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Short review

RIFM fragrance ingredient safety assessment, Citronellyl nitrile, CAS Registry Number 51566-62-2

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1. Identification

1. **Chemical Name:** Citronellyl nitrile
2. **CAS Registry Number:** 51566-62-2
3. **Synonyms:** Agrunitril; Citronellyl nitrile; 3,7-Dimethyl-6-octenenitrile; 6-Octenenitrile, 3,7-dimethyl-; Citronellal nitril; アルキル（又はアルケニル、C = 8～18）ニトリル; 3,7-Dimethyloct-6-enenitrile
4. **Molecular Formula:** $C_{10}H_{17}N$
5. **Molecular Weight:** 151.25
6. **RIFM Number:** 884

2. Physical data

1. **Boiling Point:** 233.15 °C [US EPA, 2012]
2. **Flash Point:** 175 °F; CC [FMA database]
3. **Log K_{OW}:** log Pow = 3.5 [RIFM, 1997b], 3.55 [US EPA, 2012]
4. **Melting Point:** −8.64 °C [US EPA, 2012]
5. **Water Solubility:** 37.76 mg/l [US EPA, 2012]

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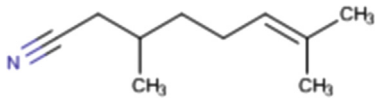
0278-6915/

Version: 053117. This version replaces any previous versions.
Name: Citronellyl nitrile
CAS Registry Number: 51566-62-2



Abbreviation 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; Safford et al., 2015; 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
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
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
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
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 under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (*i.e.*, 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Target data show that this material is not genotoxic. An acceptable MOE >100 was calculated for the repeated dose toxicity, developmental and reproductive toxicity endpoints. Data from the read across analog 2,2,5,9-tetramethyl-4,8-decadienenitrile (CAS # 58260-78-9) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and target data. The environmental endpoints were evaluated and the material was not found to be PBT as per IFRA environmental standards; its risk quotients, based on current volume of use in Europe and North America, were acceptable (PEC/PNEC < 1).

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1980a; ECHA REACH Dossier: citronellyl nitrile; RIFM, 2004)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day.	(RIFM, 2008a)
Developmental and Reproductive Toxicity: NOAEL = 500 mg/kg/day.	(RIFM, 2011)
Skin Sensitization: Not sensitizing.	(RIFM, 1975c; RIFM, 1977; RIFM, 1980c)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB; RIFM, 1980b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 69% (OECD 301F)	(RIFM, 1997a)
Bioaccumulation: Screening Level: 102 l/kg	(US EPA, 2012)
Ecotoxicity: Critical Ecotoxicity Endpoint: *Daphnia magna* 48-hr EC50: 11.4 mg/l	(RIFM, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) >1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: *Daphnia magna* 48-hr EC50: 11.4 mg/l	(RIFM, 2012b)
RIFM PNEC is: 11.4 μg/l	
• Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe <1	

6. **Specific Gravity:** 0.853 [FMA database]
7. **Vapor Pressure:** 0.0429 mm Hg @ 20 °C [US EPA, 2012], 0.06 mm Hg 20 °C [FMA database], 0.0663 mm Hg @ 25 °C [US EPA, 2012]
8. **UV Spectra:** Does not significantly absorb in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1}).
9. **Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a medium odor (fresh lemon metallic citrus waxy floral) at 10% solution or less*.

*http://www.thegoodscentscompany.com/data/rw1008932.html, retrieved 08/23/13.

