 mm Hg at 20 °C (EPI Suite v4.0), 0.0353 mm Hg at 25 °C (EPI Suite)
UV Spectra: No significant absorbance between 290 and 400 nm; molar	UV Spectra: No significant absorbance between 290 and 400 nm; molar

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absorption coefficient is below the benchmark (1000 L mol ⁻¹ • cm ⁻¹)	absorption coefficient is below the benchmark (1000 L mol ⁻¹ • cm ⁻¹)
Appearance/Organoleptic: Colorless, slightly oily liquid with a refreshing, green-minty, spearmint-like odor	Appearance/Organoleptic: A colorless, slightly oily liquid

3. Volume of use (Worldwide band)

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

4. Exposure*** to fragrance ingredient (Crema RIFM aggregate exposure model v1.0)

- 95th Percentile Concentration in Fine Fragrance:** 0.00033% (RIFM, 2017)
- Inhalation Exposure*:** 0.000064 mg/kg/day or 0.0046 mg/day (RIFM, 2017)
- Total Systemic Exposure**:** 0.00033 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Crema 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 Crema 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).

***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.

5. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

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

2. Analogs Selected:

- Genotoxicity:** None
- Repeated Dose Toxicity:** None
- Reproductive Toxicity:** None
- Skin Sensitization:** Pinocaryyl acetate (CAS # 1078-95-1)
- Phototoxicity/Photoallergenicity:** None
- Local Respiratory Toxicity:** None
- Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

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

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

Celery (*Apium graveolens* L.)
 Citrus fruits
 Dill (*Anethum* species)
 Mentha oils qualitative
 Myrtle (*Myrtus communis* L.)
 Strawberry (*Fragaria* species)
laevo-Carvyl acetate is reported to occur in the following foods by the VCF*:
 Angelica (*Angelica archangelica* L.)
 Buchu oil
 Celery (*Apium graveolens* L.)
 Citrus fruits
 Mastic (*Pistacia lentiscus*)
 Mentha oils
 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

Carvyl acetate is pre-registered for 2010; *laevo*-Carvyl acetate is pre-registered for 2013. No dossiers available as of 07/27/21.

10. Conclusion

The maximum acceptable concentrations^a in finished products for carvyl acetate are detailed below.

IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%)
1	Products applied to the lips (lipstick)	0.042
2	Products applied to the axillae	0.013
3	Products applied to the face/body using fingertips	0.25
4	Products related to fine fragrances	0.24
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.060
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.060
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.060
5D	Baby cream, oil, talc	0.060
6	Products with oral and lip exposure	0.14
7	Products applied to the hair with some hand contact	0.48
8	Products with significant anogenital exposure (tampon)	0.025
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.46
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.7
10B	Aerosol air freshener	1.7
11	Products with intended skin contact but minimal transfer of fragrance to	0.92

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IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%)
12	skin from inert substrate (feminine hygiene pad) Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: ^aMaximum 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 carvyl acetate, the basis was a skin sensitization NESIL of 550 µg/cm².

^bFor 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>).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of carvyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with carvyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 333 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Mortelmans, 1986). Under the conditions of the study, carvyl acetate was not mutagenic in the Ames test.

The clastogenic activity of carvyl acetate 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 carvyl acetate in DMSO at concentrations up to 1940 µg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 µg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h. Carvyl acetate did not induce binucleated cells with micronuclei when tested up to the cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, carvyl acetate was non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on carvyl acetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to carvyl acetate (0.33 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: 05/20/

21.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on carvyl acetate or on any read-across materials. The total systemic exposure to carvyl 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 carvyl acetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to carvyl acetate (0.33 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: 05/31/21.

11.1.4. Skin sensitization

Based on the existing data and read-across material pinocarvyl acetate (CAS # 1078-95-1), carvyl acetate is considered a skin sensitizer with a defined NESIL of 550 µg/cm².

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for carvyl acetate. Based on the existing data and read-across material pinocarvyl acetate (CAS # 1078-95-1; see Section VI), carvyl acetate is a sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, pinocarvyl acetate did not present reactions indicative of sensitization (RIFM, 1976a). In a human maximization test with 2760 µg/cm² l-carvyl acetate, no skin sensitization reactions were observed (RIFM, 1976b). In another human maximization test, no skin sensitization reactions were observed with the read-across material, pinocarvyl acetate (RIFM, 1982). In a Confirmation of No Induction in Humans test (CNIH) with 4264 µg/cm² of pinocarvyl acetate, 1/41 volunteer subjects showed a reaction indicative of skin sensitization. In another CNIH, no reactions indicative of sensitization were observed in any of the 106 volunteers when pinocarvyl acetate was tested at 550 µg/cm² (RIFM, 2013).

Based on the available data on read-across material pinocarvyl acetate, summarized in Table 1, carvyl acetate is considered to be a skin sensitizer with a defined NESIL of 550 µg/cm². 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).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/21.

