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RIFM fragrance ingredient safety assessment, citronellyl acetate, CAS Registry Number 150-84-5

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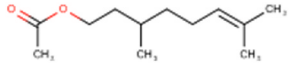

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Name: Citronellyl acetate CAS Registry Number: 150-84-5
Additional CAS Numbers*:
67601-05-2 3,7-Dimethyloct-6-enyl acetate
141-11-7 Rhodinyl acetate
*Included because the materials are isomers

Abbreviation/Definition List:

(*continued on next page*)

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(*continued*)

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

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.

Citronellyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that citronellyl acetate is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog citronellyl formate (CAS # 105-85-1) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from analog citronellyl butyrate (CAS # 141-16-2) provided a No Expected Sensitization Induction Level (NESIL) of 6400 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; citronellyl acetate is not expected to be phototoxic/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; citronellyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2000; ECHA REACH Dossier: Citronellyl acetate; ECHA, 2013)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day.	(National Toxicology Program, 1987)
Reproductive Toxicity: NOAEL = 200 mg/kg/day.	RIFM (2018b)
Skin Sensitization: NESIL = 6400 μg/cm^2.	RIFM (2018a)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 93% (OECD 310) for CAS # 150-84-5	(ECHA REACH Dossier: Citronellyl acetate; ECHA, 2013)
Bioaccumulation: Screening-level: 474 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 3.48 mg/L for CAS # 150-84-5	RIFM (2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

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

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 3.48 mg/L for CAS # 150-84-5 (RIFM, 2012b)

RIFM PNEC is: 3.48 μg/L

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

1. Identification

Chemical Name: Citronellyl acetate	Chemical Name: 3,7-Dimethyloct-6-enyl acetate (isomer)	Chemical Name: Rhodinyl acetate (isomer)
CAS Registry Number: 150-84-5	**CAS Registry Number:** 67601-05-2	**CAS Registry Number:** 141-11-7
Synonyms: 3,7-Dimethyl-6-octen-1-yl acetate; 6-Octen-1-ol, 3,7-dimethyl-, acetate; Acetic acid, citronellyl ester; 3,7-Dimethyl-6-octen-1-ol acetate; ｱﾙｹﾝｰﾙ(C = 9–18)ｱﾙｶﾝ酸(C = 1–6)ｴｽﾃﾙ; 3,7-Dimethyloct-6-en-1-yl acetate; Citronellyl acetate	**Synonyms:** 6-Octen-1-ol, 3,7-dimethyl-, 1-acetate (3S)-; 6-Octen-1-ol, 3,7-dimethyl-, acetate (S)-; l-Citronellyl acetate; 3,7-Dimethyloct-6-enyl acetate	**Synonyms:** 3,7-Dimethyl-(6-or 7-)octen-1-yl ethanoate; 3,7-Dimethyl-(6-or 7-)octen-1-yl acetate; 7-Octen-1-ol, 3,7-dimethyl-, acetate; Rhodinyl ethanoate; 3,7-Dimethyloct-7-en-1-yl acetate; Rhodinyl acetate
Molecular Formula: $C_{12}H_{22}O_2$	**Molecular Formula:** $C_{12}H_{22}O_2$	**Molecular Formula:** $C_{12}H_{22}O_2$
Molecular Weight: 198.3	**Molecular Weight:** 198.3	**Molecular Weight:** 198.3

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Chemical Name: Citronellyl acetate	Chemical Name: 3,7-Dimethyloct-6-enyl acetate (isomer)	Chemical Name: Rhodinyl acetate (isomer)
RIFM Number: 157 **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.	**RIFM Number:** 7306 **Stereochemistry:** S isomer specified. One stereocenter and 2 total stereoisomers possible.	**RIFM Number:** 372 **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

