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Short review

RIFM fragrance ingredient safety assessment, 3,12-Tridecadienenitrile CAS Registry Number 134769-33-8

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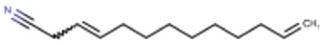


Name: 3,12-Tridecadienenitrile
CAS Registry Number: 134769-33-8
Additional CAS Numbers*:
124071-43-8 (3-Z)-3,12-Tridecadienenitrile
124071-42-7 3,12-Tridecadienenitrile, (3E)-
124358-45-8 Acetic acid, cyano-, reaction products with 10-undecenal (no reported use)
124071-40-5 E- and Z-2(+3),12-Tridecadiennitrile
*These materials were included in this assessment because they are a mixture of isomers
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 (Lhasa Limited)
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, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Target data show that this material is not genotoxic and it does not have skin sensitization potential. An acceptable MOE >100 was calculated for the repeated dose toxicity endpoint. The reproductive toxicity endpoint review was completed using citronellyl nitrile (CAS # 51566-62-2) as a read across analog, which provided an acceptable MOE > 100. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.47 mg/day); exposure < TTC (acceptable). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; the material was not phototoxic/photoallergenic. The environmental endpoints were evaluated and the material was not found to be a PBT; 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, 1990; RIFM, 1992a)
Repeated Dose Toxicity: NOAEL = 67 mg/kg/day.	(RIFM, 1993a)
Reproductive Toxicity: NOAEL = 500 mg/kg/day.	(RIFM, 2011)
Skin Sensitization: Not sensitizing.	(RIFM, 1993c; RIFM, 1989)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment
Hazard Assessment:

Persistence: Critical Measured Value: 79% (OECD 301C)	(RIFM, 1993b)
Bioaccumulation: Screening Level: 33.8 l/kg	(US EPA, 2012)
Ecotoxicity: Screening Level: 96-hr Algae EC50: 0.089 mg/l	(US EPA, 2012)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

(*continued*)

Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) > 1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-hr Algae EC50: 0.089 mg/l	(US EPA (2012))
RIFM PNEC is: 0.0089 μg/l	
• **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: <1	

1. Identification

Chemical Name: 3,12-Tridecadienenitrile	Chemical Name: (3-Z)-3,12-Tridecadienenitrile	Chemical Name: 3,12-Tridecadienenitrile, (3E)-	Chemical Name: Acetic acid, cyano-, reaction products with 10-undecenal	Chemical Name: E- and Z-2(+3),12-Tridecadiennitrile
CAS Registry Number: 134769-33-8	**CAS Registry Number:** 124071-43-8	**CAS Registry Number:** 124071-42-7	**CAS Registry Number:** 124358-45-8	**CAS Registry Number:** 124071-40-5
Synonyms: 3,12-Tridecadienenitrile; Mandaril	**Synonyms:** (3-Z)-3,12-Tridecadienenitrile; 3,12-Tridecadienenitrile,(3Z)-; Mandaril	**Synonyms:** 3,12-Tridecadienenitrile, (3E)-	**Synonyms:** Acetic acid, cyano-, reaction products with 10-undecenal; Mandaril; Trideca-3, 12-dien-nitril	**Synonyms:** 2,12-Tridecadienenitrile, (2E); E- and Z-2(+3),12-Tridecadiennitrile
Molecular Formula: $C_{13}H_{21}N$	**Molecular Formula:** $C_{13}H_{21}N$	**Molecular Formula:** $C_{13}H_{21}N$	**Molecular Formula:** $C_{11}H_{20}O.C_3H_3NO_2$	**Molecular Formula:** $C_{13}H_{13}21N$
Molecular Weight: 191.32	**Molecular Weight:** 191.32	**Molecular Weight:** 191.32	**Molecular Weight:** N/A	**Molecular Weight:** 191.32
RIFM Number: 6930	**RIFM Number:** 7269	**RIFM Number:** 7268	**RIFM Number:** 6333	**RIFM Number:** 6703

2. Physical data*

1. **Boiling Point:** 292.1 °C [RIFM, 1992b], 296.35 °C [US EPA, 2012]
2. **Flash Point:** 146 °C [GHS], 147 °C [RIFM, 1991]
3. **Log K_{OW}:** 4.91 [US EPA, 2012], 5.68 (weighted average mean of 4 signals) at 23.2 °C [RIFM, 2016a,b,c]
4. **Melting Point**: 30.79 °C [US EPA, 2012]
5. **Water Solubility:** 1.702 mg/l [US EPA, 2012]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0021 mm Hg @ 25 °C [US EPA, 2012], 0.00115 mmHg @ 20 °C [US EPA, 2012]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 l $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium citrus, sweet, tangerine, aldehydic, fresh, watery odor.**

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

** http://www.thegoodscentscompany.com/data/rw1030521.html#toorgano, retrieved 10/26/2016.

3. Exposure***

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0012% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.000025 mg/kg/day or 0.0018 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00013 mg/kg/day (RIFM, 2014)

*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 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 and Safford 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 III, High (Expert Judgment)

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

2. **Analogous Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** citronellyl nitrile (CAS # 51566-62-2)
   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

Not considered for this risk assessment.

