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Short Review

RIFM fragrance ingredient safety assessment, geranyl acetate, CAS registry number 105-87-3

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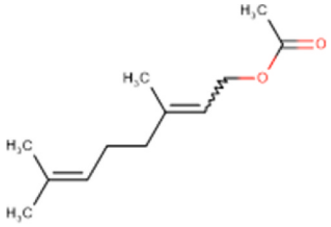

Name: Geranyl acetate CAS Registry Number: 105-87-3
Additional CAS Numbers*:
141-12-8 Neryl acetate
*This material was included in this assessment because the materials are isomers.

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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, 2024) 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
TTC - Threshold of Toxicological Concern

(*continued on next column*)

(*continued*)

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.

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 acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that geranyl acetate is not genotoxic. Data on geranyl acetate provided a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on the additional material (isomer) neryl acetate (CAS # 141-12-8) provided a calculated MOE >100 for the reproductive toxicity endpoint. Data provided a No Expected Sensitization Induction Level (NESIL) of 5000 μg/cm^2 for the skin sensitization endpoint. The photoirritation endpoint was evaluated based on data and ultraviolet/visible (UV/Vis) spectra; geranyl acetate is not photoirritating. The photoallergenicity endpoint was evaluated based on UV/Vis spectra; geranyl acetate is not expected to be 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 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 (VoU) 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. (ECHA, 2013; Shelby et al., 1993)
Repeated Dose Toxicity: NOAEL = 710 mg/kg/day. (NTP, 1987)
Reproductive Toxicity: Developmental toxicity NOAEL = 440 mg/kg/day; Fertility NOAEL = 440 mg/kg/day. (RIFM, 2016b)
Skin Sensitization: NESIL = 5000 μg/cm^2 (RIFM, 2017)
Photoirritation/Photoallergenicity: Not photoirritating/not expected to be photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 1999a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 91% (OECD 301D) for CAS # 105-87-3 (RIFM, 2000b)
Bioaccumulation:
Screening-level: 196 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Critical Ecotoxicity Endpoint: 72-h Algae EyC50: 1.58 mg/L (RIFM, 2010)
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: 72-h Algae EyC50: 1.58 mg/L for CAS # 105-87-3 (RIFM, 2010)
RIFM PNEC is: 1.58 μg/L

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

1. Identification

Chemical Name: Geranyl acetate	Chemical Name: Neryl acetate
CAS Registry Number: 105-87-3	**CAS Registry Number:** 141-12-8
Synonyms: *trans*-3,7-Dimethyl-2,6-octadien-1-yl acetate; 2,6-Octadien-1-ol, 3,7-dimethyl-, acetate, (E)-; 3,7-Dimethyl-2,6-octadien-1-ol acetate; 酢酸ｹﾞﾗﾆﾙ; 3,7-Dimethylocta-2,6-dien-1-yl acetate; Geranyl acetate	**Synonyms:** *cis*-3,7-Dimethyl-2,6-octadien-1-yl acetate; *cis*-3,7-Dimethyl-2,6-octadien-1-yl ethanoate; 2,6-Octadien-1-ol, 3,7-dimethyl-, acetate, (Z)-; 3,7-Dimethyl-2,6-octadien-1-neryl acetate; 3,7-Dimethylocta-2,6-dien-1-yl acetate
Molecular Formula: $C_{12}H_{20}O_2$	**Molecular Formula:** $C_{12}H_{20}O_2$
Molecular Weight: 196.29 g/mol	**Molecular Weight:** 196.29 g/mol
RIFM Number: 134	**RIFM Number:** 264
Stereochemistry: One stereocenter and a total of 2 stereoisomers possible. Geranyl acetate is the E-isomer, and neryl acetate is the Z-isomer.	

