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Short review

RIFM fragrance ingredient safety assessment, 3,7-dimethyl-2,6-nonadienenitrile, CAS Registry Number 61792-11-8

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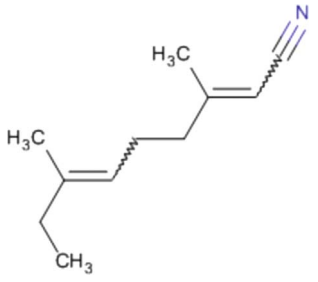

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Abbreviation list:

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; Comiskey et al., 2017) compared to a deterministic aggregate approach.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
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
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- Ultra Violet/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 the RIFM Criteria Document (Api et al., 2015) which 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.

The material (3,7-dimethyl-2,6-nonadienenitrile) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that 3,7-dimethyl-2,6-nonadienenitrile is not genotoxic. Data from the read across analog geranyl nitrile (CAS # 5146-66-7) show that 3,7-dimethyl-2,6-nonadienenitrile is not a concern for skin sensitization. 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 repeated dose and reproductive toxicity endpoint was completed using tridecene-2-nitrile (CAS # 22629-49-8) as a read across analog, which provided a MOE $>$ 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on 3,7-dimethyl-2,6-nonadienenitrile. The environmental endpoints were evaluated, 3,7-dimethyl-2,6-nonadienenitrile was found not to be PBT as per the IFRA Environmental Standards and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2002; RIFM, 2005a, b)
Repeated Dose Toxicity: NOAEL = 67 mg/kg/day. (RIFM, 2016a)
Reproductive Toxicity: NOAEL = 200 mg/kg/day. (RIFM, 2016a)
Skin Sensitization: Not sensitizing. (RIFM, 1998)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1983a; RIFM, 1983b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 70% OECD 301F (57 days) (RIFM, 2010a, b)
Bioaccumulation: Screening Level: 189 L/kg (US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint:72-hr Algae EC50 (yield):1.8 mg/L (RIFM, 2012a, b, c, d)
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: 72-hr Algae EC50 (yield): 1.8 mg/L (RIFM, 2012c)
RIFM PNEC is: 0.36 μg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name**: 3,7-Dimethyl-2,6-nonadienenitrile
2. **CAS Registry Number**: 61792-11-8
3. **Synonyms**: 3,7-Dimethyl-2,6-nonadienenitrile; Lemonile; 2,6-Nonadienenitrile, 3,7-dimethyl-; 3,7-ｼﾞﾒﾁﾙ-2,6-ﾉﾅｼﾞｴﾝﾆﾄﾘﾙ; 3,7-Dimethylnona-2,6-dienenitrile
4. **Molecular Formula**: $C_{11}H_{17}N$
5. **Molecular Weight**: 163.26
6. **RIFM Number**: 834

2. Physical data

1. **Boiling Point**: 261.99 °C (US EPA, 2012a)
2. **Flash Point**: 203 °F. TCC (95 °C)*
3. **Log K_{OW}**: log Pow = 3.1 and 3.2 (RIFM, 2010b), 3.8 to 4.0 at 35C (RIFM, 1997), 3.96 (US EPA, 2012a)
4. **Melting Point**: 3.4 °C (US EPA, 2012a)
5. **Water Solubility**: 15 mg/L (US EPA, 2012a)
6. **Specific Gravity**: 0.8678 [RIFM Database]
7. **Vapor Pressure**: 1.7 Pa at 20 C (RIFM, 2012a), 0.00888 mmHg @ 20 °C (US EPA, 2012a), 0.01 mm Hg 20C [FMA Database], 0.0143 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra**: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic**: A colorless to slightly yellow liquid with a citrusy odor

*http://www.thegoodscentscompany.com/data/rw1042831.html#tophyp, retrieved 2/21/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2011)
2. 95th Percentile Concentration in Hydroalcoholics: 0.036% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.00061 mg/kg/day or 0.044 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00066 mg/kg/day (RIFM, 2015)