Table 1

Data Summary for pinocarvyl acetate as read-across material for carvyl 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
NA	NA	550	6897	4264	550

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans 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.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, carvyl 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 carvyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, carvyl acetate 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 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for carvyl 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 carvyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0046 mg/day. This exposure is 304.3 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: 05/28/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of carvyl 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, carvyl 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 carvyl 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 ≥ 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), carvyl acetate presents no 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. Carvyl acetate (CAS # 97-42-7) and laevo-carvyl acetate (CAS # 1205-42-1) have been pre-registered for REACH with no additional data at this time.

11.2.2.4. 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	4.29	4.29
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	<1	<1

*Combined Regional Volume of Use.

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

The RIFM PNEC is 0.00267 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 VoU.

Literature Search and Risk Assessment Completed On: 05/25/21.

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>

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>2.67</u>			1000000	0.00267	

- EPA ACToR: <https://actor.epa.gov/actor/home.xhtml>
- US EPA HPVIS: https://ofmpub.epa.gov/opphpv/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 09/02/21.

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. 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.2021.112678>.

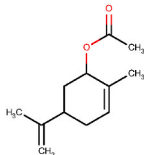
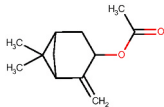
Appendix

Read-across Justification

Methods

The read-across analog was 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
Principal Name	Carvyl acetate	Pinocarvyl acetate
CAS No.	97-42-7	1078-95-1
Structure		
Similarity (Tanimoto Score)		0.56
Read-across Endpoint		• Skin Sensitization
Molecular Formula	C ₁₂ H ₁₈ O ₂	C ₁₂ H ₁₈ O ₂
Molecular Weight	194.27	194.27
Melting Point (°C, EPI Suite)	12.17	38.44
Boiling Point (°C, EPI Suite)	245.13	231.06
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.71E+00	7.04E+00
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.29	3.81
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	10.06	25.86
J_{max} (µg/cm²/h, SAM)	162.756	48.869
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	9.16E+01	3.89E+01
Skin Sensitization		
Protein Binding (OASIS v1.1)	<ul style="list-style-type: none"> • SN2 SN2 >> SN2 Reaction at a sp3 carbon atom SN2 >> SN2 Reaction at a sp3 carbon atom >> Activated alkyl esters and thioesters 	<ul style="list-style-type: none"> • SN2 SN2 >> SN2 Reaction at a sp3 carbon atom SN2 >> SN2 Reaction at a sp3 carbon atom >> Activated alkyl esters and thioesters
Protein Binding (OECD)	<ul style="list-style-type: none"> • SN2 SN2 >> SN2 reaction at sp3 carbon atom SN2 >> SN2 reaction at sp3 carbon atom >> Allyl acetates and related chemicals 	<ul style="list-style-type: none"> • SN2 SN2 >> SN2 reaction at sp3 carbon atom SN2 >> SN2 reaction at sp3 carbon atom >> Allyl acetates and related chemicals
Protein Binding Potency	<ul style="list-style-type: none"> • Not possible to classify according to these rules (GSH) 	<ul style="list-style-type: none"> • Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	<ul style="list-style-type: none"> • SN2 SN2 >> SN2 Reaction at a sp3 carbon atom SN2 >> SN2 Reaction at a sp3 carbon atom >> Activated alkyl esters and thioesters 	<ul style="list-style-type: none"> • SN2 SN2 >> SN2 Reaction at a sp3 carbon atom SN2 >> SN2 Reaction at a sp3 carbon atom >> Activated alkyl esters and thioesters
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	<ul style="list-style-type: none"> • Alert for Acyl Transfer agent identified • Alert for SN2 identified 	<ul style="list-style-type: none"> • Alert for Acyl Transfer agent identified • Alert for SN2 identified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	<ul style="list-style-type: none"> • See Supplemental Data 1 	<ul style="list-style-type: none"> • See Supplemental Data 2

Summary

There are insufficient toxicity data on carvyl acetate (CAS # 97-42-7). 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, read-across pinocarvyl acetate (CAS # 1078-95-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Pinocarvyl acetate (CAS # 1078-95-1) was used as a read-across analog for the target material carvyl acetate (CAS # 97-42-7) for the skin sensitization endpoint.
 - o The target material and the read-across analog are structurally similar and are esters of cyclic monoterpene alcohols.
 - o The target material and the read-across analog share a cyclic monoterpene alcohol and acetate ester functionality.
 - o The key difference between the target material and the read-across analog is that the target is the acetate ester of a monocyclic terpene alcohol, whereas the read-across analog is the acetate ester of a bridged monoterpene alcohol. This structural difference is toxicologically insignificant.
 - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
 - o The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
 - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
 - o The target material and the read-across analog have an SN2 reaction at the sp3 carbon center alert. The data described in the skin sensitization section above for the read-across analog confirm that the target material is a skin sensitizer. Data are consistent with *in silico* alerts.
 - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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