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Short Review

RIFM fragrance ingredient safety assessment, geranyl isovalerate, CAS Registry Number 109-20-6

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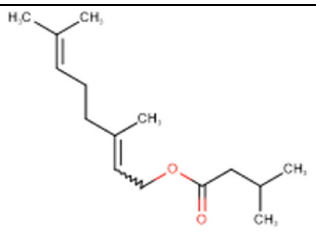


Name: Geranyl isovalerate
CAS Registry Number: 109-20-6
Additional CAS Numbers*:
3915-83-1 Neryl isovalerate (no reported use)
*This material was included in this assessment because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 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.

(*continued on next column*)

(*continued*)

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.
Geranyl isovalerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that geranyl isovalerate is not genotoxic. Data on read-across material geranyl acetate (CAS # 105-87-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 5000 μg/cm^2 for the skin sensitization endpoint. Data on read-across material neryl acetate (CAS # 141-12-8) provide an MOE >100 for the reproductive toxicity endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; geranyl isovalerate is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; geranyl isovalerate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2017a; RIFM, 2017b)
Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day.	(NTP, 1987)
Reproductive Toxicity: Developmental toxicity: NOAEL = 440 mg/kg/day; Fertility: NOAEL = 440 mg/kg/day.	(ECHA REACH Dossier: Neryl acetate; ECHA, 2017a)
Skin Sensitization: NESIL = 5000 μg/cm^2.	RIFM (2017c)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/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: 2.81 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 3495 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 0.053 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, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.053 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0053 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe <1

1. Identification

Chemical Name: Geranyl isovalerate **CAS Registry Number:** 109-20-6 **Synonyms:** Butanoic acid, 3-methyl-, 3,7-dimethyl-2,6-octadienyl ester, (E)-; *trans*-3,7-Dimethyl-2,6-octadien-1-yl isopentanoate; *trans*-3,7-Dimethyl-2,6-octadien-1-yl isovalerate; *trans*-3,7-Dimethyl-2,6-octadien-1-yl 3-methylbutanoate; Geranyl isopentanoate; Geranyl isovalerianate; Geranyl 3-methylbutanoate; ｱﾙｶﾝ酸(C = 1 ~ 6)ｼﾞﾒﾁﾙｵｸﾀｼﾞｴﾆﾙ; 3,7-Dimethylocta-2,6-dien-1-yl 3-methylbutanoate; Geranyl isovalerate **Molecular Formula:** $C_{15}H_{26}O_2$ **Molecular Weight:** 238.37 g/mol **RIFM Number:** 673 **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers are possible.	**Chemical Name**: Neryl isovalerate **CAS Registry Number:** 3915-83-1 **Synonyms:** *cis*-3,7-Dimethyl-2,6-octadien-1-yl 3-methylbutanoate; *cis*-3,7-Dimethyl-2,6-octadien-1-yl isopentanoate; *cis*-3,7-Dimethyl-2,6-octadien-1-yl isovalerate; 3,7-Dimethyl-locta-2,6-dien-1-yl 3-methylbutanoate; Butanoic acid, 3-methyl-, 3,7-dimethyl-2,6-octadienyl ester; Neryl 3-methylbutanoate; Neryl isovalerate; Neryl isovalerianate **Molecular Formula:** $C_{15}H_{26}O_2$ **Molecular Weight:** 238.37 g/mol **RIFM Number:** N/A **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data*

1. **Boiling Point:** 100 °C at 0.5 mm Hg (Fragrance Materials Association [FMA]), 288.43 °C (EPI Suite v4.11)
2. **Flash Point:** 110 °C (Globally Harmonized System [GHS]), 230 °F (closed cup) (FMA)
3. **Log K_{OW}:** 5.88 (EPI Suite v4.11)
4. **Melting Point**: 14.83 °C (EPI Suite v4.11)
5. **Water Solubility:** 0.2633 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.890 (FMA)
7. **Vapor Pressure:** 0.0021 mm Hg at 20 °C (EPI Suite v4.0), 0.001 mm Hg at 20 °C (FMA), 0.0036 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless, oily liquid. Fruity, apple-like, somewhat rosy odor with distinctly herbaceous-sweet undertones. Powerful, fruity-rosy, but not quite sweet taste. Herbaceous aftertaste (Arctander, 1969).