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

4. Derivation of systemic absorption

1. **Dermal**: 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:** Tridecene-2-nitrile (CAS # 22629-49-8)
   c. **Developmental and Reproductive Toxicity**: Tridecene-2-nitrile (CAS # 22629-49-8)
   d. **Skin Sensitization:** Geranyl nitrile (CAS # 5146-66-7)
   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 and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

3,7-Dimethyl-2,6-nonadienenitrile 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 8/1/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3,7-dimethyl-2,6-nonadienenitrile does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 3,7-Dimethyl-2,6-nonadienenitrile was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). 3,7-Dimethyl-2,6-nonadienenitrile was assessed for mutagenic potential in a GLP compliant Ames study conducted in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 3,7-dimethyl-2,6-nonadienenitrile in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of S9 metabolic activation. 3,7-Dimethyl-2,6-nonadienenitrile did not induce a dose-related increase in the number of revertant colonies in any of the five tester strains in the presence or the absence of metabolic activation (RIFM, 2002). Under the conditions of the study, 3,7-dimethyl-2,6-nonadienenitrile was considered not mutagenic in bacteria.

The clastogenic activity of 3,7-dimethyl-2,6-nonadienenitrile 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 by a single oral dose to groups of male and female NMRI mice. Doses 500, 1000 and 2000 mg/kg body-weight were administered. Mice from each dose level were euthanized at 24 and 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, 2005a, b). Under the conditions of the study, 3,7-dimethyl-2,6-nonadienenitrile was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 3,7-dimethyl-2,6-nonadienenitrile does not present a concern for genotoxic potential.

Additional References: RIFM, 2004.

Literature Search and Risk Assessment Completed on: 2/11/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 3,7-dimethyl-2,6-nonadienenitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3,7-dimethyl-2,6-nonadienenitrile. Read across material, tridecene-2-nitrile (CAS # 22629-49-8; see Section 5) has sufficient repeated dose toxicity data. A 2-week gavage, non-GLP dose range finding study was conducted on groups of 5 Sprague-Dawley Crl:CD BR strain rats/sex/group to determine the dose for an OECD 422 study. The animals were treated with test material tridecene-2-nitrile at doses of 0 (corn oil), 100, 300 and 1000 mg/kg/day. Mortality was reported among the animals of the high dose group only. Alterations in the hematological and clinical chemistry parameters were reported among the high dose females. No such alterations were reported among the mid- and low-dose animals. Decreases in body weight were reported among the high dose animals. Ulceration of the glandular stomach were commonly observed in most of the dead or moribund males. Focus of glandular stomach and thickening/perforation of the forestomach were noted in most of the dead or moribund females. No other treatment related macroscopic alterations were reported among the animals of the mid- and low-dose groups. The absolute and relative liver weights were prominently increased in one moribund male and one moribund female at 1000 mg/kg/day. The relative liver weight was significantly increased in the males of the 300 mg/kg/day group when compared to the control group. Based on the result of this study, the dose levels for the combined repeated dose toxicity study with reproduction/developmental toxicity screening test was selected to be 200 mg/kg/day for the high dose level and 20 mg/kg/day for the low dose level. Thus, the NOAEL for the repeated dose toxicity endpoint was considered to be 20 mg/kg/day (RIFM, 2016b). A gavage GLP/OECD 422 study was conducted on groups of 5 Sprague-Dawley Crl:CD SD strain rats/sex/group where the test material tridecene-2-nitrile was administered at doses of 0 (corn oil), 20, 60 and 200 mg/kg/day. Local effects on the stomach were reported among a few of the control and treated animals. Macroscopic alterations included focus on mucosa of the glandular stomach in one high dose male, one control female and mid- and low-dose females, along with polyp/thickening of mucosa in the forestomach in one high dose female. Microscopic alterations included epithelial hyperplasia/hyperkeratosis with inflammatory cell infiltration in the forestomach submucosa in one high dose female. This finding corresponded to macroscopically observed polyp/thickening of the forestomach. Erosion of the mucosa in the glandular stomach was observed in one high dose male and mid- and high-dose females. This finding was in concordance with macroscopically observed focus on mucosa of the glandular stomach. At the end of the recovery period, these findings were not observed in any animals indicating that these effects were reversible. The effects on the stomach were considered to be local effects and reversible, hence not considered towards deriving a NOAEL. Thus, the NOAEL for the repeated dose toxicity was considered to be 200 mg/kg/day, the highest dose tested. (RIFM, 2016a).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 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.

