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Short Review

RIFM fragrance ingredient safety assessment, 3,7-dimethyloctanenitrile, CAS Registry Number 40188-41-8

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Name: 3,7-Dimethyloctanenitrile
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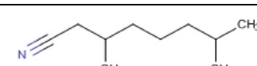

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
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

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NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe 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 includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

3,7-Dimethyloctanenitrile was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3,7-dimethyloctanenitrile is not genotoxic. Based on the existing data, 3,7-dimethyloctanenitrile does not present a safety concern for skin sensitization under the current, declared levels of use. Data on read-across material citronellyl nitrile (CAS # 51566-62-2) provided a calculated MOE > 100 for the repeated dose toxicity and reproductive and developmental toxicity endpoints. The local respiratory endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to 3,7-dimethyloctanenitrile is below the TTC (0 0.47 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 3,7-dimethyloctanenitrile is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3,7-dimethyloctanenitrile 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.

<u>**Human Health Safety Assessment**</u>

Genotoxicity: Not genotoxic.	(RIFM, 1988a BASF, 2004)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day.	RIFM (2008)
Developmental and Reproductive Toxicity: NOAEL = 500 mg/kg/day.	RIFM (2011)
Skin Sensitization: No safety concerns at current, declared use levels.	(RIFM, 2004; RIFM, 1989a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

<u>**Environmental Safety Assessment**</u>

Hazard Assessment:

Persistence: Critical Measured Value: 39% (OECD 301D)	RIFM (1989b)
Bioaccumulation: Screening-level: 116 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: *Daphnia magna* 48-h LC50: 2.82 mg/L	(ECOSAR; US EPA, 2012b)
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: *Daphnia magna* 48-h LC50: 2.82 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.282 μg/L	

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

1. Identification

1. **Chemical Name:** 3,7-Dimethyloctanenitrile
2. **CAS Registry Number:** 40188-41-8
3. **Synonyms:** 3,7-Dimethyloctanonitrile; Octanenitrile, 3,7-dimethyl-; Tetrahydrogeranylnitrile; Hypo-Lem; Dihydrocitronellylnitrile; 3,7-Dimethyloctanenitrile
4. **Molecular Formula:** $C_{10}H_{19}N$
5. **Molecular Weight:** 153.27
6. **RIFM Number:** 6306
7. **Stereochemistry:** Stereoisomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 217.9–222.3 C (0%–80% recovered) (RIFM, 1988c), 221.27 °C (EPI Suite)
2. **Flash Point:** 95 °C (GHS), 94.5 °C (RIFM, 1988c)
3. **Log K_{OW}:** Log Pow = 3.4 (RIFM, 2010), Log Pow = 3.77 at 25 °C (RIFM, 1988c), 3.64 (EPI Suite)
4. **Melting Point**: 10.09 °C (EPI Suite)
5. **Water Solubility:** 31.28 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0808 mm Hg @ 20 °C (EPI Suite v4.0), 0.123 mm Hg @ 25 °C (EPI Suite)

8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless to pale yellow or clear liquid with a medium citrus, aldehydic, lemon, fatty, metallic odor while at 10% in dipropylene glycol (Luebke, William tgsc, 2004)*

* http://www.thegoodscentscompany.com/data/rw1059281.html, retrieved 5/20/2015.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.064% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00028 mg/kg/day or 0.020 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.0020 mg/kg/day (RIFM, 2014)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

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:** Citronellyl nitrile (CAS # 51566-62-2)
   c. **Developmental and 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 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-Dimethyloctanenitrile 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available, accessed 10/06/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3,7-dimethyloctanenitrile does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The genotoxic potential of 3,7-dimethyloctanonitrile was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

The mutagenic activity of 3,7-dimethyloctanonitrile was assessed in a *Salmonella* (Ames) mutagenicity assay conducted in accordance with OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* WP2 uvrA were treated with 3,7-dimethyloctanonitrile in dimethyl sulfoxide (DMSO) at concentrations of 312.5, 625, 1250, 2500, and 5000 μg/plate in the presence and absence of S9. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1988a). Under the conditions of this study, 3,7-dimethyloctanonitrile was considered not mutagenic.

