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RIFM fragrance ingredient safety assessment, citronellyl isobutyrate, CAS Registry Number 97-89-2

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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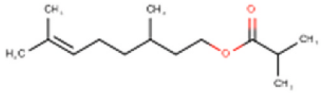

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Name: Citronellyl isobutyrate
CAS Registry Number: 97-89-2
138-23-8 Rhodinyl isobutyrate* - No Reported Use
*included because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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 isobutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog citronellyl formate (CAS # 105-85-1) show that citronellyl isobutyrate is not expected to be genotoxic and 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 isobutyrate 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 isobutyrate 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 to citronellyl isobutyrate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; citronellyl isobutyrate 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 expected to be genotoxic.	(RIFM, 2003; RIFM, 2017b; RIFM, 2017c; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 66.7 mg/kg/day.	RIFM (2018b)
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: 75% (OECD 301F) for CAS # 97-89-2	RIFM (2012)
Bioaccumulation:	
Screening-level: 1887 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Algae EC50: 0.088 mg/L for CAS # 138-23-8	(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: 0.088 mg/L for CAS # 138-23-8	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0088 μg/L

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

1. Identification

Chemical Name: Citronellyl isobutyrate	Chemical Name: Rhodinyl isobutyrate
CAS Registry Number: 97-89-2	**CAS Registry Number:** 138-23-8
Synonyms: Citronellyl 2-methylpropanoate; 3,7-Dimethyl-6-octen-1-yl 2-methylpropanoate; 3,7-Dimethyl-6-octen-1-yl isobutyrate; Propanoic acid, 2-methyl-, 3,7-dimethyl-6-octenyl ester; 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 2-methylpropanoate; 3,7-Dimethyloct-6-enyl isobutyrate; Citronellyl isobutyrate	**Synonyms:** 3,7-Dimethyl-(6-or 7-) octen-1-yl 2-methylpropanoate; 3,7-Dimethyl-(6-or 7-)octen-1-yl isobutyrate; 3,7-Dimethyloct-7-en-1-yl 2-methylpropanoate; Propanoic acid, 2-methyl-, 3,7-dimethyl-7-octenyl ester; Rhodinyl 2-methylpropanoate; Rhodinyl isobutyrate
Molecular Formula: $C_{14}H_{26}O_2$	**Molecular Formula:** $C_{14}H_{26}O_2$
Molecular Weight: 226.36	**Molecular Weight:** 226.36
RIFM Number: 351	**RIFM Number:** Not available
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 # 97-89-2	CAS # 138-23-8
Boiling Point: 249 °C (Fragrance Materials Association [FMA]), 262.03 °C (EPI Suite)	**Boiling Point:** 255.51 °C (EPI Suite)
Flash Point: >93 °C (Globally Harmonized System), >200 °F; CC (FMA)	**Flash Point:** >200 °F; CC (FMA)
Log K_{OW}: 5.47 (EPI Suite)	**Log K_{OW}:** 5.55 (EPI Suite)
Melting Point: 3.5 °C (EPI Suite)	**Melting Point:** 3.26 °C (EPI Suite)
Water Solubility: 0.6792 mg/L (EPI Suite)	**Water Solubility:** 0.582 (EPI Suite)
Specific Gravity: 0.875 (FMA)	**Specific Gravity:** Not available
Vapor Pressure: 0.00886 mm Hg at 20 °C (EPI Suite v4.0), 0.005 mm Hg at 20 °C (FMA), 0.0143 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.0203 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:** Not available
Appearance/Organoleptic: A colorless liquid that has a fresh, almost citrusy-rosy, intensely fruity, and sweet odor and a fruity-rosy, somewhat Bergamot-like taste of moderate sweetness.	**Appearance/Organoleptic:** A colorless oily liquid. Consists of a mixture of the isobutyrates of l-citronellol and geraniol, principally 3,7-dimethyl-6-octen-1-yl isobutyrate

3. Volume of use (worldwide band)

1. 1–10 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:** 0.036% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00032 mg/kg/day or 0.024 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0015 mg/kg/day (RIFM, 2019)