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

None of the materials included in this assessment have been 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

None of the materials in this assessment have been pre-registered as of 03/3/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, 3,12-tridecadienenitrile does not present a concern for genotoxicity.

10.1.2. Risk assessment

The mutagenic activity of 3,12-tridecadienenitrile 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 3,12-tridecadienenitrile in solvent DMSO (dimethyl sulfoxide) at concentrations up to 30 μl/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1990). Under the conditions of the study, 3,12-tridecadienenitrile was not mutagenic in the Ames test.

The clastogenic activity of 3,12-tridecadienenitrile 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 arachis oil name via oral administration, to groups of male and female NMRI mice (5/sex/dose). Doses of 250, 500, or 1000 mg/kg were administered. Mice from each dose level were euthanized at 24, 48 and 72 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, 1992a). Under the conditions of the study, 3,12-tridecadienenitrile was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 3,12-tridecadienenitrile does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/19/2016.

10.1.3. Repeated dose toxicity

The margin of exposure for 3,12-tridecadienenitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

There are sufficient repeated dose toxicity data on 3,12-tridecadienenitrile. In a 28-day OECD 407 gavage study, the test material was administered by gavage for 28 days to rats at doses of 40, 200 or 1000 mg/kg/day with a 2-week recovery period. The NOAEL was 200 mg/kg/day. There was a significant decrease in body weight, organ weight changes and kidney degeneration and necrosis at 1000 mg/kg/day (RIFM, 1993a).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day or OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity data is 200/3 or 67 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Therefore, the 3,12-tridecadienenitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,12-tridecadienenitrile NOAEL in mg/kg/day by the total systemic exposure to 3,12-tridecadienenitrile, 67/0.00013 or 515384.

In addition, the total systemic exposure to 3,12-tridecadienenitrile (0.13 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/25/2016.

10.1.5. Reproductive toxicity

The margin of exposure for 3,12-tridecadienenitrile is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.6. Risk assessment

There are insufficient developmental toxicity data on 3,12-tridecadienenitrile or any of the combined materials. Read across material citronellyl nitrile (CAS # 51566-62-2; see Section V) has sufficient developmental toxicity data. In an OECD 414 gavage study on the test material, citronellyl nitrile, 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 150 mg/kg and 450 mg/kg, respectively (RIFM, 2016a). In an enhanced OECD 415 one 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 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 insufficient fertility toxicity data on 3,12-tridecadienenitrile or any of the combined materials (See Section I). Read across material citronellyl nitrile (CAS # 51566-62-2; see Section V), has sufficient fertility toxicity data. In an enhanced OECD 415 one 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 dosage level tested. The NOAEL was 500 mg/kg/day, the highest dose tested (RIFM, 2011). In another study, 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, 2008). Thus, the NOAEL for the reproductive toxicity endpoint is 500 mg/kg/day, the highest dose tested.

Therefore, the 3,12-tridecadienenitrile MOE for the reproductive toxicity endpoint can be calculated by dividing the citronellyl nitrile NOAEL in mg/kg/day by the total systemic exposure to 3,12-tridecadienenitrile, 500/0.00013 or 3846153.

In addition, the total systemic exposure to 3,12-tridecadienenitrile (0.13 μg/kg/day) is below the TTC (1.5 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/25/2016.

10.1.7. Skin sensitization

Based on the existing data, 3,12-tridecadienenitrile does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the existing data, 3,12-tridecadienenitrile does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). 3,12-Tridecadienenitrile was found to be negative in a guinea pig maximization test (RIFM, 1989). In a confirmatory human repeated insult patch test in 92 subjects no reactions were observed (RIFM, 1993c). Based on weight of evidence from structural analysis, animal and human studies 3,12-tridecadienenitrile does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/26/16.