Therefore, the 3,7-dimethyl-2,6-nonadienenitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the tridecene-2-nitrile NOAEL by the total systemic exposure to 3,7-dimethyl-2,6-nonadienenitrile, 67/0.00066 or 101515.

In addition, the total systemic exposure to 2-undecenenitrile (0.66 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/21/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3,7-dimethyl-2,6-nonadienenitrile is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 3,7-dimethyl-2,6-nonadienenitrile. Read across material, tridecene-2-nitrile (CAS # 22629-49-8; see Section 5) has sufficient repeated dose toxicity data. There are sufficient reproductive toxicity data on tridecene-2-nitrile. A gavage GLP/OECD 422 study was conducted on groups of 5 Sprague-Dawley Crl:CD SD strain rats/sex/group that were administered test material, tridecene-2-nitrile at doses of 0 (corn oil), 20, 60 and 200 mg/kg/day. The NOAEL for the developmental and reproductive toxicity was considered to be 200 mg/kg/day, the highest dose tested (RIFM, 2016a). **Therefore, the 3,7-dimethyl-2,6-nonadienenitrile MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the tridecene-2-nitrile NOAEL in mg/kg/day by the total systemic exposure to 3,7-dimethyl-2,6-nonadienenitrile, 200/0.00066 or 303030.**

In addition, the total systemic exposure to 3,7-dimethyl-2,6-nonadienenitrile (0.66 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class III material at the

current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/21/2017.

10.1.4. Skin sensitization

Based on available data for 3,7-dimethyl-2,6-nonadienenitrile and read across to geranyl nitrile (CAS # 5146-66-7), 3,7-dimethyl-2,6-nonadienenitrile does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on a weight of evidence from the available data for 3,7-dimethyl-2,6-nonadienenitrile and read across to geranyl nitrile (CAS # 5146-66-7; see Section 5), 3,7-dimethyl-2,6-nonadienenitrile does not present a concern for skin sensitization. The chemical structure indicates that these materials would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In the Guinea pig maximization test, geranyl nitrile was reported to be non-sensitizing (RIFM, 1975a; RIFM, 1983c; RIFM, 1976b; RIFM, 1982; RIFM, 1998). In the local lymph node assay, geranyl nitrile was reported to be non-sensitizing (RIFM, 2005b; Kern et al., 2010). Finally, in the human repeated insult patch test (HRIPT) and the human maximization test (HMT) no reactions were observed to 3,7-dimethyl-2,6-nonadienenitrile or geranyl nitrile (RIFM, 1970, RIFM, 1962; RIFM, 1964; RIFM, 1980b; RIFM, 1980c; RIFM, 1974; RIFM, 1975b; RIFM, 1976a). Based on a weight of evidence from the available data for 3,7-dimethyl-2,6-nonadienenitrile and read across to geranyl nitrile (CAS # 5146-66-7), 3,7-dimethyl-2,6-nonadienenitrile does not present a concern for skin sensitization.

Additional References: RIFM, 1962; RIFM, 1975a; Klecak, 1985; RIFM, 1980a, b, c; RIFM, 1975b; RIFM, 1983d.

Literature Search and Risk Assessment Completed on: 02/16/17.

