Food and Chemical Toxicology 161 (2022) 112902

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, citronelloxyacetaldehyde, CAS Registry Number 7492-67-3

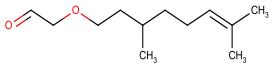
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], 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 for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel for Fragrance Safety, 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 for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel for Fragrance Safety, 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 for Fragrance Safety, 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 for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel for Fragrance Safety, 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 for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 111121. 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.



(*continued on next column*)

(*continued*)

Name: Citronelloxyacetaldehyde CAS Registry Number: 7492-67-3

Abbreviation/Definition List:

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

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2022.112902
Received 11 November 2021; Accepted 23 February 2022
Available online 26 February 2022

(*continued*)

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., 2017; Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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
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

Summary: The existing information supports the use of this material as described in this safety assessment.
Citronelloxyacetaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that citronelloxyacetaldehyde is not genotoxic. Data on read-across analog citral (CAS # 5392-40-5) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided citronelloxyacetaldehyde a No Expected Sensitization Induction Level (NESIL) of 3500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; citronelloxyacetaldehyde 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 III material, and the exposure to citronelloxyacetaldehyde is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; citronelloxyacetaldehyde was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 60 mg/kg/day.	(Ress et al., 2003)
Developmental and Reproductive Toxicity: Developmental toxicity: NOAEL = 60 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day.	(Nogueira et al., 1995; MHW, 1996)
Skin Sensitization: NESIL = 3500 μg/cm^2.	RIFM, (2016b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra, RIFM Database)	
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

(*continued on next column*)

(*continued*)

Environmental Safety Assessment

Hazard Assessment:

Critical Measured Value: 79% (OECD 301F)	RIFM, (2019c)
Bioaccumulation: Screening-level: 65.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 21.43 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: LC50: 21.43 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.02143 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Citronelloxyacetaldehyde
2. **CAS Registry Number:** 7492-67-3
3. **Synonyms:** Acetaldehyde, [(3,7-dimethyl-6-octenyl)oxy]-; Citronellyl oxyacetaldehyde; ((3,7-Dimethyl-6-octenyl)oxy)acetaldehyde; 6,10-Dimethyl-3-oxa-9-undecenal; ｼﾄﾛﾈﾘﾙｵｷｼｱｾﾄｱﾙﾃﾞﾋﾄﾞ; [(3,7-Dimethyloct-6-en-1-yl)oxy]acetaldehyde; Muguet aldehyde; Citronelloxyacetaldehyde
4. **Molecular Formula:** $C_{12}H_{22}O_2$
5. **Molecular Weight:** 198.31
6. **RIFM Number:** 384
7. **Stereochemistry:** Isomer not specified. One stereocenter is present, and 2 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 130 °C at 12.0 mm Hg (Fragrance Materials Association [FMA] Database), 260.7 °C (EPI Suite)
2. **Flash Point:** 199 °F; CC (FMA Database), 93 °C (Globally Harmonized System)
3. **Log K_{ow}:** 3.26 (EPI Suite)
4. **Melting Point**: 10.29 °C (EPI Suite)
5. **Water Solubility:** 73.94 mg/L (EPI Suite)
6. **Specific Gravity:** 0.90 (FMA Database)
7. **Vapor Pressure:** 0.00954 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg at 20 °C (FMA Database), 0.0153 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra**: Minor absorbance between 290 and 700 nm; molar absorption coefficients (0, 123, 0 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless, viscous liquid that has a powerful and moderately diffuse green-rosy, sweet lily-Muguet-like odor with comparatively good tenacity (RIFM Database)

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 v3.1.4)

1. **Maximum Level in Fine Fragrance:** 0.0090% (RIFM, 2019d)
2. **Inhalation Exposure*:** 0.000030 mg/kg/day or 0.0023 mg/day (RIFM, 2019d)
3. **Total Systemic Exposure**:** 0.00026 mg/kg/day (RIFM, 2019d)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (RIFM, 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High (Expert Judgment)

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

* See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Citral (CAS # 5392-40-5)
   c. **Developmental and Reproductive Toxicity:** Citral (CAS # 5392-40-5)
   d. **Skin Sensitization:** None
   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

Citronelloxyacetaldehyde is not reported to occur in food 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

Pre-registered for 2010; no dossier available as of 11/11/21.