2. Physical data

Chemical Name: Geranyl acetate	Chemical Name: Neryl acetate
Boiling Point: 244 °C (Fragrance Materials Association [FMA]), 248.97 °C (EPI Suite v4.11)	**Boiling Point:** 471 °C (FMA), 248.97 °C (EPI Suite v4.11)
Flash Point: >200 °F; closed cup (CC) (FMA), 110 °C (Globally Harmonized System [GHS]), 114 °C (RIFM, 2012)	**Flash Point:** >200 °F; CC (FMA), >93 °C (GHS)
Log K_{OW}: 4.3 at 35 °C (RIFM, 1999b), 4.48 (EPI Suite v4.11)	**Log K_{OW}:** 4.8 at 35 °C (EPI Suite v4.11), *cis* isomer log P_{ow} = 4.2; *trans* isomer log P_{ow} = 4.3 (RIFM, 2001)
Melting Point: no melting point between −100 °C and 30 °C (RIFM, 2013a), −6.1 °C (EPI Suite v4.11)	**Melting Point**: 6.1 °C (EPI Suite v4.11)
Water Solubility: 29 ± 2 mg/L at T = 20.0 °C ± 0.5 °C (RIFM, 2013a), 18.24 mg/L at 25 °C (EPI Suite v4.11)	**Water Solubility:** 18.24 mg/L at 25 °C (EPI Suite v4.11)
Specific Gravity: 0.902 (FMA), 0.92 g/mL (RIFM, 1994)	**Specific Gravity:** 0.91 (FMA)
Vapor Pressure: 0.03 mm Hg at 20 °C (FMA), 0.0463 mm Hg at 25 °C (EPI Suite v4.11)	**Vapor Pressure:** 0.02 mm Hg at 20 °C (FMA), 0.0463 mm Hg at 25 °C (EPI Suite v4.11)
UV Spectra: No absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: Colorless liquid with a sweet, fragrant, flower-like odor	**Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a floral, rosy, sweet, soapy, citrus, grapefruit, and fruity with a tropical nuance (Arctander, 1969)

3. Volume of use (worldwide band)

1 100–1000 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient* (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.16% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00037 mg/kg/day or 0.026 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0036 mg/kg/day (RIFM, 2018)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

**95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024).

***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, 2017; Safford et al., 2015, 2017, 2024).

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:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

ECHA REACH Dossier: Geranyl Acetate, basic toxicokinetics key study (ECHA, 2013): The hydrolysis and degradation of Geranyl acetate Extra (geranyl acetate) in the plasma, liver, and gastrointestinal tract was investigated in a GLP study. To determine hydrolysis in either compartment, the test material was incubated with plasma and liver S9 fraction from rats as well as in gastric-juice simulant and intestinal-fluid simulant. After incubation, the proteins were precipitated, and the amount of remaining substrate was analyzed in the supernatant by GC/FID. Geranyl Acetate Extra hydrolyzed within 0.5 h completely in rat plasma (100%), liver S9 fraction of rats (100%), and intestinal-fluid simulant (100%) under the test conditions used. For gastric-juice simulant, the metabolic turnover that is related to t = 0 control was calculated to be 25%, 46%, and 59% after an incubation period of 0.5, 1, and 2 h, respectively.

Additional References: None.

8. Natural occurrence

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

Cardamom (*Elletaria cardamomum* Maton.)
Citrus fruits.
Coriander seed (*Coriandrum sativum* L.)
Ginger (*Zingiber* species).
Lemon grass oil (*Cymbopogon*).
Myrtle (*Myrtus communis* L.)
Passion fruit (*Passiflora* species).
Salvia species.
Thyme (*Thymus* species).
Wormwood oil (*Artemisia absinthium* L.)

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

Cardamom (*Elletaria cardamomum* Maton.)
Citrus fruits.
Curry.
Eucalyptus oil (*Eucalyptus globulus* Labill).
Ginger (*Zingiber* species).
Hop (*Humulus lupulus*).
Lemon grass oil (*Cymbopogon*).
Myrtle (*Myrtus communis* L.)
Salvia species.
Wormwood oil (*Artemisia 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

Available for geranyl acetate and available for neryl acetate; accessed on 07/31/24.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for geranyl acetate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.38
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 acetate, the basis was a reference dose of 4.4 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 5000 μg/cm^2. As a conservative approach, we assumed that 100% of the material exposed via the skin is bioavailable (see Section V), thereby deriving the most stringent MOE. Since the MOE is > 100 (see the repeated dose and reproductive toxicity sections), we then refined the exposure to 40% using an *in silico* Skin Absorption Model to determine the Maximum Allowable Concentrations for each category listed in Section X.
[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; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk Assessment. The mutagenic activity of geranyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with geranyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 3333 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, geranyl acetate was not mutagenic in the Ames test.