CAS # 150-84-5	CAS # 67601-05-2	CAS # 141-11-7
Boiling Point: 229 °C (Fragrance Materials Association [FMA]), 237.59 °C (EPI Suite)	**Boiling Point:** Not available	**Boiling Point:** 237 °C (FMA), 230.58 °C (EPI Suite)
Flash Point: 94 °C (Globally Harmonized System), pH 7 at 20 °C t1/2 = 8191 h; pH 7 at 25 °C t1/2 = 4905 h (RIFM, 2010b), >200 °F; CC (FMA)	**Flash Point:** Not available	**Flash Point:** >200 °F; CC (FMA)
Log K_{OW}: 4.56 (EPI Suite) **Melting Point**: No melting point between −100 °C and 30 °C (RIFM, 2012a), −7.4 °C (EPI Suite)	**Log K_{OW}:** Not available **Melting Point**: Not available	**Log K_{OW}:** 4.64 (EPI Suite) **Melting Point**: -7.79 °C (EPI Suite)
Water Solubility: 5.686 mg/L (EPI Suite) **Specific Gravity:** 0.889 (FMA), 0.89 (RIFM, 1995)	**Water Solubility:** Not available **Specific Gravity:** Not available	**Water Solubility:** 4.872 mg/L (EPI Suite) **Specific Gravity:** 0.900 (FMA)
Vapor Pressure: 0.0388 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg at 20 °C (FMA), 0.0526 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** Not available	**Vapor Pressure:** 0.0493 mm Hg at 20 °C (EPI Suite v4.0), 0.0758 mm Hg at 25 °C (EPI Suite)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/ Organoleptic: Colorless liquid with fruity odor. EOA Spec no.125	**Appearance/ Organoleptic:** Gives a fresh-rosy, fruity odor to many floral compositions from geranium to muguet	**Appearance/ Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015).

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)*

1. **95**th **Percentile Concentration in Hydroalcoholics:** 3.0% (RIFM, 2016)
2. **Inhalation Exposure****: 0.0013 mg/kg/day or 0.078 mg/day (RIFM, 2016)
3. **Total Systemic Exposure*****: 0.049 mg/kg/day (RIFM, 2016)

*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 Hydroalcoholics or 97.5th 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 et al., 2017).

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

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

6.1. *Cramer classification*

Class I, Low

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

6.2.

Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** Citronellyl formate (CAS # 105-85-1)
d. **Skin Sensitization:** Citronellyl butyrate (CAS # 141-16-2)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification**: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

Alpinia species	Mace (*Myristica fragrans* Houttuyn)
Beef	*Mangifera* species
Beer	Mastic (*Pistacia lentiscus*)
Black currants (*Ribes nigrum* L.)	Mentha oils
Buchu oil	Mushroom
Celery (*Apium graveolens* L.)	Myrtle (*Myrtus communis* L.)
Cinnamomum species	Nutmeg (*Myristica fragrans* Houttuyn)
Citrus fruits	*Ocimum* species
Ginger (*Zingiber* species)	Omija fruit (*Schisandra chinensis* Baillon)
Grape brandy	Passion fruit (*Passiflora* species)
Hog plum (*Spondias mombins* L.)	Tarragon (*Artemisia dracunculus* L.)
Lemongrass oil	Tequila (*Agave tequilana*)
Litchi (*Litchi chinensis* Sonn.)	Thyme (*Thymus* species)
Litchi wine	Tomato (*Lycopersicon esculentum* Mill.)
Macadamia nut (*Macadamia integrifolia*)	Wine

*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 citronellyl acetateand 3,7-dimethyloct-6-enyl acetate; rhodinyl acetate has been pre-registered; no dossier available as of 06/04/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for citronellyl formate 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)	0.49
2	Products applied to the axillae	0.15
3	Products applied to the face/body using fingertips	2.0
4	Products related to fine fragrances	2.7
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.70
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.70
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.70
5D	Baby cream, oil, talc	0.23
6	Products with oral and lip exposure	0.82
7	Products applied to the hair with some hand contact	2.4
8	Products with significant ano-genital exposure (tampon)	0.23
9	Products with body and hand exposure, primarily rinse-off (bar soap)	5.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.41
10B	Aerosol air freshener	16
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.23
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 citronellyl formate, the basis was the reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 6400 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 v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

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

The mutagenic activity of citronellyl acetate (CAS # 150-84-5) 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 TA1535, TA1537, TA98, TA100, and TA102 were treated with citronellyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of metabolic activation (S9) (RIFM, 2000). Under the conditions of the study, citronellyl acetate was not mutagenic in the Ames test.