10. Conclusion

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

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.27
2	Products applied to the axillae	0.080
3	Products applied to the face/body using fingertips	0.40
4	Products related to fine fragrances	1.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.38
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.38
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.38
5D	Baby cream, oil, talc	0.13
6	Products with oral and lip exposure	0.88
7	Products applied to the hair with some hand contact	1.2
8	Products with significant ano-genital exposure (tampon)	0.13
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.2
10B	Aerosol air freshener	5.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.13
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 citronelloxyacetaldehyde, the basis was the reference dose of 0.6 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 3500 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; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, citronelloxyacetaldehyde does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Citronelloxyacetaldehyde was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) 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 were considered to fully assess the potential mutagenic and clastogenic effects on the target material.

The mutagenic activity of citronelloxyacetaldehyde 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* WP2uvrA were treated with citronelloxyacetaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the

mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, citronelloxyacetaldehyde was not mutagenic in the Ames test.

The clastogenic activity of methyl citronelloxyacetaldehyde 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 citronelloxyacetaldehyde in DMSO at concentrations up to 250 μg/mL in the presence and absence of S9 for 4 h and in the absence of S9 for 24 h. Citronelloxyacetaldehyde did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2014b). Under the conditions of the study, citronelloxyacetaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.2. Repeated dose toxicity

The MOE for citronelloxyacetaldehyde 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 citronelloxyacetaldehyde. Read-across material citral (CAS # 5392-40-5; see Section VI) has sufficient repeated dose toxicity data. An NTP-sponsored chronic study was conducted in compliance with GLP on groups of 50 F344/N rats/sex/group. The animals were administered test material, citral (microencapsulated), in the diet at concentrations of 1000, 2000, or 4000 ppm for 104–105 weeks. Additional groups of 50 male and 50 female rats received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). The concentrations are equivalent to approximately 50, 100, and 210 mg/kg/day. The NOAEL for treatment-related non-neoplastic effects was 100 mg/kg/day, based on decreased body weight among the animals in the high-dose group (Ress et al., 2003). In another GLP study, a group of 50 B6C3F1 mice/sex/group were fed diets containing citral at concentrations of 500, 1000, or 2000 ppm for 104–105 weeks. Additional groups of 50 male and 50 female mice received untreated feed (untreated controls) or feed containing placebo microcapsules (vehicle controls). The concentrations are equivalent to approximately 60, 120, and 260 mg/kg/day. The incidences of malignant lymphoma in females occurred with a positive trend. The incidence in 2000 ppm females was significantly greater than that in the vehicle control group but was within the historical ranges in controls (all routes). To further characterize the nature of the lymphomas in vehicle-control and exposed mice, all cases of lymphoma were sectioned and immunostained using CD-3 to identify T cells and CD-45R (B220 clone) to identify B cells. Immunostaining of the lymphomas did not reveal any differences in the immunophenotype of the lymphomas in the vehicle control and the treatment group animals. Because the incidences of lymphoma remained within the NTP historical ranges, and this effect was only observed in females, lymphomas were not considered to be related to the administration of citral. There was a positive trend in the incidences of hepatomas (hepatocellular adenoma or carcinoma) in females but of no significance. Inflammation and ulceration of the oral mucosa among the 2000 ppm group males and all treated females, adrenal cortical focal hyperplasia in high-dose group males, nephropathy among high-dose group females, and minimal tubule mineralization among the 500 and 1000 ppm group females were also reported, but the relevance of these incidences to treatment with citral could not be confirmed. The NOAEL for treatment-related non-neoplastic effects was determined to be 60 mg/kg/day (Ress et al., 2003; NTP, 2003). The most conservative NOAEL for repeated dose toxicity was determined from a dietary 104–105 week carcinogenicity study in mice to be 500 ppm, or 60 mg/kg/day, based on reduced body weights.

Therefore, the citronelloxyacetaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citronelloxyacetaldehyde, 60/0.00026, or 230769.

In addition, the total systemic exposure to citronelloxyacetaldehyde (0.26 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 0.60 mg/kg/day.

Derivation of reference dose (RfD)

