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RIFM fragrance ingredient safety assessment, carvyl propionate, CAS Registry Number 97-45-0

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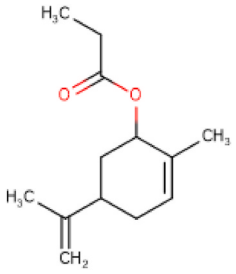
Name: Carvyl propionate

CAS Registry Number: 97-45-0



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 Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
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

(*continued on next column*)

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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 propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog carvyl acetate (CAS # 97-42-7) show that carvyl propionate is not expected to be 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; exposure to carvyl propionate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog pinocarvyl acetate (CAS # 1078-95-1) provided carvyl propionate a No Expected Sensitization Induction Level (NESIL) of 550 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; carvyl propionate is not expected to be phototoxic/photoallergenic. For the hazard assessment based on the screening data, carvyl propionate is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, carvyl propionate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (Mortelmans, 1986; RIFM, 2017a)

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

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

Skin Sensitization: NESIL = 550 μg/cm^2. RIFM (2013a)

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: 667.7 mg/L (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Not applicable

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; no Volume of Use in 2015 reported for Europe and North America

1. Identification

1. **Chemical Name:** Carvyl propionate
2. **CAS Registry Number:** 97-45-0
3. **Synonyms:** 2-Cyclohexen-1-ol, 2-methyl-5-(1-methylethenyl)- propionate; p-Mentha-6,8-dien-2-yl propionate; 5-Isopropenyl-2-methylcyclohex-2-en-1-yl propionate; laevo-Carvyl propionate; (2-Methyl-5-prop-1-en-2-yl-1-cyclohex-2-enyl) propanoate; Carvyl propionate
4. **Molecular Formula:** $C_{13}H_{20}O_2$
5. **Molecular Weight:** 208.3 g/mol
6. **RIFM Number:** 6270
7. **Stereochemistry:** Two stereocenters and 4 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 262.43 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (Fragrance Materials Association)
3. **Log K_{OW}:** 4.79 (EPI Suite)
4. **Melting Point**: 22.85 °C (EPI Suite)
5. **Water Solubility:** 3.245 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00867 mm Hg at 20 °C (EPI Suite v4.0), 0.0139 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:** Colorless, slightly oily liquid with a sweet, warm, minty-spearmint-y, herbaceous odor

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 v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00056% (RIFM, 2017b)
2. **Inhalation Exposure*:** 0.000064 mg/kg/day or 0.0046 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.00033 mg/kg/day (RIFM, 2017b)

*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

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:** Carvyl acetate (CAS # 97-42-7)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Pinocarvyl acetate (CAS # 1078-95-1)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

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

8. Natural occurrence

Carvyl propionate 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

Pre-registered for 2010; no dossier available as of 12/08/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for carvyl propionate 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)	0.042
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 ano-genital 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 skin from inert substrate (feminine hygiene pad)	0.92
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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 carvyl propionate, the basis was a skin sensitization NESIL of 550 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-I

FRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Carvyl propionate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an equi-reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic and clastogenic activity of carvyl propionate; however, read-across can be made to carvyl acetate (CAS # 97-42-7; see Section VI).

The mutagenic activity of carvyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in an equivalent manner 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 333.000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Mortelmans, 1986). Under the conditions of the study, carvyl acetate was not mutagenic in the Ames test, and this can be extended to carvyl propionate.

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 600 μg/mL in the presence and absence of metabolic activation. Carvyl acetate did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, carvyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to carvyl propionate.

Based on the data available, carvyl acetate does not present a concern for genotoxic potential, and this can be extended to carvyl propionate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/10/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on carvyl propionate or any read-across materials. The total systemic exposure to carvyl propionate 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 propionate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to carvyl propionate (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: 01/06/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on carvyl propionate or any read-across materials. The total systemic exposure to carvyl propionate 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 propionate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to carvyl propionate (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: 02/05/21.

11.1.4. Skin sensitization

Based on the existing data and the read-across material pinocarvyl acetate, carvyl propionate is a sensitizer with a defined NESIL of 550 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for carvyl propionate. Based on the existing data and read-across material pinocarvyl acetate (CAS # 1078-95-1; see Section VI), carvyl propionate is considered a sensitizer. The chemical structure of these materials indicates 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, the read-across material pinocarvyl acetate did not present reactions indicative of sensitization (RIFM, 1976a). In a human maximization test with 2760 μg/cm^2 carvyl propionate, 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/cm^2 of pinocarvyl acetate, 1/41 volunteer subjects showed a reaction indicative of skin sensitization, indicating that pinocarvyl acetate is a skin sensitizer (RIFM, 1971). In another CNIH, no reactions indicative of sensitization were observed in any of the 106 volunteers when pinocarvyl acetate was tested at 550 μg/cm^2 (RIFM, 2013a).