The clastogenic activity of geranyl acetate was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with 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 (PCEs). The test material did not induce a statistically significant increase in the incidence of micronucleated PCEs 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.

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

Additional References: RIFM, 1982; RIFM, 1983a; RIFM, 1983b; Heck et al., 1989.

Literature Search and Risk Assessment Completed On: 07/19/24.

11.1.2. Repeated Dose Toxicity

The MOE for geranyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk Assessment. There are sufficient repeated dose toxicity data on geranyl acetate.

In a carcinogenicity study, groups of 50 F344/N rats/sex/dose were administered food-grade geranyl acetate (composition of 71% geranyl acetate and 29% citronellyl acetate) via gavage (vehicle: corn oil) at doses of 0, 1000, or 2000 mg/kg/day for 103 weeks (5 days/week). Survival among high-dose males (18/50) and low-dose males (29/50) was lower than that of the controls (34/50), but this was only statistically significant at the high dose. There was a dose-related reduction in the mean body weights among high-dose males (−20%) throughout the treatment duration and high-dose females (up to −18%) after week 40. Kidney tubular cell adenomas were found in 2/50 low-dose males, but there was no dose relationship. Squamous cell papilloma was detected in 4/50 low-dose males and 1/50 high-dose males, but there was no dose relationship. Squamous cell carcinoma was detected in 1/50 low-dose males, but there was no dose relationship. However, the lack of observable dose relationships of squamous cell papillomas/carcinomas and kidney tubular cell adenomas may have been due to the premature deaths of high-dose males (thus not allowing for the development and

detection of late-appearing tumors). Thus, it cannot be determined whether these effects were treatment-related. Based on mortality and reduced body weights at 2000 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 1000 mg/kg/day (NTP, 1987).

In another carcinogenicity study, groups of 50 B6C3F1 mice/sex/dose were administered food-grade geranyl acetate (composition of 71% geranyl acetate and 29% citronellyl acetate) via gavage (vehicle: corn oil) at doses of 0, 500, or 1000 mg/kg/day 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). However, the 100% mortality rate among both sexes at the high dose may have been 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. Mean body weights were reduced in both sexes at the high dose. Incidences of cytoplasmic vacuolization in the liver and kidney were increased in males and females in a dose-related fashion. Although no evidence of carcinogenicity was found, the high number of deaths may have prevented the detection of late-appearing tumors. Due to dosing issues and widespread genital infections unrelated to treatment, a NOAEL could not be established from this study (NTP, 1987).

In a subchronic study, groups of 10 F344/N rats/sex/dose were administered food-grade geranyl acetate (composition of 71% geranyl acetate and 29% citronellyl acetate) via gavage (vehicle: corn oil) at doses of 0, 250, 500, 1000, 2000, or 4000 mg/kg/day for 13 weeks. Only bodyweight alterations and histopathological examinations were performed during the 13-week studies because this material was a part of the bioassay program. Mortality (2/10 males, 1/10 females) and decreases in body weights (approximately 8% in females, 19% in males) were reported at the high dose (4000 mg/kg/day). No treatment-related histopathological effects were observed. Based on mortality and reduced body weights at 4000 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 2000 mg/kg/day (NTP, 1987).

In another subchronic study, groups of 10 B6C3F1 mice/sex/dose were administered food-grade geranyl acetate (composition of 71% geranyl acetate and 29% citronellyl acetate) via gavage (vehicle: corn oil) at doses of 0, 125, 250, 500, 1000, or 2000 mg/kg/day for 13 weeks. Only bodyweight alterations and histopathological examinations were performed during the 13-week studies because this material was a part of the bioassay program. Mortality (7/10 males, 9/10 females) was reported at the high dose (2000 mg/kg/day). Body weights were significantly decreased in males at the high dose only. Incidences of cytoplasmic vacuolization and lipidosis in the liver, kidney, and myocardium were increased in males and females at the high dose (NTP, 1987). Based on mortality and reduced body weights at 2000 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 1000 mg/kg/day (NTP, 1987).

Based on the results observed from F344/N rats and B6C3F1 mice in carcinogenicity and subchronic studies, there were no treatment-related effects at 1000 mg/kg/day; thus, a NOAEL of 1000 mg/kg/day was considered for the repeated dose toxicity endpoint.