The clastogenic activity of citronellyl 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 2:3 DMSO/corn oil via oral gavage to groups of male NMRI mice. Doses of 375, 750, or 1500 mg/kg were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2013). Under the conditions of the study, citronellyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: RIFM, 2013a.

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

11.1.2. Repeated dose toxicity

The MOE for citronellyl 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 citronellyl acetate. In a 2-year carcinogenicity study, food-grade geranyl acetate (containing 71% geranyl acetate, CAS # 105-87-3, and 29% citronellyl acetate, CAS # 150-84-5) was administered to groups of 50 F344/N rats/dose and 50 B6C3F1 mice/sex/dose. The rats were orally administered the test material at doses of 0 (corn oil), 1000, or 2000 mg/kg/day while the doses for the mice study were 0 (corn oil), 500, or 1000 mg/kg/day for 2 years. High-dose rats showed decreased body weights, increased mortality, and increased incidences of nephropathy. The incidences of nephropathy were lacking a dose-response relationship due to increased mortality at the highest dose. Due to increased mortality in high-dose rats, a dose-response relationship could not be detected for the incidences of squamous cell papillomas/carcinomas and kidney tubular cell adenomas; thus, it could not be determined whether these effects were treatment-related. Alterations among mice included cytoplasmic vacuolation in the liver, kidney, and myocardium. Since similar incidences were not observed in treated rats,

the lipidosis incidences in treated mice were considered to be species-specific alterations without a correlation in humans. In addition, there were no incidences of treatment-related neoplasms among treated mice (National Toxicology Program, 1987). Prior to initiating the 2-year study, groups of 10 F344/N rats and B6C3F1 mice each were administered the test material via gavage for 13 weeks. Doses among rats included 0 (corn oil), 250, 500, 1000, 2000, or 4000 mg/kg/day, and doses among mice included 0 (corn oil), 125, 250, 500, 1000, or 2000 mg/kg/day. Increased mortality and decreases in body weights (approximately 8–19%) in rats of the high-dose group were reported. Alterations among mice included lipidosis of the liver, kidney, and myocardium among high-dose group animals. Only bodyweight alterations and histopathological examinations were performed during the 13-week studies because this material was a part of the bioassay program. Since there were no treatment-related effects during the 13-week treatment in both species at 500 mg/kg/day, a NOAEL of 500 mg/kg/day was considered for the repeated dose toxicity endpoint (National Toxicology Program, 1987).

Therefore, the citronellyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the citronellyl acetate NOAEL in mg/kg/day by the total systemic exposure for citronellyl acetate, 500/0.049 or 10204.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/21.