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for citronelloxyacetaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 60 mg/kg/day by the uncertainty factor, 100 = 0.60 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/15/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no developmental toxicity data on citronelloxyacetaldehyde. Read-across material citral (CAS # 5392-40-5; see Section VI) has sufficient developmental and reproductive toxicity data. An OECD 421 gavage reproduction toxicity screening test was conducted in Crj:CD (SD) rats. Citral was administered to rats via gavage at dose levels of 0, 40, 200, and 1000 mg/kg/day in males for 46 days and in females for 39–50 days, including before and through mating and gestation periods and until day 3 of lactation. Body weights of pups were reduced at 1000 mg/kg/day, though there was no effect on viability or morphogenesis. The NOAEL for developmental toxicity was determined to be 200 mg/kg/day due to decreased body weights among the high-dose group pups (MHW, 1996). A gavage developmental toxicity study was conducted on groups of 20 Wistar rats. The pregnant animals were treated with test material, citral, at dose levels of 0 (corn oil), 60, 125, 250, 500, or 1000 mg/kg/day on gestation days 6–15. The study was terminated on gestation day 21. The protocol followed was similar to the OECD 414 developmental toxicity study. Administration of citral-induced whole-litter loss at doses that were deemed to be maternally toxic (125–1000 mg/kg/day), suggesting that treatment-induced prenatal loss was a maternally mediated effect. In 125–1000 mg/kg/day dose groups, there were reduced implantation sites. Also, due to the increased proportion of resorption, the mean number of live fetuses was also reduced at doses higher than 60 mg/kg/day. No increase in visceral anomalies was found at any dose. The LOAEL for both maternal and developmental toxicity was determined to be 60 mg/kg/day, based on maternal body weights and an increased ratio of resorptions per implantations (Nogueira et al., 1995). A reproductive toxicity screening study conducted on 30 female Sprague Dawley rats/group were administered citral via gavage at dose levels of 0 (corn oil), 50, 160, and 500 mg/kg/day for 2 weeks prior to mating through gestation day 20. Mortality was observed in dams at mid (1/30) and high dose (7/30) groups. In addition, urine-stained fur and decreased motor activity were also observed in mid- and high-dose groups. A significant decrease in body weight gain during gestation and a significant increase in feed consumption during the lactation

period (1–4 days) was also observed at 160 and 500 mg/kg/day. Subsequently, the effects of citral on the development of the offspring in utero and through lactation were also reported. There was no gross external alteration attributed to the test material in the fetuses up to the highest dose tested. There was, however, a significant decrease in the average pup body weight at birth among the high-dose group animals as compared to control. Thus, the NOAEL for the developmental toxicity was determined to be 160 mg/kg/day, based on reduced fetal weights among the high-dose group animals (Hoberman et al., 1989). Another OECD 414 GLP gavage prenatal developmental toxicity study was conducted on groups of 25 pregnant female New Zealand White rabbits/group. The animals were administered test material, citral extra, via gavage at dose levels of 0 (0.5% carboxymethylcellulose suspension in drinking water [with 0.5 mg Tween 80/100 mL]), 20, 60, or 200 mg/kg/day on gestation days (GD) 6–28. At terminal sacrifice on GD 29, 17–24 females per group had implantation sites. Mortality was reported among the high-dose group does. Gross pathological examination revealed reddening of the stomach mucosa and multiple ulcerations. Clinical observations in the high-dose group animals included reduced average food consumption and net bodyweight loss. One high-dose female had 4 dead fetuses at termination, which was considered an expression of maternal toxicity in rabbits. This was related to the local irritating potential of the test material on the gastrointestinal tract. One high-dose group doe was reported to have litters having malrotated limbs; however, this was considered to be secondary to maternal toxicity since the doe was reported to have a significant bodyweight loss and reduced food consumption. There were no other reported effects of treatment on the developing fetus. Considering this, there was sufficient evidence that these fetal findings were a direct consequence of severe maternal toxicity. Therefore, the NOAEL for maternal toxicity was determined to be 60 mg/kg/day based on reduced food consumption, distinct bodyweight loss, mortality, and abortion in the most sensitive individuals in the 200 mg/kg/day group. The NOAEL for prenatal developmental toxicity was determined to be 60 mg/kg/day, based on fetal mortality and limb malrotations in the 200 mg/kg/day group (RIFM, 2016a).

The developmental toxicity study on rats (Nogueira et al., 1995) was not considered towards determining the NOAEL since the incidences of resorptions without any visceral alterations in fetuses were reported in the presence of maternal toxicity. Similar effects on the developing fetuses were not reported among rabbits treated at comparable doses during the OECD 414 study (RIFM, 2016a) or rats during the OECD 421 study (MHW, 1996). Therefore, the NOAEL for the developmental toxicity endpoint was considered to be 60 mg/kg/day, as determined from the most recent and well-conducted OECD 414/GLP developmental toxicity study on rabbits (RIFM, 2016a; ECHA, 2011).

Therefore, the citronelloxyacetaldehyde MOE for the developmental endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citronelloxyacetaldehyde, 60/0.00026, or 230769.

The OECD 421 (MHW, 1996) and the reproductive toxicity screening study (Hoberman et al., 1989) conducted on citral did not show any adverse effects towards the male or the female reproductive study. Thus, the NOAEL for reproductive toxicity was determined to be 1000 mg/kg/day.