When adjusted based on the test-material composition (71% geranyl acetate), the derived NOAEL is equal to 1000 mg/kg/day * 0.71 = 710 mg/kg/day.

Therefore, the geranyl 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 geranyl acetate, 710/0.0036, or 197222.

In addition, the total systemic exposure to geranyl acetate (3.6 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: NTP, 1987.

Literature Search and Risk Assessment Completed On: 07/23/24.

11.1.3. Reproductive Toxicity

The MOE for geranyl acetate 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 acetate. However, additional material (isomer) neryl acetate (CAS # 141-12-8) has sufficient data to support the reproductive toxicity endpoint.

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 the 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 the control animals, so this effect was not considered adverse. Thus, the developmental toxicity and fertility NOAEL for this study was considered to be 440 mg/kg/day, based on no adverse effects observed up to the highest dose tested (RIFM, 2016b).

Therefore, the geranyl acetate MOE for 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 acetate, 440/0.0036, or 122222.

In addition, the total systemic exposure to geranyl acetate (3.6 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint 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. (2020) and a reference dose (RfD) of 4.40 mg/kg/day.

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 acetate 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 = 4.40 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/23/24.

11.1.4. Skin Sensitization

Based on the existing data, geranyl acetate is considered a skin sensitizer with a defined NESIL of 5000 μg/cm^2.

11.1.4.1. Risk Assessment. Based on the existing data, geranyl acetate is considered a skin sensitizer. 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 murine local lymph node assay (LLNA), geranyl acetate was found to be sensitizing with an EC3 value of 14.17% (3542 μg/cm^2) (RIFM, 2013b). In a human maximization test, no skin sensitization reactions were observed with geranyl acetate (Greif, 1967). In 2 Confirmation of No Induction in Humans tests (CNIHs), 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, 2003b). Additionally, in another CNIH study, 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 (RIFM, 2017).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, geranyl acetate is considered a skin 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. (2020) and an RfD of 4.4 mg/kg/day.

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

Literature Search and Risk Assessment Completed On: 06/25/24.

Table 1
Data summary for geranyl acetate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
3542 (1)	Weak	5020	2760	N/A	5000

EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; 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 the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.5. Photoirritation/Photoallergenicity

Based on the available data and UV/Vis absorption spectra and *in vivo* study data, geranyl acetate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, geranyl acetate would not be expected to present a concern for photoallergenicity.

11.1.5.1. Risk Assessment. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. In a guinea pig photoirritation study, geranyl acetate was not photoirritating at 5%, 10%, and 30% concentrations (RIFM, 1999a). Based on the *in vivo* study data and the lack of absorbance, geranyl acetate does not present a concern for photoirritation. Based on the lack of absorbance, geranyl acetate does not present a concern for photoallergy.

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. Thus, it does not present a concern for photoirritant or photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/26/24.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for geranyl 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 geranyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.026 mg/day. This exposure is 53.84 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; Komori et al., 1995; Rice, 1994

Literature Search and Risk Assessment Completed On: 07/18/24.

11.2. Environmental Endpoint Summary

11.2.1. Screening-Level Assessment

A screening-level risk assessment of geranyl 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 VoU 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 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 geranyl acetate as possibly being 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 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, 2017a). 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

11.2.2. Risk assessment

Based on the current VoU (IFRA, 2019), geranyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation***

For CAS # 105-87-3. RIFM, 1994**:** The ready and ultimate biodegradability of the test material was evaluated using the sealed vessel test according to the OECD 301B method. Degradation of geranyl acetate at 10 mg/L was 82.2% after 28 days.

RIFM, 1998**:** The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. After 28 days, biodegradation was 85%.

RIFM, 1999c**:** A 28-day, closed-bottle biodegradation study was conducted with geranyl acetate at 2.7 mg/L according to the OECD 301D method. After 28 days, a degradation of 68% was observed.

RIFM, 2000b**:** A 28-day, closed-bottle biodegradation study was conducted with geranyl acetate according to the OECD 301D method. At 3 mg/L, a degradation of 91% was observed.

For CAS # 141-12-8. RIFM, 2000a: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guidelines. Biodegradation of 85% was observed after 38 days (82% after 28 days).

RIFM, 2000c: The ready biodegradability of the test material was evaluated using the closed-bottle test according to the EU Method C.4 E guidelines. Biodegradation of 46% was observed after 28 days.

