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RIFM fragrance ingredient safety assessment, farnesyl acetate, CAS Registry Number 29548-30-9

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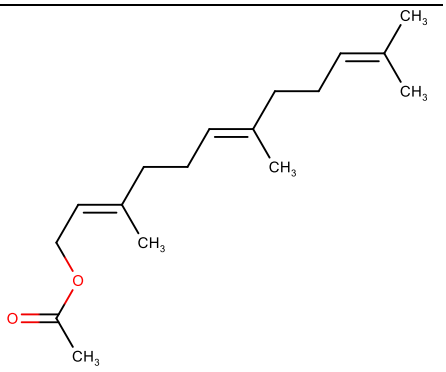


Name: Farnesyl acetate
CAS Registry Number: 29548-30-9

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; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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 et al., 2015), which should be referred to for clarifications.

(*continued on next column*)

(*continued*)

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.

Farnesyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog geranyl acetate (CAS # 105-87-3) show that farnesyl acetate is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; the exposure to farnesyl acetate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for farnesyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; farnesyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; farnesyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (ECHA REACH Dossier: Geranyl Acetate; ECHA, 2013; Shelby et al., 1993)

Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day. NTP (1987)

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

Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. (RIFM, 2013; RIFM, 1972)

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

Bioaccumulation: Screening-level: 13650 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.01 mg/L (ECOSAR; US EPA, 2012b

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.01 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.001 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Farnesyl acetate
2. **CAS Registry Number:** 29548-30-9

3. **Synonyms:** 2,6,10-Dodecatrien-1-ol, 3,7,11-trimethyl-, acetate; 3,7,11-trimethyldodeca-2,6,10-trienyl acetate; 3,7,11-trimethyl-2,6,10-dodecatrienyl acetate; 3,7,11-Trimethyl-2,6,10-dodecatrien-1-ol acetate; Farnesol acetate; ﾌｧﾈｼﾙ酢酸; 3,7,11-Trimethyldodeca-2,6,10-trien-1-yl acetate; Farnesyl acetate
4. **Molecular Formula:** $C_{17}H_{28}O_2$
5. **Molecular Weight:** 264.4 g/mol
6. **RIFM Number:** 1192
7. **Stereochemistry:** Isomer not specified. Two stereocenters present, and a total of 4 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 166 °C (Private communication to FEMA), 162 °C at 10 mm Hg (Fragrance Materials Association [FMA]), 325.86 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA), 234 °F (Dragoco)
3. **Log K_{OW}:** 6.77 (EPI Suite)
4. **Melting Point**: 7.27 °C (EPI Suite)
5. **Water Solubility:** 0.03236 mg/L (EPI Suite)
6. **Specific Gravity:** 0.92 (FMA), 0.908–0.912 (20 °C/4 °C) (Dragoco), 0.908–0.914 (Private communication to FEMA)
7. **Vapor Pressure:** 0.000288 mm Hg at 20 °C (EPI Suite v4.0), 0.000489 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless to pale yellow liquid with a very faint odor, somewhat green-floral, remotely rosy

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 v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.011% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000018 mg/kg/day or 0.0013 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00028 mg/kg/day (RIFM, 2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 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	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Geranyl acetate (CAS # 105-87-3)
   b. **Repeated Dose Toxicity:** Geranyl acetate (CAS # 105-87-3)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   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 available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

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

Citrus fruits
Mentha oils
Ocimum species
Tequila (*Agave tequilana*)
Vaccinium species

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

9. REACH dossier

Available; accessed 06/18/21 (ECHA, 2016).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of farnesyl acetate; however, read-across can be made to geranyl acetate (CAS # 105-87-3; see Section VI). The mutagenic activity of geranyl acetate has been evaluated in a bacterial reverse mutation assay conducted equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with geranyl acetate in dimethyl sulfoxide (DMSO) at

concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, geranyl acetate was not mutagenic in the Ames test, and this can be extended to farnesyl acetate.