Therefore, the citronelloxyacetaldehyde MOE for the reproductive toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citronelloxyacetaldehyde, 1000/0.00026, or 3846154.

In addition, the total systemic exposure to citronelloxyacetaldehyde (0.26 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.4. Skin sensitization

Based on the existing data, citronelloxyacetaldehyde is considered to be a skin sensitizer with a defined NESIL of 3500 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, citronelloxyacetaldehyde is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2; Toxtree v3.1.0). No predictive *in chemico* or *in vitro* skin sensitization data were available for citronelloxyacetaldehyde in the literature. In a murine local lymph node assay (LLNA), citronelloxyacetaldehyde was found to be sensitizing with an EC3 value of 28.3% (7075 μg/cm^2) (RIFM, 2010). In a human maximization test, no skin sensitization reactions were observed with citronelloxyacetaldehyde at 8% (5520 μg/cm^2) (RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) conducted with citronelloxyacetaldehyde at 4.1% (3550 μg/cm^2) in 1:3 ethanol: diethyl phthalate (EtOH:DEP), at 0.5% (271 μg/cm^2) in ethanol, and at 0.25% (96 μg/cm^2) in alcohol SDA 40, no reactions indicative of sensitization were observed in any of the 100, 40, or 41 volunteers, respectively (RIFM, 2016b; RIFM, 1964; RIFM, 1971).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, citronelloxyacetaldehyde is a sensitizer with a WoE NESIL of 3500 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, 2020b) and a reference dose of 0.60 mg/kg/day.

Literature Search and Risk Assessment Completed On: 02/06/21.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, citronelloxyacetaldehyde 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 citronelloxyacetaldehyde in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficients are below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, citronelloxyacetaldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG

Table 1
Data summary for citronelloxyacetaldehyde.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[2] (Induction) μg/cm^2	WoE NESIL[3] μg/cm^2
7075 [1]	Weak	3550	5520	NA	3500

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
Additional References: None.

101) for citronelloxyacetaldehyde were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficients (0, 123, 0 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are below the benchmark, 1000 L mol^{-1} • cm^{-1}, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on citronelloxyacetaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.0023 mg/day. This exposure is 204.3 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2019c**: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 79% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. **RIFM, 2019b:** A *Daphnia magna* immobilization test was conducted according to the OECD 202 guideline under semi-static conditions in a closed system without headspace. The 48-h EC50 value based on the mean measured concentration was reported to be 8.9 mg/L (95% CI: 8.1–9.9 mg/L).

RIFM, 2019a: An algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions in a closed system without headspace. The 72-h EC50 values based on mean measured concentration for growth rate and yield were reported to be 15 mg/L (95% CI: 14–16 mg/L) and 5.9 mg/L (95% CI: 5.6–6.3 mg/L), respectively.

11.2.2.1.3. Other available data. Citronelloxyacetaldehyde has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since citronelloxyacetaldehyde 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 et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.26	3.26
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.02143 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the currently reported volumes of use.

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

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	21.43			1000000	0.02143	

- **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 11/11/21.

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.2022.112902.

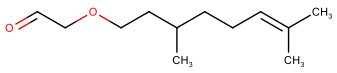
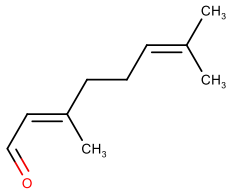
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Citronelloxyacetaldehyde	Citral
CAS No.	7492-67-3	5392-40-5
Structure		
Similarity (Tanimoto Score)		0.33
Endpoint		• Repeated dose toxicity • Reproductive Toxicity
Molecular Formula	$C_{12}H_{22}O_2$	$C_{10}H_{16}O$
Molecular Weight	198.306	152.237
Melting Point (°C, EPI Suite)	10.29	−26.74
Boiling Point (°C, EPI Suite)	260.70	227.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.04E+00	1.22E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.39E+01	1.34E+03
Log K_{OW}	3.26	3.45
J_{max} (μg/cm^2/h, SAM)	3.35	164.13
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.58E+00	3.81E+01
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)
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 citronelloxyacetaldehyde (CAS # 7492-67-3). 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, citral (CAS # 5392-40-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Citral (CAS # 5392-40-5) was used as a read-across analog for the target material citronelloxyacetaldehyde (CAS # 7492-67-3) for the reproductive toxicity and repeated dose toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to aliphatic aldehydes.
  - The target material and the read-across analog share an aldehyde functionality.
  - The key difference between the target material and the read-across analog is that the read-across analog has α,β unsaturation with β-methyl substitution. The bond between α- and β-carbon in the target material is saturated. Also, the target material has an ether link in the aliphatic chain that is not present in the read-across analog. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - There are no *in silico* alerts for the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body?: **No**
Q2. Contains functional groups associated with enhanced toxicity?: **No**
Q3. Contains elements other than C, H, O, N, divalent S?: **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate?: **No**
Q6. Benzene derivative with certain substituents?: **No**