10.1.5. Phototoxicity/photoallergenicity

Based on existing data and available UV/Vis spectra, 3,7-dimethyl-2,6-nonadienenitrile would not be expected to 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 mol^{-1} cm^{-1} (Henry et al., 2009). Phototoxicity and photoallergenicity of 10% 3,7-dimethyl-2,6-nonadienenitrile were evaluated *in vivo* in guinea pigs and there were no reactions (RIFM, 1983a; RIFM, 1983b). Based on lack of absorbance and *in vivo* study data, 3,7-dimethyl-2,6-nonadienenitrile would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/07/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3,7-dimethyl-2,6-nonadienenitrile, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3,7-dimethyl-2,6-nonadienenitrile. Based on the Creme RIFM model, the inhalation exposure is 0.044 mg/day. This exposure is 10.7 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: 2/16/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3,7-dimethyl-2,6-nonadienenitrile 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; US EPA, 2012b) 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, 3,7-dimethyl-2,6-nonadienenitrile 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 v4.1 (US EPA, 2012a) did not identify 3,7-dimethyl-2,6-nonadienenitrile as either being possibly persistent nor 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 v4.1). 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), 3,7-dimethyl-2,6-nonadienenitrile presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1995a: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. An average biodegradation of 60% was observed after 28 days.

RIFM, 1995b: The Inherent Biodegradability of the test material was determined by the Respirometric Method (modified MITI Test II) following the OECD 302C method. After 28 days, biodegradation of 45% was observed.

RIFM, 2010a: A modified manometric respirometry test was conducted following the OECD 301F method. A biodegradation of 70% was observed after 57 days.

RIFM, 2012d: A study was performed to assess the *in vitro* stability of 3,7-dimethyl-2,6-nonadienenitrile in fish liver S9 fractions. The method followed was a standardized assay. Following a preliminary range finding test, 3,7-dimethyl-2,6-nonadienenitrile (1 μM) was incubated in triplicate with trout liver S9 fraction (1 mg/ml) for 0, 5, 15, 30, and 60 min or for 0, 15, 30, 60 and 120 min at 12 °C in two main, independent experiments. Negative controls included incubation of the test substance with heat inactivated S9 protein. The disappearance of 3,7-dimethyl-2,6-nonadienenitrile as a function of time was monitored using GC-MS analysis. Metabolic turnover by trout liver S9 fractions was observed for the four isomers of Lemonile, indicating that 3,7-dimethyl-2,6-nonadienenitrile is expected to be metabolized *in vivo*.

10.2.3.2. Ecotoxicity. RIFM, 2012b: *Daphnia magna* immobilization test was conducted according to the OECD 202 method. Under the conditions of this study, the 48-h EC50 based on the mean measured test concentration was 2.7 mg/L.

RIFM, 2012c: A 72-h growth inhibition test was conducted according to the OECD 201 method. Under the conditions of this study, the EC50 for growth rate, yield and biomass at 72 h were 3.6, 1.8 and 1.9 mg/L, respectively based on measured test concentration.

10.2.3.3. Other available data. 3,7-Dimethyl-2,6-nonadienenitrile has been registered under REACH but no additional data is available.

10.3. 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 (μg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	4.007 mg/L			1,000,000	0.004007 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.408 mg/L	0.358 mg/L	0.193 mg/L	10,000	0.0193 μg/L	Vinyl/Allyl Nitriles
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.345 mg/L	1.595 mg/L	2.508 mg/L			Neutral organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish						
Daphnia		2.7 mg/L				
Algae		1.8 mg/L		5,000	0.36 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.0	4.1
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.36 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: 2/7/17.

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.

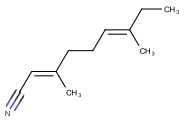
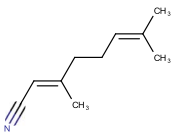
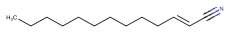
Appendix

Read across justification

Methods

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by OECD on the reporting of defined approached used within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemical Agency (ECHA) read across assessment framework or RAAF (ECHA, 2016).