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 3,12-tridecadienenitrile would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for 3,12-tridecadienenitrile in experimental models. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on lack of absorbance, 3,12-tridecadienenitrile does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.11. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3,12-tridecadienenitrile, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on 3,12-tridecadienenitrile. Based on the Creme RIFM model, the inhalation exposure is 0.0018 mg/day. This exposure is 261 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/24/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3,12-tridecadienenitrile 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, which is considered proprietary information, 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, 3,12-tridecadienenitrile 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 3,12-tridecadienenitrile as possibly 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 I.

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3,12-tridecadienenitrile presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. RIFM, 1993b: Ready biodegradability of the test material was evaluated in a Manometric Respiratory test according to the OECD 301C method. Biodegradation of 79% was observed after 28 days.

10.2.2.2. Ecotoxicity. RIFM, 1993b: *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. No immobilization was observed at 0.75 mg/l (only one concentration tested).

RIFM, 1993b: Fish (*Brachydanio rerio*) acute toxicity test was

conducted according to the OECD 203 method. There were no mortalities at the concentration tested (0.75 mg/l).

RIFM, 1994: An algae growth inhibition test was conducted according to the OECD 201 method. Under the conditions of this study, the EbC50 and the ErC50 was 0.260 and 1.0 mg/l, respectively.

10.2.2.3. Other available data. 3,12-Tridecadienenitrile has been pre-registered for REACH with no additional data at this time.

10.2.2.4. Risk assessment refinement. Since 3,12-Tridecadienenitrile 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.1904 mg/l			1,000,000	0.00019 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.125 mg/l	0.213mg/l	0.089 mg/l	10,000	0.0089 μg/l	Vinyl/Allyl Nitriles
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.387 mg/l	0.287 mg/l	0.648 mg/l			Neutral Organic

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.6	5.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1*	<1*
Risk Characterization: PEC/PNEC	<1	<1

*Combined volumes for all CAS#.

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

The RIFM PNEC is 0.0089 μg/l. The revised PEC/PNECs for EU and NA are <1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 9/14/2016.

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 https://doi.org/10.1016/j.fct.2017.09.041.

Transparency document

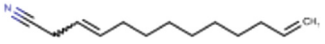
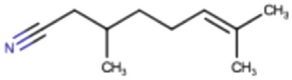
Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2017.09.041.

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).
- Developmental toxicity was estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- 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	3,12-Tridecadienenitrile	Citronellyl nitrile
CAS No.	134769-33-8	51566-62-2
Structure		
Similarity (Tanimoto score)		0.2049
Read across endpoint		• Reproductive
Molecular Formula	$C_{13}H_{21}N$	$C_{10}H_{17}N$
Molecular Weight	191.32	151.25
Melting Point (°C, EPISUITE)	30.79	−8.64
Boiling Point (°C, EPISUITE)	204.05	233.15
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.28	8.84
Log Kow (KOWWIN v1.68 in EPISUITE)	5.68[1]	3.5[3]
Water Solubility (mg/l, @ 25 °C, WSKOW v1.42 in EPISUITE)	2.01[2]	37.76
J_{max} (mg/cm^2/h, SAM)	0.364	29.120
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.52E-004	3.06E-004
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)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See supplemental data 1	See supplemental data 2

1. RIFM, 2016c.
2. RIFM, 2016b.
3. RIFM, 1997.

Summary

There are insufficient toxicity data on 3,12-tridecadienenitrile (CAS # 134769-33-8). 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 citronellyl nitrile (CAS # 51566-62-2) was identified as a proper read across material with data for its respective toxicity endpoint.

Conclusion/Rationale

- Citronellyl nitrile (CAS # 51566-62-2) could be used as a structurally similar read across analog for the target material 3,12-tridecadienenitrile (CAS # 134769-33-8) for reproductive toxicity.
  - o The target substance and read across analog are structurally similar and belong to a class of unsaturated aliphatic nitriles.
  - o The target substance and the read across analog have a heptanenitrile fragment common among them.
  - o The key difference between the target substance and the read across analog is that the target has a linear alkyl chain and vinyl as well as vinylene group while the read across only has a branched alkyl chain and a vinyl group.
  - o 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 heptanenitrile fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - o The target substance and the read across analog have similar physical-chemical properties. The J_{max} value for the read across analog is higher compared to the target substance which predicts that the read across analog will have higher skin absorption compared to the target substance. Any differences in the physical-chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for reproductive toxicity.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for reproductive toxicity are consistent between the target substance and the read across analog.
  - o The target substance and the read across analog are expected to be metabolized similarly as shown by metabolism simulator. In addition, according to metabolic simulator, the read across analog shows a greater number of metabolites as compared to the target substance, which yields more *in vivo* reactivity.

- The structural alerts for reproductive toxicity 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 reproductive toxicity.

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