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Short Review

RIFM fragrance ingredient safety assessment, citronellal, CAS registry number 106-23-0

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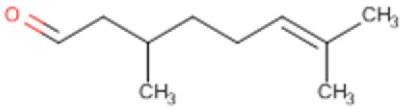

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Abbreviation/Definition List:

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

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2015, 2017; Safford et al., 2015, 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

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.

Citronellal was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that citronellal is not genotoxic. Data on read-across analog citral (CAS # 5392-40-5) provided a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and the developmental and reproductive toxicity endpoints. For the skin sensitization endpoint, the No Expected Sensitization Induction Level (NESIL) for citronellal was determined to be 7000 μg/cm^2. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; citronellal is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to citronellal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; citronellal was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(Gomes-Carneiro, 1998; RIFM, 2008b; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 20 mg/kg/day.	Ress (2003)
Developmental and Reproductive Toxicity: NOAEL = 60 mg/kg/day and 1000 mg/kg/day, respectively.	(RIFM, 2016b; MHW, 1996)
Skin Sensitization: NESIL = 7000 μg/cm^2.	(RIFM, 1977; Robinson, 1990; Basketter, 1996; Marzulli, 1980)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV spectra, RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 80%–90% (OECD 301B)	RIFM (2007)
Bioaccumulation: Screening-level: 156 L/kg	(EPI Suite v4.11; US EPA 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-hour *Daphnia magna* LC50: 1.048 mg/L	(EPI Suite v4.11; US EPA 2012a)

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: 48-hour *Daphnia magna* LC50: 1.048 mg/L	(EPI Suite v4.11; US EPA 2012a)

RIFM PNEC is: 0.1048 μg/L

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

1. Identification

Chemical Name: Citronellal	Chemical Name: 6-Octenal, 3,7-dimethyl-, (3S)-
CAS Registry Number: 106-23-0	**CAS Registry Number:** 5949-05-3
Synonyms: 3,7-Dimethyl-6-octenal; 6-Octenal, 3,7-dimethyl-; Rhodinal; 2,3-Dihydrocitral; シトロネラール; 3,7-Dimethyloct-6-enal; Citronellal Extra; Citronellal	**Synonyms:** *l*-Citronellal
Molecular Formula: $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$
Molecular Weight: 154.25	**Molecular Weight:** 154.25
RIFM Number: 156	**RIFM Number:** 6992

2. Physical data*

1. **Boiling Point:** 207 °C (Fragrance Materials Association [FMA]), 205.07 °C (EPI Suite)
2. **Flash Point:** 165 °F; CC (FMA)
3. **Log K_{OW}:** 3.53 (EPI Suite)
4. **Melting Point**: 28.33 °C (EPI Suite)
5. **Water Solubility:** 38.94 mg/L (EPI Suite)
6. **Specific Gravity:** 0.852–0.862 (FMA), 0.850–0.860 (FMA)

7. **Vapor Pressure:** 0.17 mm Hg at 20 °C (EPI Suite v4.0), 0.16 hPa at 20 °C; 0.26 hPa at 25 °C; 1.73 hPa at 50 °C, 0.1 mm Hg 20 °C (FMA), 0.254 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless to yellow liquid with intense, lemon citronella - rose odor

*Physical data is identical for both materials in this assessment.

3. Exposure***

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0019% (RIFM, 2016c)
3. **Inhalation Exposure*:** 0.000057 mg/kg/day or 0.0043 mg/day (RIFM, 2016c)
4. **Total Systemic Exposure**:** 0.0023 mg/kg/day (RIFM, 2014b)

*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 IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.1
I	I	I

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

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

Citronellal is reported to occur in the following foods and in some natural complex substances (NCS) by the VCF*:

Cardamom (*Elettaria cardamomum* Maton.)	Lemon grass oil
Celery (*Apium graveolens* L.)	Litchi (*Litchi chinensis* Sonn.)
Citrus fruits	Lovage (*Levisticum officinale* Koch)
Cocoa category	Macadamia nut (*Macadamia integrifolia*)
Ginger (*Zingiber* species)	*Ocimum* species
Juniperus comminus	Parsley (*Petroselinum* species)
Lamb's lettuce (*Valerianella locusta*)	Pepper (*Piper nigrum* L.)
Lemon balm (*Melissa officinalis* L.)	Tomato (*Lycopersicon esculentum* Mill.)

