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Short Review

RIFM fragrance ingredient safety assessment, citral, CAS Registry Number 5392-40-5

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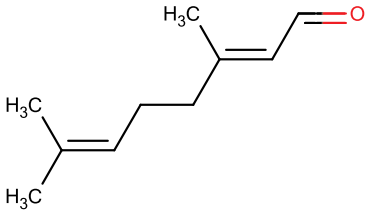
Name: Citral
CAS Registry Number: 5392-40-5
Additional CAS Numbers: 106-26-3 Neral
141-27-5 Geranial



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., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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 et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
Citral was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that citral is not genotoxic. Data on citral provide a calculated margin of exposure (MOE) $>$ 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. Data provided citral a No Expected Sensitization Induction Level (NESIL) of 1400 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet (UV) spectra; citral 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 citral is below the TTC (1.4 mg/day).The environmental endpoints were evaluated; citral 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	(NTP, 2003; ECHA REACH Dossier: Citral; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 20 mg/kg/day	(Ress et al., 2003)
Developmental and Reproductive Toxicity:	
Developmental NOAEL = 60 mg/kg/day. Reproductive NOAEL = 1000 mg/kg/day	(RIFM, 2016a; MHW, 1996)

Skin Sensitization: NESIL = 1400 μg/cm^2 RIFM (2008b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra RIFM Database; RIFM, 1975)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 92.1% (OECD 301B) RIFM (1994)
Bioaccumulation: Screening-level: 87.14 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 96-h fish LC50: 6.78 mg/L (ECHA REACH Dossier: Citral; ECHA, 2011)
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: 96-h fish LC50: 6.78 mg/L (ECHA REACH Dossier: Citral; ECHA, 2011)
RIFM PNEC is: 6.78 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

1. Identification

Chemical Name: Citral	Chemical Name: Geranial	Chemical Name: Neral
CAS Registry Number: 5392-40-5	**CAS Registry Number:** 141-27-5	**CAS Registry Number:** 106-26-3
Synonyms: Citral pure; 3,7-Dimethyl-2,6-octadienal; Geranial and neral; Lemarome; Neral and geranial; 2,6-Octadienal, 3,7-dimethyl-; Citral Lemarome N; ｼﾄﾗｰﾙ; 3,7-Dimethylocta-2,6-dienal; Citral E.Q.; Citral Extra; Citral refined; Citral P; Citral N; Citral	**Synonyms:** α-Citral; Citral a; 3,7-Dimethylocta-2,6-dienal; 2,6-Octadienal, 3,7-dimethyl-, (E)-	**Synonyms:** Citral b; 3,7-Dimethylocta-2,6-dienal; 2,6-Octadienal, 3,7-dimethyl-, (Z)-
Molecular Formula: $C_{10}H_{16}O$	**Molecular Formula:** $C_{10}H_{16}O$	**Molecular Formula:** $C_{10}H_{16}O$
Molecular Weight: 152.24	**Molecular Weight:** 152.24	**Molecular Weight:** 152.24
RIFM Number: 116	**RIFM Number:** 544	**RIFM Number:** 555

2. Physical data*

1. **Boiling Point:** 230 °C (Fragrance Materials Association [FMA]), (calculated) 217.44 °C (EPI Suite)
2. **Flash Point:** 195 °F; CC (FMA)
3. **Log K_{OW}:** 3.0 and 3.1 at 35 °C (2 isomers) (RIFM, 2006), 3.45 (EPI Suite)
4. **Melting Point**: 26.74 °C (EPI Suite)
5. **Water Solubility:** 0.07% w/V (RIFM, 1990), (calculated) 84.71 mg/L (EPI Suite)
6. **Specific Gravity:** 0.887–0.893 (FMA), 0.885–0.891 (FMA)
7. **Vapor Pressure:** 0.0596 mm Hg @ 20 °C (EPI Suite v4.0), 0.07 mm Hg 20 °C (FMA), 0.0913 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Light, oily, pale yellow liquid with strong lemon odor

*Physical data are identical for all materials included in this assessment.