Based on the weight of evidence (WoE) from structural analysis and data on the read-across material pinocarvyl acetate, carvyl propionate is a sensitizer with a WoE NESIL of 550 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020).

Table 1
Data summary for pinocarvyl acetate as read-across material for carvyl propionate.

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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/20/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, carvyl propionate 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 propionate 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, carvyl propionate 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: 01/11/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for carvyl propionate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on carvyl propionate. 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: Rice (1994).

Literature Search and Risk Assessment Completed On: 02/08/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of carvyl propionate 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. 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 propionate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify carvyl propionate 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. Not applicable.

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 propionate has been pre-registered for REACH, with no additional data available at this time.

11.2.2.4. Risk assessment refinement. Not applicable.

Literature Search and Risk Assessment Completed On: 01/11/21.

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
- **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 12/08/21.

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.2022.113230.

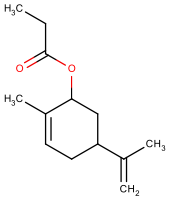
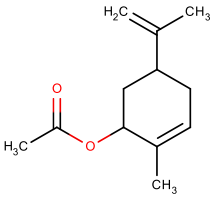
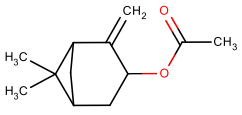
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). These criteria follow 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 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Carvyl propionate	Carvyl acetate	Pinocarvyl acetate
CAS No.	97-45-0	97-42-7	1078-95-1
Structure			
Similarity (Tanimoto Score)		0.74	0.25
Endpoint		Genotoxicity	Skin sensitization
Molecular Formula	$C_{13}H_{20}O_2$	$C_{12}H_{18}O_2$	$C_{12}H_{18}O_2$
Molecular Weight (g/mol)	208.30	194.27	194.27
Melting Point (°C, EPI Suite)	22.85	12.17	38.44
Boiling Point (°C, EPI Suite)	262.43	245.13	231.06
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.85	4.71	7.04
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.25	10.06	25.86
Log K_{OW}	4.79	4.29	3.81
J_{max} (μg/cm^2/h, SAM)	0.46	1.29	2.34
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	121.59	91.60	38.91
Genotoxicity	No alert found		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)		AN2|AN2 ≫ Schiff base formation after aldehyde release|AN2 ≫ Shiff 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	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Skin Sensitization			
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ SN2 reaction at a sp3 carbon atom|SN2 ≫ SN2 reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		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)	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals		SN2|SN2 ≫ SN2 reaction at sp3 carbon atom| SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals
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)	SN2|SN2 ≫ SN2 reaction at a sp3 carbon atom|SN2 ≫ SN2 reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		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)	Alert for Acyl Transfer agent identified.		Alert for Acyl Transfer agent identified.
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on carvyl propionate (CAS # 97-45-0). 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, carvyl acetate (CAS # 97-42-7) and pinocarvyl acetate (CAS # 1078-95-1) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusion

- Carvyl acetate (CAS # 97-42-7) was used as a read-across analog for the target material carvyl propionate (CAS # 97-45-0) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to the structural class of esters.
  - o The key difference between the target material and the read-across analog is that the target material is a propionate ester, whereas the read-across analog is an acetate ester. This structural difference between the target material and the read-across analog does not affect consideration of the toxic endpoint.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog has a Schiff base formation after aldehyde release or SN2 mechanism or acylation alert as predicted by DNA Binding (OASIS v1.4, QSAR Toolbox v4.2). This alert is due to the acetate ester that can operate via several mechanisms. However, acetate esters are generally non-mutagenic. Thus, based on the existing data and read-across analog, the target material does not pose any genotoxic concern. As a result, the predicted alerts are superseded by the available data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

- Pinocarvyl acetate (CAS # 1078-95-1) was used as a read-across analog for the target material carvyl propionate (CAS # 97-45-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the structural class of esters.
  - o The key difference between the target material and the read-across analog is that the target material is a propionate ester, whereas the read-across analog is an acetate ester. Moreover, the target material has an additional vinylene bond on the alcohol side compared to the read-across analog. These structural differences between the target material and the read-across analog do not affect consideration of the toxic endpoint.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and the read-across analog have an S_N2 reaction and an S_p3 carbon atom alert as predicted by the OASIS v1.1 and OECD tools. This alert is due to the S_N2 mechanism occurring at the activated carbon in target and read-across materials. An S_N2 mechanism occurring at the activated carbon has been suggested to be responsible for the protein reactivity of these chemicals. Based on the existing data and the read-across material pinocarvyl acetate, carvyl propionate is a sensitizer with a defined NESIL of 550 μg/cm^2.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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