*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 or 97.5th percentile, 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:** Citronellyl formate (CAS # 105-85-1)
b. **Repeated Dose Toxicity:** Citronellyl formate (CAS # 105-85-1)
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 isobutyrate and isomer rhodinyl isobutyrate are 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 CAS # 97-89-2 (accessed 05/17/21); no dossier available for CAS # 138-23-8 (pre-registered for 2010).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for citronellyl isobutyrate 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	0.14
4	Products related to fine fragrances	0.85
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	0.28
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.28
5D	Baby cream, oil, talc	0.095
6	Products with oral and lip exposure	1.3
7	Products applied to the hair with some hand contact	0.28
8	Products with significant ano-genital exposure (tampon)	0.095
9	Products with body and hand exposure, primarily rinse-off (bar soap)	3.3
10A	Household care products with mostly hand contact (hand dishwashing detergent)	5.7
10B	Aerosol air freshener	2.7
11	Products with intended skin contact but minimal transfer of fragrance to	0.095

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IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	skin from inert substrate (feminine hygiene pad)	
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	95

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 isobutyrate, 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

11.1.1.1. Risk assessment. Citronellyl isobutyrate was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: <80% relative cell density), negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). 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.

There are no data assessing the mutagenic and clastogenic activity of citronellyl isobutyrate; however, read-across can be made to citronellyl formate (CAS # 105-85-1; see Section VI).

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 absence and presence of S9; therefore, 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 showed again 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 preincubation 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 mutagenic (RIFM, 2003). Follow-up Ames and HRPT 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, and this can be extended to citronellyl isobutyrate.

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 in the presence of S9, for 4 h. 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), and this can be extended to citronellyl isobutyrate. The Ames assay was positive only in the plate incorporation study and not in the preincubation study. Based on the negative outcomes in the follow-up Ames assay and the biologically relevant mammalian cell line mutagenicity study, citronellyl formate is not considered to be mutagenic, and the increases in the plate incorporation study can be considered to be biologically irrelevant.

Taken together, citronellyl formate is not considered to be mutagenic, and this can be extended to citronellyl isobutyrate.

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 a DRF study, and micronuclei analysis was conducted at concentrations up to 320 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. A statistically significant increase in the frequency of micronucleated binucleated (MNBN) cells was observed in the 3-h treatment 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 irrelevant 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, and this can be extended to citronellyl isobutyrate.

Based on the data available, citronellyl formate does not present a concern for genotoxic potential, and this can be extended to citronellyl isobutyrate.

Additional References: RIFM, 2015.

Literature Search and Risk Assessment Completed On: 04/28/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on citronellyl isobutyrate. Read-across material citronellyl formate (CAS 105-85-1; see Section VI) has sufficient repeated dose toxicity data. 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 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 the 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 recovery females (RIFM, 2018b).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). 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 isobutyrate, 66.7/0.0015 or 44467.

In addition, the total systemic exposure for citronellyl isobutyrate (1.5 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 (RfD) of 0.67 mg/kg/day.

Derivation of 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 RfD for citronellyl isobutyrate 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, 1980.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on citronellyl isobutyrate. 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 isobutyrate 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 isobutyrate, 200/0.0015, or 133333.**

In addition, the total systemic exposure to citronellyl isobutyrate (1.5 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, 1980.

Literature Search and Risk Assessment Completed On: 05/07/21.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for citronellyl isobutyrate. Based on the existing data and read-across material citronellyl butyrate (CAS # 141-16-2), citronellyl isobutyrate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material citronellyl butyrate was found to be sensitizing with an EC1.6 value of 26.4% (6600 μg/cm^2) (RIFM, 2017a). However, in guinea pigs, an open epicutaneous test (OET) with citronellyl isobutyrate did not present reactions indicative of sensitization (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with citronellyl isobutyrate up to 4% or 2760 μg/cm^2 or with read-across material citronellyl butyrate up to 5% or 3450 μg/cm^2 (RIFM, 1972). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 6495 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, 2018a).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material citronellyl butyrate, citronellyl isobutyrate is a sensitizer with a WoE NESIL of 6400 μg/cm^2 (Table 1). **Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2)**

Table 1
Data Summary for citronellyl butyrate as read-across material for citronellyl isobutyrate.