6-Octenal, 3,7-dimethyl-, (3S)- is reported to occur in the following foods by the VCF*:

Citrus fruits.

*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.

8. Reach dossier

Available; accessed 04/22/19. 6-Octenal, 3,7-dimethyl-, (3S)- (CAS # 5949-05-3) dossier is available; accessed 04/22/19.

9. Conclusion

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

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.41
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	0.026
4	Products related to fine fragrances	0.49
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.33
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.051
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.10
5D	Baby cream, oil, talc	0.017
6	Products with oral and lip exposure	0.82
7	Products applied to the hair with some hand contact	0.077
8	Products with significant ano-genital exposure (tampon)	0.017
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.4
10B	Aerosol air freshener	2.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.017
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 citronellal, the basis was the reference dose of 0.60 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 7000 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).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and usage levels, citronellal does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Citronellal was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2015). The mutagenic activity of citronellal (CAS # 106-23-0) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the revised plate incorporation method of Maron and Ames (Maron, 1983). *Salmonella typhimurium* strains TA97a, TA98, TA100, and TA102 were treated with citronellal in ethanol at concentrations up to 300 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Gomes-Carneiro, 1998). Under the conditions of the study, citronellal was not mutagenic in the Ames test. A mammalian cell gene mutation assay (HPRT) was also conducted according to OECD TG 476 and GLP guidelines. Chinese hamster lung cells (V79) were treated with citronellal in dimethyl sulfoxide (DMSO) at concentrations up to 128 μg/mL for 4 h. Effects were evaluated both with and without metabolic activation. No significant increases in the frequency of mutant colonies were observed with any dose of the test material, either with or without metabolic activation (RIFM, 2008b).

The clastogenic activity of citronellal 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 citronellal in DMSO at concentrations up to 1540 μg/mL in the presence and absence of metabolic activation (S9) at the 4-hour and 24-hour time points. Citronellal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems at the 4-hour time point. A statistically significant increase (Fisher's exact test) in binucleated cells with micronuclei was observed at the 24-hour time point without S9-activation but these increases were not dose-dependent. In order to confirm the effects observed at the 24-hour time point and also to comply with new OECD 487 guidelines adopted on September 26, 2014, the assay was repeated for a 24-hour non-activated treatment condition. Citronellal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in the non-activated test system at the 24-hour time point (RIFM, 2016a). Under the conditions of the study, citronellal was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: RIFM, 2006; EFSA, 2013.

Literature Search and Risk Assessment Completed On: 09/08/16.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on citronellal. The read-across analog citral (CAS # 5392-40-5; see Section V) has sufficient repeated dose toxicity data. A National Toxicology Program (NTP)-sponsored chronic dietary study was conducted in compliance with GLP on groups of 50 F344/N rats/sex/group. The animals were administered the test material citral (microencapsulated) 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, 2003). In another GLP study, groups 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. There were significant decreases in body weights among mid- and high-dose group male mice. Body weights were also significantly decreased among all treated females. 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 origin of the lymphomas in the vehicle control and the treatment-group animals. There was a positive trend in the incidences of hepatomas (hepatocellular adenoma or carcinoma) in females but of no statistical 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 among males was considered to be 60 mg/kg/day, and the LOAEL for non-neoplastic effects among females was considered to be 60 mg/kg/day, based on a decrease in body weight among treated animals. A NOAEL of 20 mg/kg/day was derived by dividing the LOAEL of 60 mg/kg/day among female mice by an uncertainty factor of 3 (Ress, 2003 [data also available in NTP, 2003];). The most conservative NOAEL for repeated dose toxicity was determined from a dietary 104- to 105-week carcinogenicity study in mice to be 20 mg/kg/day, based on reduced body weights. **Therefore, the citronellal 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 citronellal, 20/0.0023 or 8696.**

In addition, the total systemic exposure to citronellal (2.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Derivation of reference dose (RfD):

Section IX 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, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.6 mg/kg/day.