3. Exposure

1. **Volume of Use (Worldwide Band):** > 1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.059% (RIFM, 2016b)
3. **Inhalation Exposure*:** 0.00074 mg/kg/day or 0.055 mg/day (RIFM, 2016b)
4. **Total Systemic Exposure**:** 0.0029 mg/kg/day (RIFM, 2016b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

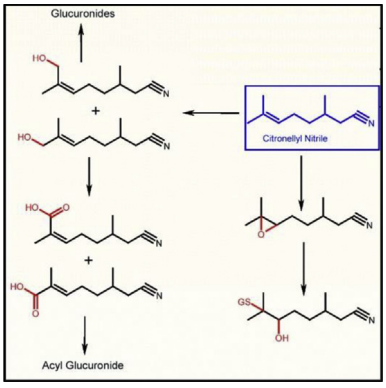
1. **Cramer Classification:** Class III, High

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2,2,5,9-tetramethyl-4,8-decadienenitrile (CAS # 58260-78-9)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read across justifications:** None

6. Metabolism

Kemper et al., 2006: The metabolism of test material, citronellyl nitrile was evaluated in primary hepatocytes of mice, rats and humans in order to identify the major metabolites of the test material. Primary human, mouse and rat hepatocytes were used for the metabolism studies. The test material was incubated with the hepatocytes for 60 min at a concentration of 250 μM after which the cells were lysed, processed and later analyzed via GC/MS (organic part) and LC/MS (aqueous phase). The phase 1 metabolites were identified via GC/MS and phase 2 metabolites were identified via LC/MS. The metabolic clearance rates were determined from the rate of disappearance of the test material. The mouse hepatocytes were observed to clear the test material 2 times faster than the rats. Differences in the human hepatocytes were also reported, where 2 of the 3 hepatocyte donors metabolized the test material much more slowly as compared to the rodents and the third donor metabolized the test material at rates comparable to the rats. From the rat hepatocytes, only 5 phase 1 metabolites could be identified by comparison to the synthetic standards used or spectral similarity to the standards or published spectra. Of the phase 1 metabolites identified, 4 of them were common among all species tested. The phase 1 metabolites identified included: 1) 6,7-epoxy-citronellyl nitrile (isomers), 2) 5-hydroxycitronellyl nitrile (humans only), 3) 8-hydroxy-citronellyl nitrile (all species) and 4) 9-hydroxy citronellyl nitrile (humans). The phase 2 metabolites identified included: 1) Glutathione conjugate of 6,7-hydroxycitronellyl nitrile (rats, humans), 2) glucuronide conjugate of citronellyl nitrile (mouse) and 3) acyl glucuronide of citronellyl nitrile (humans). The metabolism scheme for citronellyl nitrile is provided below:



Adapted from Kemper et al., 2005.

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

Citronellyl nitrile is not reported to occur in food by the VCF*.

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

8. IFRA standard

None.

9. REACH Dossier

Available; accessed on 06/18/13.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, citronellyl nitrile does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Citronellyl nitrile was tested in the BlueScreen and was found negative for genotoxicity in the presence and absence of metabolic activation, indicating a lack for genotoxic concern (RIFM, 2013b). The mutagenic activity of citronellyl nitrile has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with citronellyl nitrile in DMSO (dimethyl sulfoxide) at concentrations up to 0.06 mg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1980a). Under the conditions of the study, citronellyl nitrile was not mutagenic in the Ames test. The mutagenic activity of citronellyl nitrile was also assessed in an *in vitro* mammalian gene mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 476. No toxicologically significant increases in the frequency of mutant colonies were observed with any dose of the test item, either with or without metabolic activation (ECHA REACH Dossier: citronellyl nitrile). Under the conditions of these studies, citronellyl nitrile was considered not mutagenic.

The clastogenic activity of citronellyl nitrile was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral route of administration, to groups of male and female NMRI mice (10/sex/dose). Doses of 500, 1000, or 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2004). Under the conditions of the study, citronellyl nitrile was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: RIFM, 2008b; RIFM, 2009; RIFM, 2012a; RIFM, 2012d; RIFM, 2013b; RIFM, 2013a.

