Food and Chemical Toxicology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, citronellyl formate, CAS Registry number 105-85-1

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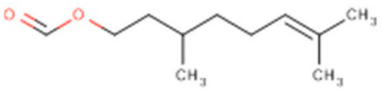
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 060,321. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: Citronellyl formate
CAS Registry Number: 105-85-1
Additional CAS Numbers: 141-09-3 Rhodinyl formate*

Abbreviation/Definition List:

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https://doi.org/10.1016/j.fct.2021.112621
Received 8 June 2021; Received in revised form 16 September 2021; Accepted 15 October 2021
Available online 19 October 2021

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*Included because the materials are isomers

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, 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, 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 formate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that citronellyl formate is not genotoxic. Data on citronellyl formate provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog citronellyl butyrate (CAS # 141-16-2) provided citronellyl formate 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 (UV) spectra; citronellyl formate 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, and the exposure to citronellyl formate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; citronellyl formate 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2003; RIFM, 2017b; RIFM, 2017c; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 66.7 mg/kg/day. RIFM (2018c)
Reproductive Toxicity: NOAEL = 200 mg/kg/day. RIFM (2018c)
Skin Sensitization: NESIL = 6400 μg/cm^2. RIFM (2018b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 88% (OECD 310) for CAS # 105-85-1 RIFM (2013b)
Bioaccumulation:
Screening-level: 206.6 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 96-h Algae EC50: 0.751 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 0.751 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0751 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1

1. Identification

Chemical Name: Citronellyl formate	Chemical Name: Rhodinyl formate
CAS Registry Number: 105-85-1	**CAS Registry Number:** 141-09-3
Synonyms: 3,7-Dimethyl-6-octen-1-yl formate; 6-Octen-1-ol, 3,7-dimethyl-, formate; アルケノール(C-9 ~ 18)アルカン酸(C = 1 ~ 6)エステル; 3,7-Dimethyloct-6-en-1-yl formate; Citronellyl formate	**Synonyms:** 3,7-Dimethyl-(6-or 7-)octen-1-yl formate; 3,7-Dimethyloct-7-en-1-yl formate; 7-Octen-1-ol, 3,7-dimethyl-, formate; Rhodinyl formate
Molecular Formula: $C_{11}H_{20}O_2$	**Molecular Formula:** $C_{11}H_{20}O_2$
Molecular Weight: 184.27	**Molecular Weight:** 184.27
RIFM Number: 158	**RIFM Number:** 559
Stereochemistry: No isomer specified. One stereocenter and 2 total stereoisomers possible.	**Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

CAS # 105-85-1	CAS # 141-09-3
Boiling Point: 99 °C at 11 mm Hg (Fragrance Materials Association [FMA]), 220.77 °C (EPI Suite)	**Boiling Point:** 213.45 °C (EPI Suite)
Flash Point: 91 °C (Globally Harmonized System), 195 °F; CC (FMA)	**Flash Point:** 195 °F; CC (FMA)
Log K_{OW}: 4.01 (EPI Suite)	**Log K_{OW}:** 4.09 (EPI Suite)
Melting Point: 9.76 °C (EPI Suite)	**Melting Point:** 10.24 °C (EPI Suite)
Water Solubility: 19.61 mg/L (EPI Suite)	**Water Solubility:** 16.8 mg/L (EPI Suite)
Specific Gravity: 0.896 (FMA)	**Specific Gravity:** 0.91 (FMA), 0.9028 (ECHA, 2017 Sample 74–149)
Vapor Pressure: 0.083 mm Hg at 20 °C (EPI Suite v4.0), 0.05 mm Hg at 20 °C (FMA), 0.126 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.122 mm Hg at 20 °C (EPI Suite v4.0), 0.183 mm Hg at 25 °C (EPI Suite)
UV Spectra: No absorbance between 290 and 400 nm; the molar extinction coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No significant absorbance between 290 and 700 nm; the molar extinction coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
Appearance/Organoleptic: A colorless mobile liquid that has a powerful leafy green, fruity-rosy, fresh, and light odor reminiscent of Geranium leaves with a somewhat dry and honeylike undertone	**Appearance/Organoleptic:** Arctander, 1969: Colorless, mobile liquid. Very slightly soluble in water, soluble in alcohol and oils. Fresh, leafy green, delicately rosy yet powerful odor of moderate tenacity. Givaudan Index (1961). Consists of a mixture of the formates of 1-citronellol and geraniol, principally 3,7-dimethyl-6-octen-1-yl formate

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.018% (RIFM, 2018a)
2. **Inhalation Exposure*:** 0.000048 mg/kg/day or 0.0035 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure**:** 0.00063 mg/kg/day (RIFM, 2018a)

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

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

***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, inhalation exposure, and total exposure.

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:** 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

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

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

Black currants (*Ribes nigrum* L.)
Citrus fruits
Ginger (*Zingiber* species)
Honey
Laurel (*Laurus nobilis* L.)
Lovage (*Levisticum officinale* Koch)

Rhodinyl formate is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Available for citronellyl formate (accessed on 06/03/21); rhodinyl formate has been pre-registered for 2010; no dossier available as of 06/03/21.