The RfD for citronellal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity

sections) of 20 mg/kg/day by the uncertainty factor 35, 20 mg/kg/day/35 = 0.6 mg/kg/day.

The RfD was derived based on the ECHA-REACH Derived No Effect Level for citral for General Population - Hazard via oral route (ECHA, 2011a; accessed 08/01/17).

Additional References: Jackson (1987); Dieter (1993); Hagan (1967); Bar (1967); Abramovici et al. (1983); Sandbank (1988); Abramovici et al. (1985); RIFM, 1958; Leach (1956); Shillinger (1950); Abramovici (1980); Toaff (1979); Howes (2002); Geldof (1992); Servadio (1986a); Servadio (1986b); Servadio (1987); Abramovici (1987); Scolnik (1994a); Scolnik (1994b); Engelstein (1996); Kessler (1998); Golomb (2001); Diliberto (1988a); Diliberto (1990); Diliberto (1989); Diliberto (1988b); Ishida (1989); Boyer (1990); Phillips (1976); Barbier (1983).

Literature Search and Risk Assessment Completed On: 12/23/16.

10.1.3. Developmental and reproductive toxicity

The MOE for citronellal is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on citronellal. The read-across analog citral (CAS # 5392-40-5; see Section V) has sufficient developmental and reproductive toxicity data.

A gavage developmental toxicity study was conducted on groups of 20 Wistar rats. The pregnant animals were treated with citral at dose levels of 0 (corn oil), 60, 125, 250, 500, or 1000 mg/kg/day on gestation days (GDs) 6–15. The study was terminated on GD 21. 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. 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 increased ratio of resorptions per implantations at higher doses (Nogueira, 1995).

An OECD 421 gavage reproductive 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 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 GD 20. 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. However, there was a significant decrease in the average pup body weight at birth among the high-dose group animals as compared to the control. Thus, the NOAEL the developmental toxicity was determined to be 160 mg/kg/day, based on reduced fetal weights among the high-dose group animals (Hoberman, 1989).

Another OECD/GLP 414 GLP gavage prenatal developmental toxicity study was conducted on groups of 25 pregnant female New Zealand white rabbits/group. The animals were administered the 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 GDs 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, and 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 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, 2016b).

The developmental toxicity study on rats (Nogueira, 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, 2016b) or among rats during the OECD 421 study (MHW, 1996). Furthermore, in the current ECHA dossier for citral, there is a proposal to conduct an OECD 443 extended one-generation reproductive toxicity study in rats. The safety assessment can be updated following the completion and review of that study, but the current data for citral based on OECD 421, OECD 414, and 2 additional reproductive toxicity studies are robust and sufficient to describe the developmental toxicity and fertility parameters (ECHA, 2011a).

Thus, 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/GLP 414 developmental toxicity study on rabbits (RIFM, 2016b; ECHA, 2011a).

Therefore, the citronellal MOE for the developmental toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citronellal, 60/0.0023 or 26087.

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

Therefore, the citronellal MOE for the reproductive toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citronellal, 1000/0.0023 or 434783.