RIFM, 2000d: The ready biodegradability of the test material was evaluated using the closed-bottle test according to the OECD 301D guidelines. The mean degradation value on day 28, calculated from the ratio of biochemical oxygen demand/chemical oxygen demand, was 74%.

Ecotoxicity

For CAS # 105-87-3

RIFM, 2003a**:** The acute toxicity of the test material to the fathead minnow was evaluated according to the OECD 203 method under static renewal conditions in sealed vials without headspace to minimize loss of the test material to the atmosphere. The 96-h LC50 value based on the mean measured concentration was reported to be 6.12 mg/L.

RIFM, 1999c**:** An acute toxicity study was conducted with *Daphnia magna* according to the Council Directive 92-69-EEC C.2 method under static conditions. The 48-h EC0/EC100 for geranyl acetate was 14.1 mg/L (geometric mean).

RIFM, 2010**:** A 72-h algae inhibition test was conducted with geranyl acetate according to the OECD 201 method under static conditions. Under the conditions of this study, the ErC50 (concentration resulting in 50% inhibition of growth rate) was 3.72 mg/L based on the measured initial concentration (14.1 mg/L based on the nominal concentration), and the EyC50 (concentration resulting in 50% inhibition of yield) was 1.58 mg/L based on the measured initial concentration (4.55 mg/L based on the nominal concentration).

For CAS # 141-12-8

RIFM, 2000c**:** A *Daphnia magna* acute toxicity study was conducted according to the 92/69/EEC.1 method. The EC0 value after 48 h, calculated using the arithmetic mean of the analytical measured values, was >16.8 mg/L (5% immobilization).

RIFM, 2016a**:** A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value based on measured exposure concentrations was reported to be 9.97 mg/L (neryl acetate plus impurities). The 48-h EC50 value estimated for neryl acetate only was 9.06 mg/L.

Other available data

Geranyl acetate (CAS # 105-87-3) and neryl acetate (CAS # 141-12-8) have been registered under REACH and have the following additional data at this time:

The ready biodegradability of the test material was determined according to the EEC directive 79–831, Annex V, Part C, 5.2. Under the conditions of the study, biodegradation of >70% was observed after 28 days (ECHA, 2013).

A 28-day closed bottle test in accordance with OECD guideline 301D was conducted on the test material at an initial concentration of 2 mg/L. Based on the O2 consumption, the test material biodegraded 90% on day 28 (ECHA, 2017b).

11.2.3. Risk assessment Refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.641			1000000	0.002641	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.941	1.5	0.431			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.552	1.862	0.405	10000	0.0405	Vinyl/Allyl Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.965	0.688	1.319			Neutral Organics
Tier 3: Measured Data (including REACH)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	6.12					
Daphnia		9.06				
Algae		1.58		1000	1.58	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.3	4.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band[d]	100–1000	100–1000
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Combined Regional VoU for both CAS #s.

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

The RIFM PNEC is 1.58 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: 06/28/24.

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 07/31/24.

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.

References

Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118 (104805).

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Buchbauer, G., Jirovetz, L., Jager, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. J. Pharmaceut. Sci. 82 (6), 660–664.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECETOC, 2003. Contact Sensitisation: Classification According to Potency. ECETOC Technical Report No. 87.

ECHA, 2013. Geranyl acetate registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/5962/1/2.

ECHA, 2017a. Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Neryl acetate registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/21334/1/2.

Greif, N., 1967. Cutaneous safety of fragrance material as measured by the maximization test. American Perfumer and Cosmetics 82, 54–57.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9 (1), 257.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2019. Volume of Use Survey, January-December 2019.

Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (Suppl. 2), 230–240.

Klecak, G., 1979. The open epicutaneous test (OET), a predictive test procedure in the Guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. International Federation Societies Cosmetic Chemists, 9/18/79.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. Curr. Probl. Dermatol. 14, 152–171.

Komori, T., Fujiwara, R., Tanida, M., Nomura, J., 1995. Potential antidepressant effects of lemon odor in rats. Eur. Neuropsychopharmacol 5 (4), 477–480.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352.