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.

described by Api et al. (RIFM, 2020) and a reference dose of 0.67 mg/kg/day.

Additional References: ECHA, 2017a.

Literature Search and Risk Assessment Completed On: 05/10/21.

11.1.5. Phototoxicity/photoallergenicity

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

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for citronellyl isobutyrate 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 isobutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.024 mg/day. This exposure is 58.3 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of citronellyl isobutyrate 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 isobutyrate 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 isobutyrate 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, 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 isobutyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. **Biodegradation**

For CAS # 97-89-2.

RIFM, 2012**:** The ready biodegradability of the test material was evaluated using the manometric respirometry test following the OECD 301F method. Under the conditions of the study, biodegradation of 75% was observed after 28 days.

Ecotoxicity

No data available.

Other available data

Citronellyl isobutyrate (CAS # 97-89-2) has been registered for REACH with the following additional data available (ECHA, 2017a):

A *Daphnia* acute immobilization test was conducted according to the OECD 202 Guidelines under static conditions. The 48-h EC50 value based on measured concentration was reported to be 18.7 mg/L (95% CI: 16.4–21.3 mg/L).

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h 50 value based

on measured concentration for growth rate was reported to be 53.5 mg/L (95% CI: 46.9–61.1 mg/L).

11.2.3. Risk assessment refinement

Since citronellyl isobutyrate 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 Environmental Framework: Salvito, 2002).

Exposure	Europe	North America
Log K_{ow} Used	5.55	5.55
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

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

The RIFM PNEC is 0.0088 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: 05/04/21.

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 05/17/21.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112690.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.249			1000000	0.000249	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	0.256	0.364	0.088	10000	0.0088	Esters

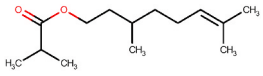
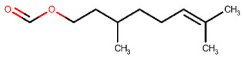
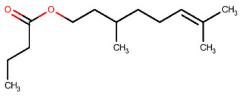
Appendix

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, 2017b).

- 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 isobutyrate	Citronellyl formate	Citronellyl butyrate
CAS No.	97-89-2	105-85-1	141-16-2
Structure			
Similarity (Tanimoto Score)		0.75	0.91
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity • Reproductive Toxicity	• Skin Sensitization
Molecular Formula	$C_{14}H_{26}O_2$	$C_{11}H_{20}O_2$	$C_{14}H_{26}O_2$
Molecular Weight	226.36	184.27	226.36
Melting Point (°C, EPI Suite)	3.50	−9.76	13.92
Boiling Point (°C, EPI Suite)	262.03	220.77	272.03
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.907	16.799	1.101
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.47	4.01	5.54
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.67920	19.61	0.58780
J_{max} (μg/cm^2/h, SAM)	7.237	12.555	5.157
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.16E+02	3.23E+02	4.16E+02
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• No alert found	• No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Aldehyde-type Compounds	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	• 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			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
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 isobutyrate (CAS # 97-89-2). 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 isobutyrate (CAS # 97-89-2) for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of citronellyl esters.
  - o The target material and the read-across analog share a citronellol alcohol moiety.
  - o The key difference between the target material and the read-across analog is that the target material has an isobutyric acid moiety, whereas the read-across analog has a formic acid moiety. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40% and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog has an oncologic alert for aldehyde-type compounds. This alert is due to the carbonyl group within the formic acid moiety. This alert can be ignored because formates are not part of its training set. Therefore, the predictions are superseded by the data.
  - 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.
- Citronellyl butyrate (CAS # 141-16-2) was used as a read-across analog for the target material citronellyl isobutyrate (CAS # 97-89-2) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of citronellyl esters.
  - o The target material and the read-across analog are structural isomers and share a citronellol alcohol moiety.
  - o The key difference between the target material and the read-across analog is that the target material has an isobutyric acid moiety, whereas the read-across analog has a butyric acid moiety. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o 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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