In addition, the total systemic exposure to citronellal (2.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) **for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.**

Additional References: Jackson (1987); Dieter (1993); Hagan (1967); Bar (1967); Abramovici et al. (1983); Sandbank (1988); Abramovici et al. (1985); RIFM, 1958; Leach (1956); Shillinger (1950); Abramovici (1980); Toaff (1979); Howes (2002); Geldof (1992); Servadio (1986a); Servadio (1986b); Servadio (1987); Abramovici (1987); Scolnik (1994a); Scolnik (1994b); Engelstein (1996); Kessler (1998); Golomb (2001); Diliberto (1988a); Diliberto (1990); Diliberto (1989); Diliberto (1988b); Ishida (1989); Boyer (1990); Phillips (1976); Barbier (1983).

Literature Search and Risk Assessment Completed On: 12/23/16.

10.1.4. Skin sensitization

Based on the material specific data, citronellal is considered to be a weak skin sensitizer with a defined NESIL of 7000 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, citronellal does not present a concern for skin sensitization. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree v2.6.6; OECD Toolbox v3.3). In a Guinea Pig Maximization Test (GPMT), 4 of the 8 guinea pigs exhibited reactions indicative of sensitization with 3% citronellal (RIFM, 1977). In a human maximization test conducted on 25 subjects, no reactions indicative of sensitization were observed with 4% citronellal (2760 μg/cm^2) (RIFM, 1973). In a human repeat insult patch test (HRIPT), citronellal did not induce sensitization reactions at 6% or 7086 μg/cm^2 (RIFM, 2014a). Based on the material specific data, citronellal is considered to be a weak skin sensitizer with a defined NESIL of 7000 μg/cm^2 (Table 1). Section IX 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, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.6 mg/kg/day.

Additional References: Marzulli (1980); Klecak (1977); Klecak (1979); Ishihara et al. (1986); Robinson (1990); Kashima et al. (1993a); Kashima et al. (1993b); Basketter (1996); Coutant (1999); Klecak (1985).

Literature Search and Risk Assessment Completed On: 09/21/16.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, citronellal would not be expected to present a concern for phototoxicity or photoallergenicity.

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

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/16.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are insufficient inhalation data available on citronellal. Based on the Creme RIFM Model, the inhalation exposure is 0.0043 mg/day. This exposure is 326 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: Jager (1992): Buchbauer (1993): Rice (1994).bib_Rice_and_Coats_1994

Literature Search and Risk Assessment Completed On: 03/20/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of citronellal 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, citronellal 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 citronellal as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 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

Table 1
Data summary for citronellal.

Local Lymph Node Assay (LLNA) weighted mean EC3 value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
>7500 [1]	Weak	7086[d]	2760[d]	NA	7000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in HRIPT or HMT studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL.

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.

10.2.2. Risk assessment

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

10.2.2.1. Key studies. ***Biodegradation:***

RIFM, 1994: The ready biodegradability of the test material was determined by the Manometric Respirometry test following the OECD 301F method. Citronellal at 100 mg/L underwent 61% biodegradation after 28 days.

RIFM, 2007: A study was conducted to determine the ready biodegradability of the test material by the measurement of formed carbon dioxide according to the OECD 301B method. 80%–90% CO_2/ThCO_2 was observed after an exposure period of 28 days (mean value from 2 assays).

Ecotoxicity: No data available.

Other available data:

Citronellal has been registered under REACH and the following additional data is available:

A 96-hour fish (*Leuciscus idus*) acute study was conducted according to the DIN 38 412 part L15 method. The 96-hour LC50 was reported to be 22 mg/L.

A *Daphnia magna* acute toxicity test according to EU Directive 78/831 EEC Annex 5 part C was conducted with citronellal. The 48-hour EC50 was reported to be 8.7 mg/L.

A 72-hour algae inhibition test was conducted according to the DIN 38 412 part 9 method. The EbC50 and ErC50 were reported to be 133 mg/L and 6.76 mg/L, respectively (ECHA, 2011b).

10.2.3. Risk assessment refinement

Since citronellal has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.53	3.53
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100*	10–100*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined volumes for both CAS #s.