Literature Search and Risk Assessment Completed on: 10/20/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for citronellyl nitrile 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 citronellyl nitrile. In an enhanced OECD 408 90-day gavage study, rats received doses of 10, 30, 100 or 300 mg/kg/day of citronellyl nitrile. Marginal centrilobular hepatocyte enlargement was observed in both sexes at 300 mg/kg/day and in 2 males and 1 female at 100 mg/kg/day, and was considered to be adaptive in nature. A higher incidence of lower grades of severity of adipose infiltration of the marrow was noted in the 300 mg/kg/day females but was not statistically significant and was considered to be a marginal effect as there were no corresponding hematological changes. There were no other adverse findings during necropsy or the histopathological examination. Thus, the NOAEL was determined to be 300 mg/kg/day, the highest dose tested (RIFM, 2008a, also available in Letizia et al., 2009). In addition, an enhanced OECD 415 gavage 1-generation rat reproductive toxicity study on citronellyl nitrile was conducted on 25 Sprague-Dawley rats/sex/group. The animals were treated with citronellyl nitrile at doses of 0 (corn oil), 75, 200 or 500 mg/kg/day. The NOAEL for general toxicity was de 200 mg/kg/day, based on reduction in body weight gains and terminal body weights among the high dose group males. No such effects were reported among the treated females. Also, there were no other treatment-related adverse effects reported up to the highest dose tested (RIFM, 2011). Therefore, the citronellyl nitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the citronellyl nitrile NOAEL in mg/kg/day by the total systemic exposure to citronellyl nitrile, 300/0.0029 or 103448.

Additional References: Kemper et al., 2005; Kemper et al., 2006; Potter et al., 2000, 2001.

Literature Search and Risk Assessment Completed on: 02/14/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for citronellyl nitrile 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 toxicity data on citronellyl nitrile. In an OECD 414 gavage study, pregnant rats received doses of 50, 150 or 450 mg/kg/day. Maternal effects in the high dose group included changes in clinical chemistry parameters and increased liver weight. There were no adverse effects on the fetuses. The NOAEL for maternal and developmental toxicity was determined to be 150 mg/kg/day and 450 mg/kg/day, respectively (RIFM, 2016a). In an enhanced OECD 415 1-generation gavage study in rats, citronellyl nitrile was administered at doses of 75, 200 or 500 mg/kg/day. There were no adverse effects on the offspring. The NOAEL for developmental toxicity was determined to be 500 mg/kg/day, the highest dose tested (RIFM, 2011). Thus, the NOAEL for developmental toxicity endpoint was determined to be 500 mg/kg/day, the highest dose tested.

There are sufficient reproductive toxicity data on citronellyl nitrile. In an enhanced OECD 415 1-generation gavage study in rats, citronellyl nitrile was administered at doses of 75, 200 or 500 mg/kg/day. There were no apparent effects of citronellyl nitrile on mating and fertility, reproductive organs and the sperm and estrus cycling parameters at any dose level tested. The NOAEL was determined to be 500 mg/kg/day, the highest dose tested (RIFM, 2011). In another study, test material citronellyl nitrile was administered via gavage to a group of 10 Sprague-Dawley Crl:CD(SD)IGS BR rats/sex. The study was conducted according to the OECD 408 protocol. The animals were treated with citronellyl nitrile at doses of 0 (corn oil), 10, 30, 100 or 300 mg/kg/day. In addition to the systemic toxicity endpoints, the male (sperm analysis) and female (estrous cycling) parameters were also reported. There were no effects on the male and female reproductive parameters up to the highest dose tested (RIFM, 2008a, also available in Letizia et al., 2009). Thus, the NOAEL for the reproductive toxicity endpoint was determined to be 500 mg/kg/day, the highest dose tested.

Therefore, the citronellyl nitrile MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the citronellyl nitrile NOAEL in mg/kg/day by the total systemic exposure to citronellyl nitrile, 500/0.0029 or 172414.

Additional References: Kemper et al., 2005; Kemper et al., 2006; Potter et al., 2000, 2001.