The clastogenic activity of 3,7-dimethyloctanonitrile 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 olive oil via oral gavage at concentrations of 450, 900, or 1800 mg/kg (males) and 312.5 mg/kg, 625 mg/kg, or 1250 mg/kg (females). Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (BASF, 2004). Under the conditions of the study, 3,7-dimethyloctanonitrile was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 3,7-dimethyloctanonitrile does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/02/18.

10.1.2. repeated dose toxicity

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

10.1.2.1. Risk assessment. There are limited repeated dose toxicity data on 3,7-dimethyloctanenitrile. In a GLP-compliant subchronic oral toxicity study, 3,7-dimethyloctanenitrile in corn oil was administered to groups of 5 CD rats/sex/dose at doses of 0, 5, 55, or 600 mg/kg/day for 28 days. One high-dose male rat died on day 24. The cause of death was unclear since changes in the heart, stomach, and spleen were observed during macroscopic and microscopic examination with abnormal clinical findings for most of the treatment period. At 600 mg/kg/day, salivation, hunched posture, decreased body weight and food consumption, statistically significant decreased red blood cell parameters (red blood cell counts, packed cell volume), and statistically significant changes in clinical chemistry parameters (albumin, globulin, alkaline phosphatase, urea nitrogen, GPT) were reported. A statistically significant increase in the relative liver weight and microscopic changes in the liver (cytoplasmic rarefaction of periportal hepatocytes) and spleen (hemosiderin deposition) were also observed. At 55 mg/kg/day, there were transient clinical signs of toxicity (hunched posture and salivation) and minor changes in clinical chemistry parameters (albumin and globulin) in males only. However, these clinical chemistry alterations were low in magnitude with no associated morphological changes. The NOAEL was considered to be 55 mg/kg/day (RIFM, 1989c).

Since there are limited data on the target material, read-across material citronellyl nitrile (CAS # 51566-62-2; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. In an enhanced OECD 408 90-day oral gavage study, groups of 10 Sprague Dawley rats received doses of 0, 10, 30, 100, or 300 mg/kg/day of citronellyl nitrile in corn oil. Marginal centrilobular hepatocyte hypertrophy 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 hypoplasia in the bone marrow was observed in the 300 mg/kg/day females; this was not statistically significant and was considered a marginal effect as there were no corresponding hematological changes. There were no other adverse findings during necropsy or histopathological examination. The NOAEL was considered to be 300 mg/kg/day, the highest dose tested (RIFM, 2008; also available in Letizia et al., 2009).

In addition, an enhanced OECD 415 oral gavage 1-generation reproductive toxicity study was conducted in groups of 25 Sprague Dawley rats/sex. The animals were treated with citronellyl nitrile at doses of 0, 75, 200, or 500 mg/kg/day in corn oil. Administration began before the cohabitation period (83 days for males; 14 days for females); continued through cohabitation (maximum of 14 days); and continued until the day before euthanasia (for males only), to day 25 of presumed gestation for females that did not deliver, or to day 22 of lactation for females that delivered. F1 generation rats selected for continued evaluation were euthanized on day 60 ± 3 postpartum. The NOAEL for general toxicity was considered to be 200 mg/kg/day, based on reduction in bodyweight gains and terminal body weights among the high-dose group males. No such effects were reported among the treated females. There were no other treatment-related adverse effects reported up to the highest dose tested (RIFM, 2011).

Since the doses selected for the 28-day study on the target material were not well spread out (5, 55, 600 mg/kg/day for the low-, mid-, and high-dose groups, respectively), data on a read-across material was included as part of this safety assessment. Alterations in hematology, clinical chemistry or microscopic findings in the spleen or liver were not observed in the more robust OECD 408 and 415 studies (as seen in the 28-day study on the target material). Thus, the NOAEL for the repeated dose toxicity endpoint was considered to be 300 mg/kg/day for this safety assessment.