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	0.59
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

(*continued on next page*)

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.59
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.70
5D	Baby cream, oil, talc	0.20
6	Products with oral and lip exposure	1.2
7	Products applied to the hair with some hand contact	0.30
8	Products with significant ano-genital exposure (tampon)	0.20
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.2
10B	Aerosol air freshener	3.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.20
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 0.67 mg/kg/day, a predicted skin absorption value of 40%, 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 and use levels, citronellyl formate does present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Citronellyl formate 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, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of citronellyl formate 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and TA102 were treated with citronellyl formate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Results from the standard plate incorporation assay for strain TA100 showed ≥2.0-fold increases in the number of revertant colonies compared to the control in the presence and absence of metabolic activation (S9); thus, an additional experiment was performed to verify this result. The test material was tested in strain TA100 up to concentrations of 2500 μg/plate in the presence and absence of S9. In the verification standard plate incorporation assay, citronellyl formate again showed up to 2.0- and 2.4-fold, dose-related, increases in the number of revertant colonies compared to the control in the absence and presence of S9, respectively. Although the pre-incubation assay did not show any increases in the frequency of revertant mutations, the increases observed in the standard plate incorporation assay were considered to be biologically relevant, and thus, citronellyl formate was considered to be potentially mutagenic (RIFM, 2003). Follow-up Ames and mammalian cell gene mutation (HPRT) assays were conducted.

The mutagenic activity of citronellyl formate 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with citronellyl formate in DMSO at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017b). Under the conditions of the study, citronellyl formate was not mutagenic in the Ames test.

A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476 and GLP guidelines. Chinese hamster V79 cells were treated with citronellyl formate in DMSO at concentrations of 5.85, 8.78, 13.17, 19.75, 29.63, and 44.44 μg/mL in the absence of S9 and concentrations of 12.5, 25, 50, and 100 μg/mL for 4 h in the presence of S9. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2017c).

An OECD TG 471 study was also conducted on additional material rhodinyl formate (CAS # 141-09-3) and was concluded to be negative in the bacterial reverse mutation assay (RIFM, 2016). Under the conditions of the study, citronellyl formate was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of citronellyl formate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with citronellyl formate in DMSO at concentrations up to 1845 μg/mL in the dose range finding (DRF) study and micronuclei analysis was conducted at concentrations up to 320 μg/mL in the presence and absence of S9 for 3 h and in the absence of S9 for 24 h. A statistically significant increase in the frequency of micronucleated binucleated (MNBN) cells was observed in the 3-h treatment period at 245 μg/mL without S9 and at 105 and 320 μg/mL with S9. However, the MNBN frequencies at these concentrations were within the vehicle historical control ranges. Therefore, the statistically significant increases at these concentrations were considered biologically non-relevant and not indicative of clastogenic effects. Citronellyl formate did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, citronellyl formate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: RIFM, 2015c; RIFM, 2016.

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

11.1.2. Repeated dose toxicity

The MOE for citronellyl formate 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 formate. In an OECD 422 and GLP-compliant study, 12 Crj:CD(SD) rat/sex/dose were administered citronellyl formate (purity: 95.6%) through gavage at doses of 0 (corn oil), 50, 200, and 800

mg/kg/day. Treatment duration in males was 49 days, while in females, the treatment was continued until postpartum day 13. Recovery groups of 6 animals/sex/dose were maintained for an additional 2 weeks for control and high-dose groups. No treatment-related adverse effects were reported for mortality, clinical signs, food consumption, functional behavior examination, motor activity examination, urinalysis, and histopathology at any dose level. Body weights in high-dose pregnant females were lower during treatment. Although some treatment-related effects were reported for hematology, clinical chemistry, thyroid hormone, and organ weights, these were not considered to be of toxicological significance either due to the lack of a dose-response or small magnitude of change or due to values being within historical control ranges. Several reproductive effects were reported during the study, but no significant systemic toxicity was reported in maternal or paternal animals. A significant decrease in T4 was noted in males at 800 mg/kg/day, but this effect was not associated with any abnormal microscopic findings in the thymus and was reversed in the recovery group. However, there was an increase in absolute thyroid weight (25%–30%) in recovery group females at 800 mg/kg/day, which was also not associated with any microscopic findings. Therefore, the NOAEL was considered to be 200 mg/kg/day, based on the decrease in T4 in high-dose males and the increase in absolute thyroid weight in high-dose females of the recovery group (RIFM, 2018c).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012a). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 200/3 or 66.7 mg/kg/day.

Therefore, the citronellyl formate MOE for the repeated dose toxicity endpoint can be calculated by dividing the citronellyl formate NOAEL in mg/kg/day by the total systemic exposure for citronellyl formate, 66.7/0.00063 or 105,873.

In addition, the total systemic exposure for citronellyl formate (0.63 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.67 mg/kg/day.