3. Exposure***

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.075% (RIFM, 2016b)
3. **Inhalation Exposure*:** 0.00090 mg/kg/day or 0.066 mg/day (RIFM, 2016b)
4. **Total Systemic Exposure**:** 0.0072 mg/kg/day (RIFM, 2016b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 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 et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 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

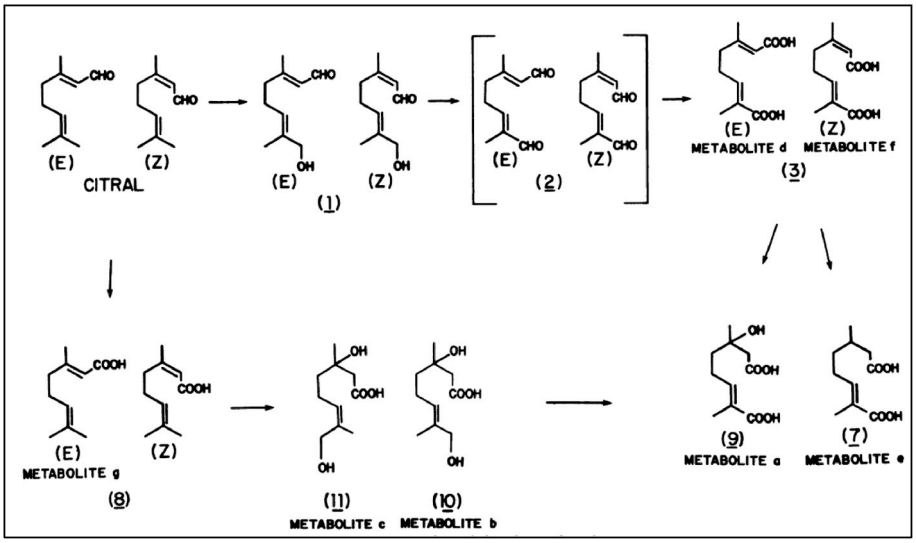
Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

6. Metabolism

Diliberto et al., 1990: Male fisher 344 rats were administered citral (2:1 mixture of geranial/neral) either via gavage or i.v. The citral dosing solutions for gavage studies were prepared in 1:1:3 ethanol:emulphor EL-620:water and administered at doses of 5 or 500 mg/kg/day. For i.v. dosing, the solution was prepared in 1:1:8 ethanol:emulphor EL-620:water and administered via femoral vein at a dose of 5 mg/

kg/day. Radiolabeled citral was diluted as needed with unlabeled citral to administer 1 μCi per rat. The animals that were gavaged with citral were housed in individual metabolism cages for separate collection of excreta over 24 h. An HPLC analysis was performed, and since there was no difference between the metabolites observed, further studies were done with only the high dose to obtain more mass for NMR and mass spectrometry identification of metabolites. For the animals that were treated with i.v. administration, their common bile duct was cannulated, and the bile was collected for further analysis. Urine was collected after administration via both routes of administration. The urine was collected and sampled for analysis at 2, 7, and 24 h after dosing. The bile was collected at 5, 30, 60, and 270 min after dosing. The pooled samples of urine and bile from treated animals were analyzed for metabolite identification. The urine and bile samples were subjected to hydrolysis by β-glucuronidase or sulfatase by incubation for 16–36 h at 37 °C. The analysis of the samples was done via HPLC, GC, liquid scintillation counting, UV-absorbance, 1H-NMR spectra, and mass spectrometry. Elimination in urine was rapid, with approximately 50% of the dose excreted in 24 h. A total of 7 urinary metabolites were characterized, with 4 unequivocally identified by comparison of NMR spectra with synthetic standards and 3 tentatively identified based on spectra alone. The identified metabolites result from reduction or hydration of the 2,3-double bond, oxidation of the aldehyde function, and allylic oxidation at C-8, and possibly, C-9. Enzymatic hydrolysis did not appear to affect the chromatographic profile of urinary radioactivity. However, the biliary profile changed after glucuronidase treatment. Sulfatase treatment appeared to have no effect. The authors concluded that although citral is an α,β-unsaturated aldehyde and thus has the potential of being reactive, the urinary metabolites appear to arise from metabolic pathways other than nucleophilic addition to the double bond. The metabolites identified included: 3-hydroxy-3,7,dimethyl-6-octenedioic acid; 3,8-dihydroxy-3,7-dimethyl-6-octenoic acid; 3,9-dihydroxy-3,7-dimethyl-6-octenoic acid; E − 3,7-dimethyl-2,6-octadienedioic acid; 3,7-dimethyl-6-octenedioic acid; Z-3,7-dimethyl-2,6-octadienedioic acid. E − 3,7-Dimethyl-2,6-octadienoic acid and glucuronic acid conjugates were only present in bile. The general proposed metabolic scheme is given below:



Diliberto et al., 1988b: The effect of citral dosing on the route of administration, absorption, distribution, and elimination in male Fischer 344 rats was studied. Male rat Fischer 344 rats (n ≥ 3) were administered citral via gavage, dermal, or intravenous routes. The radiolabeled citral was diluted with unlabeled citral to administer 1 μCi/rat for oral administration and 0.5 μCi/rat for i.v. administration. Gavage doses were 5, 50 or 500 mg/kg/day, and the i.v. dose administered was 5 mg/kg/day. For dermal application, [^{14}C]-Citral was administered at 5 and 50 mg/kg/day on the animal's intrascapular area after removing the fur. The urine, feces, expired air, blood, liver, kidneys, adrenals, thymus, spleen, brain, heart, lungs, testes, skin, adipose tissue, muscle, stomach contents, small intestine contents, large intestine contents, tail site (for i.v. application), and bile were sampled for analysis. The excreta samples were collected at various time points from 2 to 72 h; tissue samples were collected at sacrifice after 72 h; bile samples were collected at various time points from 5 to 240 min after dosing by cannulation of the common bile duct; blood samples were collected at various time points from 1 to 240 min p.a. by cannulation of the jugular vein. The total air flow through the metabolism cages was continuously passed through 2 consecutive traps for air sample analysis, a charcoal trap to collect volatile air, and a bubbler trap containing a mixture of ethanolamine and ethylene glycol mono-methyl ether to trap expired CO_2. After oral administration, 83% of the administered dose was recovered within 72 h. The major portion was recovered in the urine (51%) followed by CO_2 (17%), feces (12%), tissues (3%), and exhaled as [^{14}C]-citral (< 1%). The chemical disposition was not affected by increasing dose, thus indicating that the disposition was not affected by dose and overall transport and metabolism of citral was not saturated by dose. Citral-derived radioactivity was widely distributed in the body 72 h after exposure, with the highest amount in the muscle, skin, adipose tissue, liver, and blood. There was no evidence of depot after citral administration. The principal route of excretion was urine, but the liver and lungs were also important excretory organs for citral. During mass balance after dermal application of citral, 24% of the administered dose was found on the charcoal metallic caps and hence was not available for absorption. Approximately 29% of the administered dose was excreted within 72 h. Total recovery of radioactivity was approximately 68%, of which 17% was recovered in the urine, about 8% recovered in the tissues, 3% in feces, 4% in expired air, and 8% at the dermal application site. The loss of citral was attributed to evaporation from the site of application and not due to loss of citral-derived radioactivity from the air flow system. After i.v. administration, the recovery of radioactivity was 79% within 72 h, of which 57% was recovered in the urine, 6% in tissues, 7% in feces, and 8% in expired air. After i.v. exposure, most of the citral-derived radioactivity was rapidly eliminated from the body with a whole-body half-life of 8 h. Although feces was not the major route of elimination for citral after i.v. administration, elimination via bile was studied to determine whether enterohepatic circulation played a role in the

distribution of citral-derived radioactivity. Bile was collected for 4.5 h after treatment. At 5 mg/kg/day, 20% of the total dose was excreted in the bile within the first hour, and another 7% appeared by 4.5 h of administration. The amount excreted in the bile was 4 times higher than that excreted in the feces within 3 days. Overall, the metabolism of citral was both rapid and extensive. Within 5 min of i.v. dosing, no unmetabolized citral could be detected in the blood. The rapid excretion of citral suggested that there may not be a significant increase in citral bioaccumulation. In conclusion, cumulative excretion profiles of citral-derived radioactivity for different routes of administration were similar. Citral was well absorbed orally and appeared to be moderately absorbed dermally, considering the volatility of the compound. The tissue distribution was widespread, and there was no evidence of depot.

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

Citral is reported to occur in the following foods by the VCF*:
Citrus fruits.
Lemon peel oil (*Citrus limon Burm.* f.)
Lime oil (coldpressed).
Pistacia atlantica.
Pistacia atlantica, Oleoresin ess. oil.
Thyme (*Thymus* species).