*Physical data for both materials included in this assessment are identical.

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.2.6)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0055 % (RIFM, 2022)
2. **Inhalation Exposure**:** 0.00033 mg/kg/day or 0.024 mg/day (RIFM, 2022)
3. **Total Systemic Exposure**:** 0.0064 mg/kg/day (RIFM, 2022)

*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 or 95th percentile, inhalation exposure, and total exposure.

**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; and Comiskey, 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; and Comiskey, 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:** None
b. **Repeated Dose Toxicity:** Geranyl acetate (CAS # 105-87-3)
c. **Reproductive Toxicity:** Neryl acetate (CAS # 141-12-8)
d. **Skin Sensitization:** Geranyl acetate (CAS # 105-87-3)
e. **Photoirritation/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

Geranyl isovalerate is reported to occur in the following foods by the VCF*:

Citrus Fruits
Lovage (*Levisticum officinale* Koch)
Wormwood oil (*Artemsia absinthium* L.)

Neryl isovalerate is reported to occur in the following foods by the VCF:

Wormwood oil (*Artemsia absinthium* L.)

*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

Both materials included in this assessment have been pre-registered for 2010; no dossiers available as of 06/23/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for geranyl isovalerate 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)	0.38
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	2.3
4	Products related to fine fragrances	2.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.54
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.54
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.54
5D	Baby cream, oil, talc	0.18
6	Products with oral and lip exposure	1.3
7	Products applied to the hair with some hand contact	4.4
8	Products with significant ano-genital exposure (tampon)	0.18
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.2
10A	Household care products with mostly hand contact (hand dishwashing detergent)	15
10B	Aerosol air freshener	15
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.18
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 geranyl isovalerate, the basis was the reference dose of 4.4 mg/kg/day, a predicted skin absorption value of 10%, and a skin sensitization NESIL of 5000 μg/cm^2.

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

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.7..

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, geranyl isovalerate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Geranyl isovalerate 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 (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of geranyl isovalerate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with geranyl isovalerate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017b). Under the conditions of the study, geranyl isovalerate was not mutagenic in the Ames test.

The clastogenic activity of geranyl isovalerate 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 geranyl isovalerate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h. Geranyl isovalerate did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations or up to limits of precipitation in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, geranyl isovalerate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

The MOE for geranyl isovalerate 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 geranyl isovalerate. 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 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. 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).

In another carcinogenicity study, groups of 50 B6C3F1 mice/sex/dose were administered geranyl acetate at doses of 0, 500, or 1000 mg/kg/day via gavage (vehicle: corn oil) for 103 weeks (5 days/week). Survival among high-dose males and females (0/50 for both sexes) and low-dose females (15/50) was statistically significantly lower than the controls (31/50 males and 28/50 females). Mean body weights were reduced in both sexes at the high dose. However, the 100% mortality rate among both sexes at the high dose was due to an accidental error in dosing (mice were mistakenly dosed at 2800 mg/kg/day instead of 1000 mg/kg/day). Furthermore, mortality in female rats of the control and low-dose groups was likely increased by widespread genital infections rather than by the treatment material. Based on these confounding factors, a NOAEL could not be determined for this study (NTP, 1987).

Therefore, the geranyl isovalerate 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 geranyl isovalerate, 1000/0.0064, or 156250.

In addition, the total systemic exposure for geranyl isovalerate (6.4

μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 207) for the repeated dose toxicity endpoint at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/21.

11.1.3. Reproductive toxicity

The MOE for geranyl isovalerate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on geranyl isovalerate. Read-across material neryl acetate (CAS # 141-12-8; see Section VI) has sufficient data to support the fertility and developmental toxicity endpoints.