11.1.3. Derivation of reference dose (RfD)

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for citronellyl formate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 66.7 mg/kg/day by the uncertainty factor, 100 = 0.67 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: RIFM, 2017g.

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

11.1.4. Reproductive toxicity

The MOE for citronellyl formate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.4.1. Risk assessment. There are sufficient reproductive toxicity data on citronellyl formate. 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 secondarily to an exacerbated/moribund condition. 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 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, 2018c). **Therefore, the citronellyl formate 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 formate, 200/0.00063 or 317,460.**

In addition, the total systemic exposure to citronellyl formate (0.63 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2017g.

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

11.1.5. Skin sensitization

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

11.1.5.1. Risk assessment. Limited skin sensitization studies are available for citronellyl formate. Based on the existing data and read-across material citronellyl butyrate (CAS # 141-16-2; see Section VI), citronellyl formate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react directly with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), citronellyl formate was found to be sensitizing with an EC3 value of 32.4% (8087 μg/cm^2) (RIFM, 2015a). In another 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, 2017a). In a human maximization test, no skin sensitization reactions were observed with citronellyl formate up to 4% (2760 μg/cm^2) (RIFM, 1970). 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, 1972a).

Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 7.5% or 5813.95 μg/cm^2 of citronellyl formate in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 44 volunteers (RIFM, 1972b). In another CNIH with 5.5% or 6496 μg/cm^2 of read-across material citronellyl butyrate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2018b).

Based on the weight of evidence (WoE) from structural analysis and human studies and the data on the read-across material, citronellyl formate 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 0.67 mg/kg/day.

Additional References: Klecak (1985).

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

11.1.6. Phototoxicity/photoallergenicity

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

11.1.6.1. Risk assessment. There are no phototoxicity studies available for citronellyl formate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, citronellyl formate does not present a concern for phototoxicity or photoallergenicity.

11.1.7. UV spectra analysis

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

Additional References: None.

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

11.1.8. Local Respiratory Toxicity

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

11.1.8.1. Risk assessment. There are no inhalation data available on citronellyl formate. Based on the Creme RIFM Model, the inhalation exposure is 0.0035 mg/day. This exposure is 400 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

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

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

LLNA Weighted Mean EC1.6 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
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.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of citronellyl formate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. 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 formate 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 formate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012b). 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.

11.2.1.1. Risk assessment. Based on the current VoU (2015), citronellyl formate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. For CAS # 105-85-1.

RIFM, 2013b: The ready biodegradability of the test material was evaluated using a sealed-vessel carbon dioxide evolution test according to the OECD 310 guidelines. Under the conditions of this study, biodegradation of 88% was observed after 28 days.

RIFM, 2015b: The ready biodegradability of the test material was

evaluated using the manometric respirometry test according to the OECD 301F guidelines. Under the conditions of this study, biodegradation of 82% was observed after 28 days.

11.2.2.2. Ecotoxicity. ***For CAS # 105-85-1.***

RIFM, 2017e: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 value based on the mean measured concentration was reported to be 7.6 mg/L (95% CI: 6.8–8.4 mg/L).

RIFM, 2017f: The 96-h acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 value was reported to be 1.3 mg/L (95% CI: 1.1–1.6 mg/L) based on the arithmetic mean measured concentration.

RIFM, 2017d: An algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 values based on mean measured concentration for growth rate and yield were reported to be 3.1 mg/L (95% CI: 3.0–3.2 mg/L) and 1.6 mg/L (95% CI: 1.5–1.7 mg/L), respectively.

11.2.2.3. Other available data. Citronellyl formate (CAS # 105-85-1) has been registered for REACH with no additional data available at this time.

11.2.2.4. Risk assessment refinement. Since citronellyl formate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	4.09	4.09
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Combined Regional Volume of Use for both CAS #

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

The RIFM PNEC is 0.0751 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/25/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 6/03/21.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	3.78			1000000	0.00378	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.479	2.457	0.751	10000	0.0751	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	2.001	1.378	2.282			Neutral organics SAR (Baseline toxicity)

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112621.

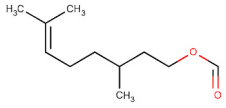
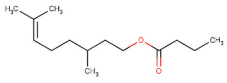
Appendix

Read-across Justification

Methods

The read-across analog was 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
Principal Name	Citronellyl formate	Citronellyl butyrate
CAS No.	105-85-1	141-16-2
Structure		
Similarity (Tanimoto Score)		0.77
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{11}H_{20}O_2$	$C_{14}H_{26}O_2$
Molecular Weight	184.27	226.36
Melting Point (°C, EPI Suite)	−9.76	13.92
Boiling Point (°C, EPI Suite)	220.77	272.03
Vapor Pressure (Pa @ 25°C, EPI Suite)	16.799	1.10124
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.01	5.54
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	19.61	0.5878
J_{max} (μg/cm^2/h, SAM)	12.555	5.157
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.23E+002	4.16E+002
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

Summary

There are insufficient toxicity data on citronellyl formate (CAS # 105-85-1). 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 butyrate (CAS # 141-16-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

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

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