Q7. Heterocyclic?: **No**
Q16. Common terpene?: **No**
Q17. Readily hydrolyzed to a common terpene?: **No**
Q19. Open chain?: **Yes**
Q20. Aliphatic with some functional groups (see Cramer et al., 1978)?: **No**
Q22. A common component of food?: **No**
Q33. Has a sufficient number of sulfonate or sulfamate groups?: **No**, Class High (Class III)

References

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

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

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

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010a. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

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

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., et al., 2010, July. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (S1), S4 (Springer International Publishing.).

ECHA, 2011. Citral Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/13515/1/2.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2017. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

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

Hoberman, A.M., Christian, M.S., Bennett, M.B., Vollmuth, T.A., 1989. Oral general reproduction study of citral in female rats. Toxicologist 9 (1), 271.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

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

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

Ministry of Health and Welfare, 1996. Simplified Reprotoxicity Rat Study on Citral. Unpublished.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance skin sensitization evaluation and human testing. Dermatitis. https://doi.org/10.1097/DER.0000000000000684. November 16, 2020. Volume Publish Ahead of Print Issue. Retrieved from.

National Toxicology Program, 2003. Toxicology and Carcinogenesis Studies of Citral (Microencapsulated) (CAS No. 5392-40-5) in F344/N Rats and B6C3F1 Mice (Feed Studies). NTP-TR-505. NIH Publication No. 03-4439.

Nogueira, A.C.M.A., Carvalho, R.R., Souza, C.A.M., Chahoud, I., Paumgartten, F.J.R., 1995. Study on the embryofeto-toxicity of citral in the rat. Toxicology 96 (2), 105–113.

OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox v3.2–4.2. http://www.qsartoolbox.org/.

Ress, N.B., Hailey, J.R., Maronpot, R.R., Bucher, J.R., Travlos, G.S., Haseman, J.K., Orzech, D.P., Johnson, J.D., Hejtmancik, M.R., 2003. Toxicology and carcinogenesis studies of microencapsulated citral in rats and mice. Toxicol. Sci. 71 (2), 198–206.

RIFM Research Institute for Fragrance Materials, Inc, 1964. Repeated Insult Patch Test with Citronelloxyacetaldehyde (Muguet Aldehyde "70") in Humans. Unpublished Report from IFF. RIFM Report Number 55037. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1971. Repeated Insult Patch Test with Citronelloxyacetaldehyde (Muguet Aldehyde) in Humans. Unpublished Report from IFF. RIFM Report Number 55039. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 1973. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1802. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2010. Local Lymph Node Assay: Citronelloxyacetaldehyde. RIFM Report Number 61887. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2013. Report on the Testing of Citronelloxyacetaldehyde in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65295. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2014a. Citronelloxyacetaldehyde: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM Report Number 67499. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2014b. Citronelloxyacetaldehyde: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM Report Number 67611. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2015. Novel Database for Exposure to Fragrance Ingredients in Cosmetics and Personal Care Products. RIFM Report Number 68681. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2016a. Citral: Prenatal Developmental Toxicity Study in New Zealand White Rabbits Oral Administration (Gavage). Unpublished Report from RIFM Report Number 71160. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2016b. Citronelloxyacetaldehyde: Repeated Insult Patch Test (RIPT). RIFM Report Number 71562. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2019a. Citronelloxyacetaldehyde (Citronellyl Oxyacetaldehyde): Effect on Pseudokirchneriella Subcapitata in a 72 Hour Algal Growth Inhibition Test. Unpublished Report from Givaudan. RIFM Report Number 76700. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2019b. Citronelloxyacetaldehyde (Citronellyl Oxyacetaldehyde): Acute Toxicity to Daphnia Magna in a 48-hour Immobilization Test. Unpublished Report from Givaudan. RIFM Report Number 76701. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2019c. Citronelloxyacetaldehyde (Citronellyl Acetaldehyde): Ready Biodegradability. Unpublished Report from Givaudan. RIFM Report Number 76702. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2019d. Exposure Survey 25, October 2019.

RIFM Research Institute for Fragrance Materials, Inc, 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM Report Number 76272. RIFM, Woodcliff Lake, NJ, USA.

RIFM Research Institute for Fragrance Materials, Inc, 2020b. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. RIFM, Woodcliff Lake, NJ, USA.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.