In a GLP/OECD 422-compliant study, groups of 5 Crl:CD(SD) rats/sex/dose (10 males/dose at low-dose and mid-dose) were administered neryl acetate (purity: 90.1%) via diet at doses of 0, 1000, 2500, and 7500 ppm (equivalent to 0, 61, 150, and 440 mg/kg/day for males and 0, 65, 150, and 465 mg/kg/day for females, according to the study report). Males were treated for 3 weeks before pairing, throughout pairing, and up to necropsy after a minimum of 5 consecutive weeks. Females were treated daily for 3 weeks before pairing, throughout pairing, gestation, and until day 6 of lactation. An additional 5 Crl:CD (SD) rats/sex/dose at 0 and 7500 ppm were maintained as recovery groups for 2 weeks after the treatment period. No parental mortality was observed throughout the study period. There were no treatment-related effects on estrous cycle, pre-coital interval, mating performance, fertility, gestation length, gestation index, reproductive organ weights, gross pathology, or seminiferous tubule histopathology. There were no treatment-related effects on litter size, post-implantation survival index, mean live birth index, viability index, sex ratio, or gross pathology. Body weights and bodyweight gains in pups of both sexes were reduced at the high dose, but their growth curves were equivalent to those of control animals, so this effect was not considered adverse. Thus, the fertility and developmental NOAEL for this study was considered to be 440 mg/kg/day, based on no adverse effects observed up to the highest dose tested in males (ECHA, 2017a).

Therefore, the geranyl isovalerate MOE for effects on the developmental toxicity and fertility endpoints can be calculated by dividing the neryl acetate NOAEL in mg/kg/day by the total systemic exposure to geranyl isovalerate, 440/0.0064, or 68750.

In addition, the total systemic exposure to geranyl isovalerate (6.4 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.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose (RfD) of 4.4 mg/kg/day.

11.1.3.1.1. Derivation of RfD. The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for geranyl isovalerate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 440 mg/kg/day by the uncertainty factor, 100 = 4.4 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/21.

11.1.4. Skin sensitization

Based on the existing data and read-across analog geranyl acetate (CAS # 105-87-3), geranyl isovalerate is considered a skin sensitizer with a defined NESIL of 5000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for geranyl isovalerate. Based on the existing data and read-across analog geranyl acetate (CAS # 105-87-3; see Section VI), geranyl isovalerate is considered a weak skin sensitizer with a defined NESIL of 5000 μg/cm^2. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across analog geranyl acetate was found to be sensitizing with an EC3 value of 14.17% (3542 μg/cm^2) (RIFM, 2013a). In a human maximization test, no skin sensitization reactions were observed with geranyl isovalerate or additional material neryl isovalerate (RIFM, 1975a; RIFM, 1975b). In another human maximization test, no skin sensitization reactions were observed with read-across analog geranyl acetate (Greif, 1967). In 2 Confirmation of No Induction in Humans tests (CNIHs), read-across geranyl acetate did not induce sensitization reactions in 42 or 47 subjects at 5% (3876 μg/cm^2) or 10% (5000 μg/cm^2), respectively (RIFM, 1972; RIFM, 2003). Additionally, in another CNIH, read-across geranyl acetate did not induce sensitization in any of the 111 subjects at 4.25% (5020 μg/cm^2) in 1:3 ethanol:diethyl phthalate (EtOH:DEP) (RIFM, 2017c).

Based on weight of evidence (WoE) from structural analysis, human studies, and read-across analog geranyl acetate, geranyl isovalerate is a sensitizer with a WoE NESIL of 5000 μg/cm^2 (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. (RIFM, 2020) and an RfD of 4.4 mg/kg/day.

Additional References: RIFM, 1999; Ishihara et al., 1986; Klecak (1979); Klecak (1985); RIFM, 1980.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, geranyl isovalerate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available

Table 1
Data summary for geranyl acetate as read-across for geranyl isovalerate.