Geranial is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):
Acerola (*Malpighia*).
Apricot (*Prunus armeniaca* L.)
Black currants (*Ribes nigrum* L.)
Calabash nutmeg (*Monodora myristica* Dunal).
Cape gooseberry (*Physalis peruviana* L.)
Cardamom (*Ellettaria cardamomum* Maton.)
Chervil (*Anthriscus cerefolium* L.)
Chinese quince (*Pseudocydonia sinensis* Schneid).
Cinnamomum species Citrus fruits Cloves (*Eugenia caryophyllata* Thunberg).
Coriander seed (*Coriandrum sativum* L.)
Dragonhead (*Dracocephalum moldavica* L.)
Elderberry (*Sambucus nigra* L.)
Ginger (*Zingiber* species).
Grape (*Vitis* species).
Guava and feyoa Hop (*Humulus lupulus*).
Kiwifruit (*Actinidia chinensis*, syn. *A. deliciosa*).
Laurel (*Laurus nobilis* L.)
Lemon balm (*Melissa officinalis* L.)
Lemon grass oil Litchi (*Litchi chinensis* Sonn.)
Lovage (*Levisticum officinale* Koch).
Macadamia nut (*Macadamia integrifolia*).
Mangifera species Mastic (*Pistacia lentiscus*).
Mate (*Ilex paraguayensis*).
Melon Mentha oils Myrtle (*Myrtus communis* L.)
Ocimum species Origanum (Spanish) (*Coridothymus cap*.(L.) Rchb.)
Passion fruit (*Passiflora* species).
Pistachio oil (*Pistacia* vera).
Plum (*Prunus* species).
Quince, marmelo (*Cydonia oblonga* Mill.)
Raspberry, blackberry, and boysenberry Rooibos tea (*Aspalathus linearis*).
Salvia species Syzygium species Tamarind (*Tamarindus indica* L.)
Tapereba, caja fruit (*Spondias lutea* L.)
Tea Thyme (*Thymus* species).
Tomato (*Lycopersicon esculentum* Mill.)
Turpentine oil (*Pistacia terebinthus*).
Vaccinium species Wormwood oil (*Artemisia absinthium* L.)

Neral is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):
Acerola (*Malpighia*).
Cardamom (*Ellettaria cardamomum* Maton.)
Celery (*Apium graveolens* L.)
Chervil (*Anthriscus cerefolium* L.)
Chinese quince (*Pseudocydonia sinensis* Schneid).
Cinnamomum species Citrus fruits Curry (*Bergera koenigii* L.)
Dragonhead (*Dracocephalum moldavica* L.)
Elderberry (*Sambucus nigra* L.)
Ginger (*Zingiber* species).
Grape (*Vitis* species).
Guava and feyoa Honey Hop (*Humulus lupulus*).
Kiwifruit (*Actinidia chinensis*, syn. A. deliciosa).
Laurel (*Laurus nobilis* L.)
Lemon balm (*Melissa officinalis* L.)
Lemon grass oil Litchi (*Litchi chinensis* Sonn.)
Lovage (*Levisticum officinale* Koch).
Macadamia nut (*Macadamia integrifolia*).
Mangerifera speciesMastic (*Pistacia lentiscus*).
Mate (*Ilex paraguayensis*).
Melon Mentha oils Myrtle (*Myrtus communis* L.)
Ocimum species Okra (*Hibiscus esculentus* L.)
Origanum (Spanish) (*Coridothymus cap*.(L.) Rchb.)
Passion fruit (*Passiflora* species).
Pistachio oil (*Pistacia vera*).
Plum (*Prunus* species).
Quince, marmelo (*Cydonia oblonga* Mill.)
Raspberry, blackberry, and boysenberry Rooibos tea (*Aspalathus linearis*).
Salvia species Syzygium species Tamarind (*Tamarindus indica* L.)
Tea Tequila (*Agave tequilana*).
Thyme (*Thymus* species).
Tomato (*Lycopersicon esculentum* Mill.)
Walnut (*Juglans* species).
Wormwood oil (*Artemisia absinthium* L.)

*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 03/17/20.

9. Conclusion

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

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.11
2	Products applied to the axillae	0.032
3	Products applied to the face/body using fingertips	0.10
4	Products related to fine fragrances	0.60
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.15
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.15
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.15
5D	Baby cream, oil, talc	0.051

6	Products with oral and lip exposure	0.35
7	Products applied to the hair with some hand contact	0.20
8	Products with significant ano-genital exposure (tampon)	0.051
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.2
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.2
10B	Aerosol air freshener	4.2
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.051
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 citral, the basis was the reference dose of 0.6 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 1400 μg/cm^2.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Citral was tested in the BlueScreen assay and was found positive for genotoxicity in the presence of metabolic activation, indicating genotoxic potential (RIFM, 2013). The mutagenic activity of citral was assessed in an Ames assay conducted according to OECD 471 using the preincubation method. *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with citral at concentrations ranging from 1 to 220 μg/plate in the presence and absence of metabolic activation (S9). There were no significant increases in revertant colonies (NTP, 2003). Under the conditions of the study, citral was considered negative for mutagenicity 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 citral in dimethyl sulfoxide (DMSO) at concentrations up to 100 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, either with or without metabolic activation (ECHA, 2011).