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, the appropriate read across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints. (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analogs were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012a, b).
- J_{max} were calculated using RIFM skin absorption model (SAM), and the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated 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.2.1.7 and 2.1.6, respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- 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	3,7-Dimethyl-2,6-nonadienenitrile	Geranyl nitrile	Tridecene-2-nitrile
CAS No.	61792-11-8	5146-66-7	22629-49-8
Structure			
Similarity (Tanimoto score)		0.94	0.56
Read across endpoint		• Skin sensitization	• Repeated dose • Developmental and reproductive
Molecular Formula	$C_{11}H_{17}N$	$C_{10}H_{15}N$	$C_{13}H_{23}N$
Molecular Weight	163.26	149.24	193.34
Melting Point (°C, EPISUITE)	3.40	−7.29	32.27
Boiling Point (°C, EPISUITE)	261.99	244.67	297.46
Vapor Pressure (Pa @ 25°C, EPISUITE)	1.9	4.82	0.256
Log Kow (KOWWIN v1.68 in EPISUITE)	3.96	3.47	5.04
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	15	138[a]	0.27[b]
J_{max} (mg/cm^2/h, SAM)	15.856	14.985	0.047
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.92E-003	1.45E-003	2.76E-003
Repeated dose toxicity			
Repeated Dose (HESS)	• Aliphatic Nitriles (Hepatotoxicity) alert		• Aliphatic nitriles (Hepatotoxicity) alert
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)
Skin Sensitization			

Protein binding by OASIS v1.4	• AN2 • Michael addition	• AN2 • Michael addition	
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 v1.4	• 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 and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

[a] RIFM, 2001.
[b] RIFM, 2016c.

Summary

There are insufficient toxicity data on the target material 3,7-dimethyl-2,6-nonadienenitrile (CAS # 61792-11-8). Hence, *in silico* evaluation was conducted to determine suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the geranyl nitrile (CAS # 5146-66-7) and tridecene-2-nitrile (CAS # 22629-49-8) were identified as read across materials with data for their respective toxicological endpoints.

Conclusion/Rationale

- For the target material 3,7-dimethyl-2,6-nonadienenitrile (CAS # 61792-11-8), geranyl nitrile (CAS # 5146-66-7) was used as a read across analog for the skin senzitization endpoint and tridecene-2-nitrile (CAS # 22629-49-8) was used as a read across analog for the repeated dose, developmental and reproductive toxicity endpoints.
  - o The target substance and the read across analogs are structurally similar and belong to the structural class of aliphatic alpha, beta-unsaturated branched nitriles.
  - o The target substance and the read across analogs share an alpha,beta-unsaturated nitrile group and a six-carbon branched aliphatic chain with another non-conjugated alkene.
  - o The key difference between the target substance and the read across analogs is that the target substance has one carbon longer aliphatic chain than the read across analog geranyl nitrile, whereas the read across analog tridecene-2-nitrile is a straight chain aliphatic nitrile. This structural difference between the target substance and the read across analogs does not affect consideration of the toxicity endpoint.
  - o Similarity between the target substance and the read across analogs is indicated by the Tanimoto scores in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - o The physical chemical properties of the target substance and the read across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicity endpoints are consistent between the target substance and the read across analogs.
  - o According to the HESS categorization, the target substance and the read across analog tridecene-2-nitrile are categorized as aliphatic nitriles with hepatotoxicity alerts. The data presented in the repeated dose section above shows that the margin of exposure for the read across analog tridecene-2-nitrile is adequate at the current level of use. Therefore, this alert is superseded by the data.
  - o The target substance as well as the read across analog geranyl nitrile shows protein binding alerts and both are predicted to be sensitizers with low reliability. The data described in the skin sensitization section above confirms that the read across analog geranyl nitrile does not present a concern for the skin sensitization endpoint. Therefore, these alerts will be superseded by the data.
  - o The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.09.047.

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