11.1.3. Reproductive toxicity

The MOE for citronellyl 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 citronellyl acetate. Read-across material citronellyl formate (CAS # 105-85-1; see Section VI) has sufficient reproductive toxicity data. An OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered the test material citronellyl formate via oral gavage once daily at doses of 0, 50, 200, or 800 mg/kg/day in corn oil for 7 days per week. Males were dosed for 49 days (2 weeks prior to mating, 2 weeks of mating, and 21 days post-mating), and females were dosed for 2 weeks prior to mating, throughout gestation, and for 13 days after delivery. Additional groups of 6 rats/sex/dose were assigned to the control and high-dose groups to serve as the 14-day treatment-free recovery groups and were not mated. In addition to systemic toxicity, reproductive toxicity parameters were also assessed. One dam in the main group and 1 dam in the recovery group were found dead at 0 mg/kg/day. Three pregnant females of the main group were found dead at 800 mg/kg/day before or during parturition. Stillbirth was observed in 1 female at 800 mg/kg/day, and 4 dams whose pups were all dead were observed at 800 mg/kg/day. Atrophy of the lymphoid organs, adrenocortical hypertrophy, and/or serous atrophy of the bone marrow were noted in the 3 dead females at 800 mg/kg/day; these findings were considered to be stress-related. Thymic atrophy and/or atrophy of white pulp in the spleen were observed in dams whose pups were all dead at 800 mg/kg/day. There was a statistically significant decrease in body weight observed among the high-dose group dams during gestation days 14 and 20 for the main group. No treatment-related adverse effects were observed in the estrous cycle, mating index, male and female fertility indexes, gestation index, mean litter size, external examination of pups, sex ratio, and body weights of pups. A statistically significant increase in post-implantation loss rate and decreases in the birth index (not statistically significant) and viability index (statistically significant) of pups on postnatal days 0 and 4 were noted at 800 mg/kg/day. Abnormal delivery was observed in 1 control female and 3 high-dose group females. The NOAEL for fertility effects was considered to be 800 mg/kg/day, the highest dose tested for males, and 200 mg/kg/day for females, based on mortality during parturition and increased incidences of abnormal delivery among the high-dose group dams. The NOAEL for developmental toxicity was considered to be 200 mg/kg/day, based on increased post-implantation loss rate and decreases in birth and viability indexes among the high-dose group pups (RIFM, 2018b). **Therefore, the citronellyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the citronellyl formate NOAEL in mg/kg/day by the total systemic exposure to citronellyl acetate, 200/0.049 or 4082.**

11.1.3.1.1. Derivation of reference dose (RfD). 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 of 2 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The reference dose for citronellyl acetate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 2 mg/kg/day.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the existing data and read-across material citronellyl butyrate (CAS # 141-16-2), citronellyl acetate is considered a skin sensitizer with a defined NESIL of 6400 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for citronellyl acetate. Based on the existing data and read-across material citronellyl butyrate (CAS # 141-16-2; see Section VI), citronellyl acetate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), the non-radioactive, BrdU-ELISA method was used to show that the read-across material citronellyl butyrate is a skin sensitizer with an EC1.6 value of 26.4% (6600 μg/cm^2) (RIFM, 2017). In a guinea pig Buehler test, citronellyl acetate did not present reactions indicative of sensitization when tested up to 100% (ECHA, 2013; RIFM, 2015). In a human maximization test, no skin sensitization reactions were observed with citronellyl acetate up to 4% (2760 μg/cm^2) (RIFM, 1971). In another human maximization test, no skin sensitization reactions were observed with read-across material citronellyl butyrate up to 5% (3450 μg/cm^2) (RIFM, 1972). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 5.5% or 6495 μg/cm^2 of read-across material citronellyl butyrate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 102 volunteers (RIFM, 2018a).

Based on weight of evidence (WoE) from structural analysis, human studies, and the data on the read-across material, citronellyl acetate is a sensitizer with a WoE NESIL of 6400 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 2 mg/kg/day.

Additional References: Klecak (1985).

Literature Search and Risk Assessment Completed on: 05/28/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, citronellyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for citronellyl acetate in experimental models. UV/Vis absorption

Table 1
Data summary for citronellyl butyrate as a read-across material for citronellyl acetate.

LLNA Weighted Mean EC1.6 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[2] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
6600 [1]	Weak	6495	3450	NA	6400

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.
[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2] Data derived from CNIH or HMT.
[3] WoE NESIL limited to 2 significant figures.

spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, citronellyl acetate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on citronellyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.078 mg/day. This exposure is 17.9 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/28/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of citronellyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, citronellyl 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 citronellyl acetate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), citronellyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

*11.2.2.1.1. Biodegradation. **For CAS # 150-84-5**.*

RIFM, 1995: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. After 28 days of incubation, biodegradation was 82.1%.