Therefore, the 3,7-dimethyloctanenitrile 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 3,7-dimethyloctanenitrile, 300/0.002 or 150000.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/19/17.

10.1.3. developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are insufficient developmental toxicity data on 3,7-dimethyloctanenitrile. Read-across material, citronellyl nitrile (CAS # 51566-62-2; see section V) has sufficient developmental toxicity data to support the developmental toxicity endpoint. In an OECD 414 oral gavage study, groups of 25 pregnant female Wistar rats received doses of 0, 50, 150, or 450 mg/kg/day of citronellyl nitrile in corn oil. Maternal effects in the high-dose group included alterations in clinical chemistry parameters and increased liver weight. There were no adverse effects on the fetuses. The NOAEL for maternal and developmental toxicity was considered to be 150 mg/kg/day and 450 mg/kg/day, respectively (RIFM, 2016). In an enhanced OECD 415 1-generation oral gavage study, citronellyl nitrile was administered at doses of 0, 75, 200, or 500 mg/kg/day in corn oil to groups of 25 Sprague Dawley rats/sex. There were no adverse effects on the offspring. The NOAEL for developmental toxicity in this study was considered to be 500 mg/kg/day, the highest dose tested (RIFM, 2011). The NOAEL for the developmental toxicity endpoint was considered to be 500 mg/kg/day, the highest dose tested.

There are insufficient reproductive toxicity data on 3,7-dimethyloctanenitrile. Read-across material citronellyl nitrile (CAS # 51566-62-2; see section V) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. In an enhanced OECD 415 1-generation oral gavage study, citronellyl nitrile was administered at doses of 0, 75, 200, or 500 mg/kg/day in corn oil to groups of 25 Sprague Dawley rats/sex. There were no apparent effects of citronellyl nitrile on mating and fertility, reproductive organs, or sperm and estrus cycling parameters at any dose level tested. The NOAEL was considered to be 500 mg/kg/day, the highest dose tested (RIFM, 2011). In another study, citronellyl nitrile was administered via oral gavage to groups of 10 Sprague Dawley rats/sex. The study was conducted according to the OECD 408 protocol. The animals were treated with citronellyl nitrile at doses of 0, 10, 30, 100, or 300 mg/kg/day in corn oil. In addition to systemic toxicity parameters, 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; also available in Letizia et al., 2009). The NOAEL for the reproductive toxicity endpoint was considered to be 500 mg/kg/day, the highest dose tested.

Therefore, the 3,7-dimethyloctanenitrile 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 3,7-dimethyloctanenitrile, 500/0.002 or 250000.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/19/17.

10.1.4. skin sensitization

Based on the existing data, 3,7-dimethyloctanenitrile does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, 3,7-dimethyloctanenitrile does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v4.1). In a murine local lymph node assay (LLNA), 3,7-dimethyloctanenitrile was found to be negative up to the maximum tested concentration of 30%, which resulted in a Stimulation Index (SI) of 1.22 (RIFM, 2004). In guinea pigs, a Buehler test did not present reactions indicative of sensitization (RIFM, 1988b). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 1000 μg/cm^2 of 3,7-dimethyloctanenitrile in alcohol SDA 39C, no reactions indicative of sensitization was observed in any of the 52 volunteers (RIFM, 1989a).

Based on weight of evidence from structural analysis and animal and human studies, 3,7-dimethyloctanenitrile does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/02/18.

10.1.5. Phototoxicity/photoallergenicity

	Phototoxicity	Photoallergenicity
Step 1: UV benchmark (1000 L mol^{-1} · cm^{-1})	**Below**	
Step 2: Study data		
Step 3: Exposure benchmark		
Step 4: Read-across		
Step 5: Generate data		

Based on UV/Vis absorption spectra, 3,7-dimethyloctanenitrile would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3,7-dimethyloctanenitrile in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, 3,7-dimethyloctanenitrile does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/22/15.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 3,7-dimethyloctanenitrile 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-dimethyloctanenitrile. Based on the Creme RIFM Model, the inhalation exposure is 0.020 mg/day. This exposure is 23.5 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: None.