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
3542 [1]	Weak	5020	2760	N/A	5000

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.1352			1000000	0.0001352	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.174	0.239	0.055			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.390	0.767	0.148			Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.065	0.053	0.172	10000	0.0053	Neutral Organics

for geranyl isovalerate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, geranyl isovalerate does not present a concern for photoirritation or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/24/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for geranyl isovalerate 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 geranyl isovalerate. Based on the Creme RIFM Model, the inhalation exposure is 0.024 mg/day. This exposure is 58.3 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: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of geranyl isovalerate 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, geranyl isovalerate 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) identified geranyl isovalerate as not persistent but 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, 2017b). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish

bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), geranyl isovalerate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. ***Biodegradation***:
No data available.
Ecotoxicity:
No data available.

11.2.1.3. Other available data. Geranyl isovalerate has been pre-registered for REACH with no additional data at this time.

11.2.2. 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 et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.88	5.88
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional Volume of Use for both CAS #s.

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

The RIFM PNEC is 0.0053 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 volumes of use.

Literature Search and Risk Assessment Completed On: 08/10/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 08/18/22.

CRediT authorship contribution statement

G. Sullivan: Writing – review & editing.

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.2023.114285.

Appendix

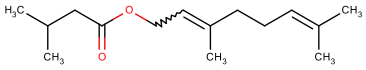
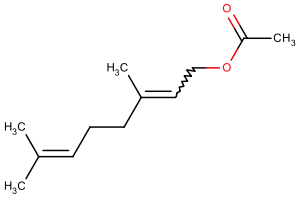
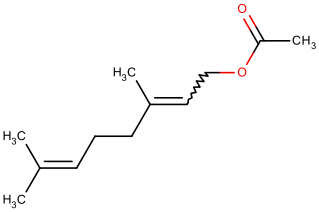
Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	Geranyl isovalerate	Geranyl acetate	Neryl acetate
CAS No.	109-20-6	105-87-3	141-12-8
Structure			
Similarity (Tanimoto Score)		0.67	0.42
Endpoint		• Skin sensitization • Repeated dose toxicity	• Reproductive toxicity
Molecular Formula	$C_{15}H_{26}O_2$	$C_{12}H_{20}O_2$	$C_{12}H_{20}O_2$
Molecular Weight (g/mol)	238.37	196.29	196.29
Melting Point (°C, EPI Suite)	14.83	−6.10	−6.10
Boiling Point (°C, EPI Suite)	288.43	240.00	240.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.48	4.40	4.40
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.26	18.24	18.24
Log KOW	5.88	3.98	3.98
Jmax (μg/cm^2/h, SAM)	0.04	1.85	1.85
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	573.50	245.21	245.21
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Non-toxicant (low reliability)
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 geranyl isovalerate (CAS # 109-20-6). 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, geranyl acetate (CAS # 105-87-3) and neryl acetate (CAS # 141-12-8) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Geranyl acetate (CAS # 105-87-3) was used as a read-across analog for the target material, geranyl isovalerate (CAS # 109-20-6), for the skin sensitization and repeated dose toxicity endpoints.
  - o The target material and the read-across analog belong to the class of branched unsaturated esters.
  - o The target material and the read-across analog are esters of alcohols containing the same number of isopentyl units.
  - o The key difference between the target material and the read-across analog is that the target material is an ester of isovaleric acid, whereas the read-across analog is an ester of acetic acid. 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 reflects the similarity of these geranyl alcohol esters. 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 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 target material and the read-across analog have several protein binding alerts for skin sensitization. Data described in the skin sensitization section above 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.
- Neryl acetate (CAS # 141-12-8) was used as a read-across analog for the target material, geranyl isovalerate (CAS # 109-20-6), for the reproductive toxicity endpoint.
  - o The target material and the read-across analog belong to the class of branched unsaturated esters.
  - o The target material and the read-across analog are esters of alcohols containing the same number of isopentyl units.
  - o The key difference between the target material and the read-across analog is that the target material is an ester of isovaleric acid, whereas the read-across analog is an ester of acetic acid. 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 reflects the similarity of these geranyl alcohol esters. 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 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 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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