The clastogenic activity of citral was assessed by the National Toxicology Program (NTP). In an *in vitro* Sister Chromatid Exchange (SCE) assay (OECD TG 479), citral was shown to induce SCEs in Chinese hamster ovary cells (CHO) with and without S9 mix at doses > 7.5 mg/mL in the presence of S9 and at all doses tested in absence of S9. A subsequent *in vitro* chromosome aberration study (OECD TG 473) demonstrated no significant increase in chromosomal aberrations after exposure, with or without S9. To confirm these results, an *in vivo* micronucleus assay was conducted in accordance with OECD TG 474. Groups of male B6C3F1 mice were injected intraperitoneally 3 times at 24-h intervals with 250–1000 mg/kg body weight in corn oil. Animals were euthanized 24 h after the third injection and bone marrow was assessed. There were no increases in polychromatic erythrocytes in the treatment groups compared to the control (National Toxicology Program, 2003). Under the conditions of the study, citral was considered negative in the *in vivo* micronucleus assay.

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

Additional References: Ishidate et al., 1984; Lutz et al., 1982; Eder et al., 1982; Yoo (1986); Zeiger et al., 1987; Kuroda et al., 1984; Carneiro et al., 1997; Gomes-Carneiro et al., 1998; Duerksen-Hughes et al., 1999; Yoo, 1986; Oda et al., 1978; Lopez et al., 2011.

Literature Search and Risk Assessment Completed On: 09/07/16.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on citral. There are no repeated dose toxicity data on neral or geranial. An NTP-sponsored chronic dietary study was conducted in compliance with GLP on groups of 50 F344/N rats/sex/group. The animals were administered 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 et al., 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 that were 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 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. The derived NOAEL was determined to be 20 mg/kg/day (Ress et al., 2003; data also available in NTP, 2003). The most conservative NOAEL for repeated dose toxicity was determined from a dietary 104–105 week carcinogenicity study in mice to be 20 mg/kg/day, based on reduced body weights. **Therefore, the citral 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 citral, 20/0.0072 or 2778.**

In addition, the total systemic exposure to citral (7.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1.1. 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

Table 1
Data summary for citral.

LLNA weighted mean EC3 value [No. Studies] μg/cm[b]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm[b]	NOEL-HMT (induction) μg/cm[b]	LOEL[b] (induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
1414 [11]	Weak	1400	NA	3876	1400

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.

Risk Assessment (QRA2) described by Api et al. (RIFM, 2008b; 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 reference dose for citral 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 = 0.6 mg/kg/day.

The RfD was derived based on the ECHA-REACH DNEL for citral for General Population - Hazard via oral route (ECHA, 2011; accessed 08/01/17).

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

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

10.1.3. Developmental and Reproductive Toxicity

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

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on citral. There are no developmental and reproductive toxicity data on neral or geranial.

A gavage developmental toxicity study was conducted on groups of 20 Wistar rats. The pregnant animals were treated with the 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. 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 et al., 1995).

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 (Ministry of Health and Welfare, 1996).

A reproductive toxicity screening study was conducted on 30 female Sprague Dawley rats/group that 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. 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. 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 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 (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 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 the 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, 2106).

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, 2106) 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, 2106a; ECHA, 2011).

Therefore, the citral MOE for the developmental toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citral, 60/0.0072 or 8333.

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. The NOAEL for reproductive toxicity was determined to be 1000 mg/kg/day.

Therefore, the citral MOE for the reproductive toxicity endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to citral, 1000/0.0072 or 138889.

In addition, the total systemic exposure to citral (7.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

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

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

10.1.4. Skin Sensitization

Based on the available data, citral is considered to be a skin sensitizer with a defined NESIL of 1400 μg/cm^2.