*11.2.2.1.2. Ecotoxicity. **For CAS # 150-84-5**.*

RIFM, 2010a: A 72-h algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. Under the conditions of the study, the 72-h EC50 values based on measured concentration for yield and growth rate were reported to be 5.26 mg/L and >7.20 mg/L, respectively.

RIFM, 2012b: A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 guideline under semi-static conditions. The 48-h EC50 value based on the mean measured test concentration was reported to be 3.48 mg/L.

11.2.2.1.3. Other available data. Citronellyl acetate (CAS # 150-84-5) has been registered under REACH, and the following additional data is available (ECHA, 2013):

The ready biodegradability of the test material was evaluated by using the Headspace test according to OECD 310 guidelines. Biodegradation of 93% was observed after 28 days.

A 96-h fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 203 guideline under semi-static conditions. The 96-LC50 value based on measured concentration was reported to be 6.1 mg/L.

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. Cells with an "X" indicate they are not applicable.

Exposure information and PEC Calculation (following RIFM Framework; Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.56	4.56
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	100–1000	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use.

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

The RIFM PNEC is 3.48 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 05/26/21.

12. Literature search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 06/04/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg /L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.585			1000000	0.001585	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.847	1.339	0.38	10000	0.038	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.817	0.588	1.163			Neutral Organics
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	6.1					
Daphnia		3.48		1000	3.48	
Algae		5.26				

Appendix F. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112710.

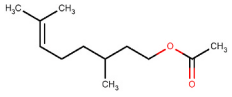
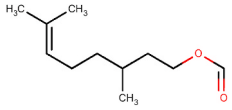
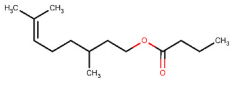
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	Citronellyl acetate	Citronellyl formate	Citronellyl butyrate
CAS No.	150-84-5	105-85-1	141-16-2
Structure			
Similarity (Tanimoto Score)		0.84	0.92
Read-across Endpoint		• Reproductive Toxicity	• Skin Sensitization
Molecular Formula	$C_{12}H_{22}O_2$	$C_{11}H_{20}O_2$	$C_{14}H_{26}O_2$
Molecular Weight	198.30	184.27	226.36
Melting Point (°C, EPI Suite)	−7.40	−9.76	13.92
Boiling Point (°C, EPI Suite)	237.59	220.77	272.03
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.0127	16.799	1.10124
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.56	4.01	5.54
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.686	19.61	0.5878
J_{max} (μg/cm^2/h, SAM)	16.093	12.555	5.157
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.36E+002	3.23E+002	4.16E+002
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)	• No alert found		• No alert found
Protein Binding (OECD)	• No alert found		• No alert found
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)	• No alert found		• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found
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 citronellyl acetate (CAS # 150-84-5). Hence, *in silico* evaluation was conducted to determine read-across

analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, citronellyl formate (CAS # 105-85-1) and citronellyl butyrate (CAS # 141-16-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Citronellyl formate (CAS # 105-85-1) was used as a read-across analog for the target material citronellyl acetate (CAS # 150-84-5) for the reproductive toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of unsaturated branched esters.
  - The target material and the read-across analog are both citronellyl esters.
  - The key difference between the target material and the read-across analog is that the target material has an acetic acid branch whereas the read-across analog has a formic acid branch. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Citronellyl butyrate (CAS # 141-16-2) was used as a read-across analog for the target material citronellyl acetate (CAS # 150-84-5) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of unsaturated branched esters.
  - The target material and the read-across analog are both citronellyl esters.
  - The key difference between the target material and the read-across analog is that the target material has an acetic acid branch whereas the read-across analog has a butyric acid branch. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$80%, and the J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. 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.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - 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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