National Toxicology Program, 1987. Carcinogenesis Studies of Food Grade Geranyl Acetate (71% Geranyl Acetate, 29% Citronellyl Acetate) (CAS No.105-87-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP-TR-252. Unpublished.

Rice, P.J., Coats, J.R., 1994. Insecticidal properties of monoterpenoid derivatives to the house fly (Diptera; Muscidae) and red flour beetle (Coleoptera: tenebrionidae). Pestic. Sci. 41 (3), 195–202.

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Repeated Insult Patch Test with Geranyl Acetate. Unpublished Report from International Flavors and Fragrances. RIFM Report Number 51141. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Mutagenicity Evaluation of Geranyl Acetate in the Mouse Lymphoma Forward Mutation Assay. Private Communication to FEMA. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 36367. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983a. Mutagenicity Evaluation of Geranyl Acetate in the Ames Salmonella/microsome Plate Test. Private Communication to FEMA. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 36372. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983b. Mutagenicity Evaluation of Geranyl Acetate in an in Vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells. Unpublished Report from Lorillard Tobacco Company. RIFM Report Number 38391. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1994. The Biodegradability of Perfume Ingredients in the Sealed Vessel Test. Unpublished Report from Quest International. RIFM Report Number 49675. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1998. Ready Biodegradability of Geranyl Acetate. Unpublished Report from Givaudan. RIFM Report Number 51431. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999a. Toxicology Studies of Geranyl Acetate in the guinea Pig. Unpublished Report from Takasago International Corporation. RIFM Report Number 35054. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999b. Partition Coefficient N-Octanol/water of Geranyl Acetate. Unpublished Report from Givaudan. RIFM Report Number 51502. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999c. Investigation into the Ecological Properties of Geranyl Acetate: Daphnia Toxicity and Biodegradability. Unpublished Report from Symrise. RIFM Report Number 53645. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. Ready Biodegradability of Neryl Acetate. Unpublished Report from Givaudan. RIFM Report Number 49725. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. Geranyl Acetate: Ready Biodegradability in the Closed Bottle Test. Unpublished Report from Symrise. RIFM Report Number 53646. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000c. Investigation of the Ecological Properties of Neryl Acetate. Unpublished Report from Symrise. RIFM Report Number 53719. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000d. Study on the Ready Biodegradability of Neryl Acetate. Unpublished Report from Symrise. RIFM Report Number 53720. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Partition Coefficient N-Octanol/water of Neryl Acetate. Unpublished Report from Givaudan. RIFM Report Number 49724. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Acute Toxicity Test with Geranyl Acetate and the Fathead Minnow, Pimephales promelas. Unpublished Report from Ward, T.J., Wyskiel, D.C. & Boeri, R.L. RIFM Report Number 50662. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Geranyl Acetate: Repeat Insult Patch Test. Unpublished Report from Givaudan. RIFM Report Number 57088. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Geranyl Acetate: Growth Inhibition Study in Unicellular Green Algae Desmodesmus Subspicatus CHODAT. Unpublished Report from BASF. RIFM Report Number 58417. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012. Evaluation of Physical and Chemical Properties According to Regulation (EC) No 440/2008 with Geranyl Acetate. Unpublished Report from BASF. RIFM Report Number 64633. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. Physico-chemical Properties of Geranyl Acetate. Unpublished Report from BASF. RIFM Report Number 64632. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Geranyl Acetate (Geranylacetat Extra): Skin Sensitization: Local Lymph Node Assay. Unpublished Report from BASF. RIFM Report Number 65577. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Neryl Acetate: Acute Toxicity to Daphnia Magna in a Static 48-hour Immobilisation Test. Unpublished Report from Firmenich. RIFM Report Number 78917. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Neryl Acetate: Combined Repeat Dose Toxicity Study with Recovery Phase and Reproductive/developmental Toxicity Screening Study in the Rat. Unpublished Report from Firmenich. RIFM Report Number 78919. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Geranyl Acetate: Repeated Insult Patch Test (RIPT). RIFM Report Number 72939. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Exposure Survey 22, November 2018.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2024. Corrigendum to "Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products". Regul. Toxicol. Pharmacol. 72 (3), 673-68]. Regul Toxicol Pharmacol. 105545.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Shelby, M.D., Erexson, G.L., Hook, G.L., Tice, R.R., 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environ. Mol. Mutagen. 21 (2), 160–179.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.