10.1.4.1. Risk assessment. Citral is predicted to be reactive to skin proteins by both a Schiff base and Michael addition mechanism (OECD Toolbox V3.1; Roberts and Natsch, 2009; Toxtree 2.5.0). The weighted mean EC3 value from 11 Local Lymph Node Assay (LLNA) studies was 1414 μg/cm^2 (RIFM, 2008b). In a human repeat insult patch test (HRIPT) citral did not induce sensitization reactions at 1.2% (1400 μg/cm^2) (RIFM, 2004c) but did induce 5 sensitization reactions at 5% (3876 μg/cm^2) (RIFM, 1964b). The available data demonstrate that citral is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 1400 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: Brulos et al., 1977; Sharp (1978); Maisey and Miller, 1986 RIFM, 1971a; Klecak et al., 1977; Steltenkamp et al., 1980; Ishihara et al., 1986; RIFM, 1974; RIFM, 1971b; Johnson and Goodwin, 1985; Goodwin and Johnson, 1985; RIFM, 1973; RIFM, 1972a; RIFM, 1972b; RIFM, 1972c; RIFM, 1964a; RIFM, 1965; Basketter and Allenby, 1991; Basketter et al., 1991; Basketter et al., 1991; Hatao et al., 1995; Coutant et al., 1999; Watanabe et al., 2001; Basketter et al., 2002; RIFM, 2002; RIFM, 2003a; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; RIFM, 2003e; RIFM, 2003f; RIFM, 2003g; RIFM, 2003h; RIFM, 2003i; Basketter et al., 2003; Klecak (1985); RIFM, 2003j; Lalko and Api, 2004a; RIFM, 2004a; RIFM, 2004b; RIFM, 1982; Lalko and Api, 2004b; Takeyoshi et al., 2005; Lalko and Api, 2006; RIFM, 2005a; RIFM, 2005b; Patlewicz et al., 2003; Piccotti et al., 2007; Azam et al., 2005; Environmental Protection Agency, 1972; RIFM, 1984; RIFM, 1977; RIFM, 1981a; RIFM, 1981b.

Literature Search and Risk Assessment Completed On: 06/06/16.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra and data from a human study, citral does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In an exploratory human phototoxicity study, moderate erythema was observed in 3/29 subjects following application of 20% citral and UV irradiation (RIFM, 1975), but the authors did not deem it phototoxic. In addition, the maximum acceptable concentration in finished products (see Section IX) is limited based on skin sensitization to well below the level at which reactions were seen in the human study. Based on the lack of significant absorbance in the critical range and available human data, citral does not present a concern for phototoxicity or photoallergenicity at the current levels of use.

10.1.5.2. UV spectra analysis. The available UV/Vis spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/16.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There is insufficient data available on citral. Based on the Creme RIFM Model, the inhalation exposure is 0.066 mg/day. This exposure is 21.2 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

10.1.6.2. Key studies. None.

Additional References: RIFM, 1978; York et al., 1989; Boyd and Sheppard, 1970; Cattarelli et al., 1977; Gaworski et al., 1992; UGCM, 1997; Buchbauer et al., 1993; Gaworski et al., 1993; Komori et al., 1995; Ellis and Baxendale, 1997; Rice and Coats, 1994.

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of citral was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the

PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, citral 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, 2012b) did not identify citral as persistent and bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

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

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 2007: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Citral at 100 mg/L underwent 58% biodegradation after 28 days.

RIFM, 1991a: A biodegradation test was conducted with citral according to the Method F in The Assessment of Biodegradability method. Biodegradation was 99.5% by day 19.

RIFM, 1991b: The Ready Biodegradability of the test material was determined by the Respirometric Method (modified MITI Test) according to the OECD 301C method. Citral at 100 mg/L underwent 72% biodegradation after 28 days.

RIFM, 1994: A biodegradation study was carried out with citral using the sealed vessel test based on OECD 301B guideline. Citral at 10 mg/L underwent 92.1% biodegradation after 28 days.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.3. Other available data. Citral is registered under REACH and additional data is available (ECHA, 2011).

A 96-h fish (*Leuciscus idus*) acute study was conducted according to the DIN 38412 part L method. The LC50 was reported to be 6.78 mg/L.

A *Daphnia magna* 48-h acute toxicity test was conducted according to the Directive 79/831 EWG, C2 annex V. The EC50 of 6.8 mg/L was reported.

A 72-h algae acute study according to the DIN 38412 L9 method. The EbC50 (concentration at which a 50% reduction of biomass is observed) and ErC50 (concentration at which a 50% inhibition of growth rate is observed) were reported to be 16.1 mg/L and 103.8 mg/L, respectively.

10.2.2. Risk assessment Refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	27.70			1,000,000	0.0277	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.162	5.794	5.143	10,000	0.0162	Vinyl/Allyl Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	7.018	4.823	3.762			Neutral Organic
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	6.78			1000	6.78	
Daphnia		6.8				
Algae		16.1				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.0	3.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 6.78 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/13/19.

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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 06/03/19.

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.

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