There are no studies assessing the clastogenic activity of farnesyl acetate. However, read-across can be made to geranyl acetate (CAS # 105-87-3; see Section VI). The clastogenic activity of geranyl acetate was evaluated in an *in vivo* micronucleus test conducted equivalent to OECD TG 474. The test material was administered in corn oil via intraperitoneal injection to groups of male and female B6C3F1 mice. Doses of 450, 900, or 1800 mg/kg were administered. Mice from each dose level were euthanized at 24 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (Shelby et al., 1993). Under the conditions of the study, geranyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test. Additionally, the read-across material was administered in DMSO:corn oil (2:3) via oral gavage to groups of male and female B6C3F1 mice. Doses of 375, 750, or 1500 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2013).

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for farnesyl 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 farnesyl acetate. Read-across material, geranyl acetate (CAS # 105-87-3; see Section VI), has sufficient repeated dose toxicity data. A 2-year repeated dose carcinogenicity study was conducted on F344/N rats. Groups of 50 rats/sex/dose were administered test material, geranyl acetate (71% geranyl acetate and 29% citronellyl acetate) at doses of 0, 1000, or 2000 mg/kg/day in corn oil, 5 days per week for 103 weeks. There was a reduction in the mean body weights among high-dose male rats (−20%) throughout the treatment duration and high-dose female rats (up to −18%) after week 40. These reductions in body weight and bodyweight gain were dose-related. There were no alterations in clinical signs reported among the treated animals. Survival among high-dose males (18/50) was statistically significantly lower than the controls (34/50). There were no neoplastic or non-neoplastic lesions that were related to treatment with geranyl acetate. Thus, the NOAEL was considered to be 1000 mg/kg/day, based on decreased survival in high-dose males and decreased body weights among high-dose group animals (NTP, 1987). **Therefore, the farnesyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the geranyl acetate NOAEL in mg/kg/day by the total systemic exposure to farnesyl acetate, 1000/0.00028, or 3571429.**

In addition, the total systemic exposure to farnesyl acetate (0.28 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on farnesyl acetate or any read-across materials. The total systemic exposure to farnesyl 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 farnesyl acetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to farnesyl acetate (0.28 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 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, farnesyl acetate presents no concern for skin sensitization under the current, declared levels of use.

Table 1
Supported concentrations for farnesyl acetate that present no appreciable risk for skin sensitization based on a tested exposure of 2094 μg/cm^2 in the CNIH.

IFRA Category[a]	Description of Product Type	Supported Concentrations in Finished Products Based on a NOEL of 2094 μg/cm^2	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.16%	1.3×10^{-4}%
2	Products applied to the axillae	0.048%	0.0021%
3	Products applied to the face using fingertips	0.97%	2.5×10^{-4}%
4	Fine fragrance products	0.90%	0.010%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.23%	0.0025%
6	Products with oral and lip exposure	0.53%	0.0014%
7	Products applied to the hair with some hand contact	1.8%	2.6×10^{-4}%
8	Products with significant ano-genital exposure	0.094%	No Data[b]
9	Products with body and hand exposure, primarily rinse-off	1.8%	0.0010%
10	Household care products with mostly hand contact	6.3%	0.0026%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	3.5%	No Data[b]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.060%

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

11.1.4.1. Risk assessment. Based on the existing data, farnesyl acetate presents no concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a human maximization test conducted on 33 subjects, no reactions indicative of sensitization were observed with 2% (1380 μg/cm^2) farnesyl acetate (RIFM, 1980). In 2 separate Confirmation of No Induction in Humans tests (CNIHs), farnesyl acetate did not induce sensitization in 108 and 44 subjects at 3.8% (2094 μg/cm^2) in 1:3 ethanol:DEP and 2.5% (1938 μg/cm^2) in alcohol SDA 39C, respectively (RIFM, 2013; RIFM, 1972).