Literature Search and Risk Assessment Completed on: 02/14/2017.

10.1.4. Skin sensitization

Based on the existing data and read across to 2,2,5,9-tetramethyl-4,8-decadienenitrile (CAS # 58260-78-9), citronellyl nitrile does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and read across to 2,2,5,9-tetramethyl-4,8-decadienenitrile (CAS # 58260-78-9), citronellyl nitrile does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In a guinea pig sensitization study conducted with citronellyl nitrile, no sensitization reactions were observed (RIFM, 1980c). Similarly, in a human maximization test with citronellyl nitrile, there were no reactions indicative of sensitization (RIFM, 1977). Moreover, in human repeated insult patch tests read across material 2,2,5,9-tetramethyl-4,8-decadienenitrile did not result in sensitization reactions (RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d). Based on weight of evidence from structural analysis, animal data and human data, citronellyl nitrile does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/27/13.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available data, citronellyl nitrile does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 $L \cdot mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). In a guinea pig phototoxicity/photoallergenicity study, topical application of diluted citronellyl nitrile (25, 50, and 75% in 80% ethanol), and neat citronellyl nitrile did not result in reactions indicative of either phototoxicity or photoallergenicity (RIFM, 1980b). Based on lack of absorbance, and the *in vivo* study data, citronellyl nitrile does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/14/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, citronellyl nitrile, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There is limited inhalation data available on citronellyl nitrile. Based on the Creme RIFM model, the inhalation exposure is 0.055 mg/day. This exposure is 8.5 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: RIFM, 1989.

Literature Search and Risk Assessment Completed on: 10/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of citronellyl nitrile was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 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, citronellyl nitrile 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 EPISuite ver 4.1 did not identify citronellyl nitrile as persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (*e.g.,* OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (*e.g.,* USEPA's BIOWIN and BCFBAF found in EPISuite ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2011), citronellyl nitrile presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 1999**: A Modified MITI Test was conducted according to OECD Guidelines 301C with 2 samples of citronellyl nitrile. The BOD in sample 1 and 2 was 52% and 48%, respectively.

RIFM, 1987: The biodegradation of the test material in sludge was determined according to the OECD 301C method. A biodegradation of 60% was observed.

RIFM, 1997a: Biodegradability of the test material was evaluated using the Manometric Respiratory Test according to OECD guideline 301F. Citronellyl nitrile at 100 mg/l was incubated for 28 days. The rate of biodegradation after 10 and 28 days was 68% and 69%, respectively.

RIFM, 1994: Biodegradation was evaluated by the sealed vessel test according to the OECD 301B method. The rate of degradation after 28 days was 59.9%.

10.2.3.2. Ecotoxicity. **RIFM, 1990**: A 96-h fish (golden orle) acute test was conducted according to the OECD 203 method under flow-through conditions. Based on nominal concentration the LC50 of the test material was greater than 22 mg/l and lower than 46 mg/l.

RIFM, 2012b: A study according to the OECD 202 method was conducted to determine the acute effects of the test material on

Daphnia magna, during a 48-h exposure period under static test conditions. The EC50 based on nominal concentration was reported to be 11.4 mg/l.

RIFM, 2012c: A 72-h algae acute test was conducted according to the OECD 201 guidelines under static conditions. Under the test conditions and based on nominal concentration the EC50 for growth rate was reported to be 14.5 mg/l.

10.2.3.3. Other available data. Citronellyl nitrile has been registered under REACH, but no additional data is available.

10.2.4. 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)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	9.145 mg/l			1,000,000	0.00914 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** Ver 1.11	5.034 mg/l	5.218 m/l	3.570 mg/l	10,000	0.3570 µg/l	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	22 mg/l					
Daphnia		11.4 mg/l		1000	11.4 µg/l	
Algae		14.5 mg/l				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.55	3.55
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 11.4 µg/l. The revised PEC/PNECs for EU and NA are <1 and 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: 08/27/13.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

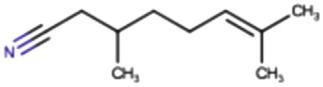
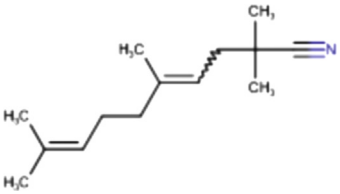
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.07.043.

- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material
Principal Name	Citronellyl nitrile	2,2,5,9-Tetramethyl-4,8-decadienenitrile
CAS No.	51566-62-2	58260-78-9
Structure		
Similarity (Tanimoto score)		0.472
Read across endpoint		• Skin sensitization
Molecular Formula	$C_{10}H_{17}N$	$C_{14}H_{23}N$
Molecular Weight	151.25	205.45
Melting Point (°C, EPISUITE)	−8.64	12.75
Boiling Point (°C, EPISUITE)	233.15	293.92
Vapor Pressure (Pa @ 25 °C, EPISUITE)	8.84	0.359
Log Kow (KOWWIN v1.68 in EPISUITE)	3.55	5.32
Water Solubility (mg/l, @ 25 °C, WSKOW v1.42 in EPISUITE)	37.76	0.639
J_{max} (mg/cm^2/h, SAM)	23.710	0.105
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	3.06E-004	9.78E-004
Skin Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)	• Sensitizer (low reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See supplemental data 1	See supplemental data 2

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.07.043.

Appendix

Read across justification

Methods

- The identified read across analogs were confirmed by using expert judgment.
- The physical-chemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA, 2012.
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

Summary

There are insufficient toxicity data on citronellyl nitrile (CAS # 51566-62-2). Hence, *in silico* evaluation was conducted by determining read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, analog 2,2,5,9-tetramethyl-4,8-decadienenitrile (CAS # 58260-78-9) was identified as a proper read across material with data for their respective toxicity endpoints.

Conclusion/Rational

- 2,2,5,9-Tetramethyl-4,8-decadienenitrile (CAS # 58260-78-9) could be used as a structurally similar read across analog for the target material citronellyl nitrile (CAS # 51566-62-2) for skin sensitization.
  - The target substance and the read across analog are structurally similar and belong to a class of unsaturated aliphatic nitriles.
  - The target substance and the read across analog has a seven carbon long, unsaturated, branched chain (heptanenitrile) fragment common among them.
  - The key difference between the target substance and the read across analog is that the read across analog has two vinyl groups and the nitrile group is attached at the tertiary carbon while the target substance has only one vinyl group and the nitrile group is attached at the primary carbon.

- The target substance and the read across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the seven carbon long, unsaturated, branched chain (heptanenitrile) fragment with a nitrile group. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
- The target substance and the read across analog have similar physical-chemical properties except for the J_{max}. The read across is predicted to have skin absorption up to 10% while the target is predicted to have skin absorption up to 80%. This difference in the skin absorption prediction is not significant between the toxicity and bioavailability of the substance. Any differences in the physical-chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for skin sensitization.
- According to the QSAR OECD Toolbox (v3.4), structural alerts for skin sensitization are consistent between the target substance and the read across analog. The CAESAR model predicts the target and the read across analog 2,2,5,9-tetramethyl-4,8-decadienenitrile to be a sensitizer. Other protein binding alerts for both of the substances are negative. The data described in the skin sensitization section above shows that the read across analog does not pose a concern for skin sensitization. Therefore, this alert was superseded by the availability of data.
- The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator. The target substance shows a greater number of metabolites possibly due to a less sterically hindered nitrile group compared to the read across analog. The structural alerts due to the metabolite does not alter the toxicity profile of the target substance compared to the read across analog for skin sensitization.
- The structural alerts for skin sensitization are consistent between the metabolites of the read across analog and the target substance.
- The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant for skin sensitization.

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