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

The RIFM PNEC is 0.1048 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, citronellal does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/14/19.

11. 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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	9.707			1000000	0.0097	
ECOSAR Acute Endpoints **(Tier 2) *v1.11***	1.393	1.048	2.261	10000	0.1048	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2) *v1.11***	5.348 l	3.498	4.674			Neutral Organics

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 04/22/19.

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

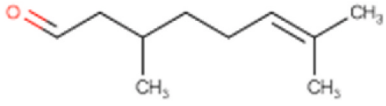
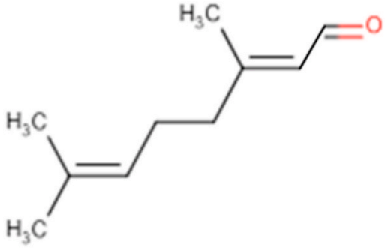
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.111991.

Appendix

Read-across Justification

Methods

- The identified read-across analog was confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and read-across analog were calculated using EPI Suite v4.11 developed by US EPA (US EPA, 2012a).
- The J_{max} values were calculated using the RIFM skin absorption model (SAM), and the parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were estimated using the OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental and reproductive toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target material and read-across analog were determined and evaluated using the OECD QSAR Toolbox (v3.4) (OECD, 2018).

	Target Material	Read-across Material
Principal Name	6-octenal, 3,7-dimethyl (citronellal)	3,7-dimethyl-2,6-octadienal (citral)
CAS No.	**106–23–0** and 5949-05-3	5392-40-5
Structure		
Similarity (Tanimoto Score)		0.863
Read-across Endpoint		• Repeated dose toxicity • Developmental and Reproductive toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{16}O$
Molecular Weight	154.25	152.23
Melting Point (°C, EPI Suite)	−28.33	−26.74
Boiling Point (°C, EPI Suite)	205.07	217.44
Vapor Pressure (Pa @ 25 °C, EPI Suite)	33.9	12.2
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.83	3.00
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	38.94	1340
J_{max} (μg/cm^2/h, SAM)	52.35	119.841
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.88E+001	3.81E+001
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Respiratory		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Respiratory Sensitization OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Metabolism		
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2
Rat Liver S9 Metabolism Simulator		

Summary

There is insufficient toxicity data on citronellal (CAS # 106-23-0). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, citral (3,7-dimethyl-2,6-octadienal) (CAS # 5392-40-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Citral (3,7-dimethyl-2,6-octadienal) (CAS # 5392-40-5) can be used as a structurally similar read-across analog for the target material citronellal (CAS # 106-23-0) for the developmental and reproductive toxicity and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target material and the read-across analog have the 1-methyl hex-1-ene fragment common among them.
  - o The key difference between the target material and the read-across analog is that the read-across is an α,β-unsaturated aldehyde, while the target material does not have α-β-unsaturation to the aldehyde group. Because the read-across analog has an activated aldehyde group, it will form a direct-acting Schiff base and be a Michael acceptor, therefore raising toxicity compared to the target material for systemic toxicity endpoints and will be more reactive for the developmental and reproductive toxicity and repeated dose toxicity endpoint perspective.
  - o The target material and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the 1-methyl hex-1-ene fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicity endpoint perspective.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the respiratory toxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for respiratory toxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints are consistent between the target material and the read-across analog.
  - o According to the metabolic simulator, the read-across analog is expected to undergo metabolism and form a Schiff base at the activated aldehyde group. The target material will not have similar metabolism as seen for the read-across analog. The read-across analog, however, has a methyl-substituted β-carbon, which electronically hinders the Michael addition as well as Schiff base formation reactions by orders of magnitude since the proton is not available on the β-carbon. Therefore, although the read-across analog has more reactive and different metabolic pathways of bioactivation, the probability for this route is low.
  - o The structural alerts for respiratory toxicity, developmental and reproductive toxicity, and repeated dose toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

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