The current exposure from the 95th percentile concentration is below the supported concentrations allowed by the No Observed Effect Level (NOEL) of 2094 μg/cm^2 when evaluated in all QRA categories (RIFM, 2019). Table 1 provides the supported concentrations for farnesyl acetate that present no appreciable risk for skin sensitization. These levels represent supported concentrations based on the NOEL, a tested exposure of 2094 μg/cm^2 in the CNIH (RIFM, 2013). However, additional studies may show it could be used at higher levels.

Based on the weight of evidence (WoE) from structural analysis and human studies, farnesyl acetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1977.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV absorption spectra, farnesyl 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 farnesyl acetate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, farnesyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for farnesyl acetate 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 farnesyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0013 mg/day. This exposure is 1076.9 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Buchbauer et al., 1993.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of farnesyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 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, farnesyl acetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify farnesyl acetate as possibly persistent but possibly bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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), farnesyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. Farnesyl acetate has been registered under REACH, with no additional data available at this time.

11.2.1.5. 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 Environmental Framework: Salvito et al., 2002)

Exposure	Europe	North America
Log K_{ow} Used	6.77	6.77
Biodegradation Factor Used	1	1

(*continued on next page*)

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.025			1000000	2.5E-05	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.058	0.072	0.014			Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.305	0.425	0.076			Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.011	0.01	0.046	10000	0.001	Neutral Organic

(*continued*)

Exposure	Europe	North America
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.001 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

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

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 12/15/21.

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.2022.112952.

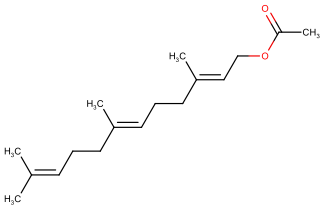
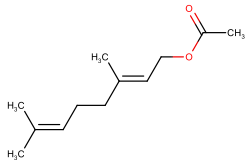
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 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
Principal Name	Farnesyl acetate	Geranyl acetate
CAS No.	29548-30-9	105-87-3
Structure		
Similarity (Tanimoto Score)		0.92
SMILES	CC(=O)OCC=C(C)CCC=C(C)CCC=C(C)C	CC(=O)OCC=C(C)CCC=C(C)C
Endpoint		Genotoxicity Repeated dose toxicity
Molecular Formula	$C_{17}H_{28}O_2$	$C_{12}H_{20}O_2$
Molecular Weight (g/mol)	264.409	196.29
Melting Point (°C, EPI Suite)	7.27	−6.10
Boiling Point (°C, EPI Suite)	325.86	240.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.52E-02	4.40E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.24E-02	1.82E+01
Log KOW	6.77	3.98
J_{max} (μg/cm^2/h, SAM)	0.01	1.85
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.05E+03	2.45E+02
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	AN2|AN2 ≫ Shiff 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	AN2|AN2 ≫ Shiff 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

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
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
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on farnesyl acetate (CAS # 29548-30-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, geranyl acetate (CAS # 105-87-3) was identified as read-across materials with sufficient data for toxicological evaluation.

Conclusion

- Geranyl acetate (CAS # 105-87-3) was used as a read-across analog for the target material, farnesyl acetate (CAS # 29548-30-9), for the genotoxicity and repeated dose endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters.
  - o The target material and the read-across analog share a common acid portion on the ester and an aliphatic β-unsaturated fragment on the alcohol portion of the ester.
  - o The key difference between the target material and the read-across analog is that the target has a C12 aliphatic chain on the alcohol portion, whereas the read-across analog has a C8 aliphatic chain on the alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the aliphatic β-unsaturated fragment on the alcohol portion of the ester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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 Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target material and $\leq 80\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - 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 read-across analog is predicted to have DNA binding alerts by OASIS for genotoxicity. All the other alerts are negative. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data superseded predictions in this case.
  - o In addition, the read-across analog and the target material are also predicted to have positive protein binding alerts by the OASIS model for skin sensitization. All the other alerts for skin sensitization were predicted to be negative. Data superseded predictions in this case.
  - 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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