Literature Search and Risk Assessment Completed On: 01/05/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3,7-dimethyloctanenitrile was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3,7-dimethyloctanenitrile was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 did not identify 3,7-dimethyloctanenitrile as being either possibly persistent nor bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (IFRA, 2015), 3,7-dimethyloctanenitrile presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 1989b**:** Biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. The test material attained 39% biodegradation within 28 days.

10.2.2.2. Ecotoxicity. RIFM, 1988d**:** A study was conducted to assess the acute toxicity of the test material to rainbow trout (*Salmo gairdneri*) according to the OECD 203 method under semi-static conditions. The 96-h LC50 based on nominal test concentrations was 7.1 mg/L.

RIFM, 1988e: A study was performed to assess the acute toxicity of the test material to *Daphnia magna* according to the OECD 202 method. The 48-h EC50 for the test material based on measured test concentrations was 1.7 mg/L.

10.2.2.3. Other available data. 3,7-Dimethyloctanenitrile has been registered under REACH with no additional data at this time.

10.2.3. 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	7.738	X	X	1,000,000	0.007738	X
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.271	2.820	3.924	10,000	0.282	Neutral Organics

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002; #40315).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.64	3.64
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 1
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 0.282 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 06/01/15.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- 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://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/06/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.024.

Appendix

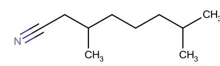
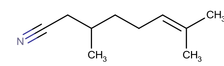
Read-across Justification

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). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.

- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	3,7-Dimethyloctanenitrile	Citronellyl nitrile
CAS No.	40188-41-8	51566-62-2
Structure		
Similarity (Tanimoto Score)		0.98
Read-across Endpoint		• Repeated dose toxicity • Developmental toxicity • Reproductive toxicity
Molecular Formula	$C_{10}H_{19}N$	$C_{10}H_{17}N$
Molecular Weight	153.27	151.25
Melting Point (°C, EPI Suite)	−10.09	−8.64
Boiling Point (°C, EPI Suite)	221.27	233.15
Vapor Pressure (Pa @ 25 °C, EPI Suite)	16.4	8.84
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.64	3.55
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	31.28	37.76
J_{max} (mg/cm^2/h, SAM)	4.30	5.01
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.95E-004	3.06E-004
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Aliphatic nitriles rank B	• Aliphatic nitriles rank B
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 3,7-dimethyloctanenitrile (CAS # 40188-41-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, citronellyl nitrile (CAS # 51566-62-2) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Citronellyl nitrile (CAS # 51566-62-2) was used as a read-across analog for the target material 3,7-dimethyloctanenitrile (CAS # 40188-41-8) for the repeated dose toxicity and developmental and reproductive toxicity endpoints.
  - The target substance and the read-across analog are structurally similar and belong to the class of aliphatic nitriles.
  - The target substance and the read-across analog share a 3,7-diemthyloctanenitrile structure.
  - The key difference between the target substance and the read-across analog is that the read-across analog has an unsaturated vinyl group while the target is completely saturated. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the branched aliphatic nitrile. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - Both the target substance and the read-across analog show structural alerts for aliphatic nitrile rank B for Repeated Dose (HESS) categorization. It is known that exposure to humans and experimental animals to some aliphatic nitriles leads to systemic toxicity. Although for many aliphatic nitriles, such toxicity has been suggested to result largely from the liberation of cyanide in the body, the mechanism and the extent of the liberation and consequently the acute toxicity have been shown to vary with the nitriles, the animal species, and the route of administration. Aliphatic organic compounds that contain a cyanide group (without a ring structure) are defined as the structural boundary of the category. The length of the carbon chain, the presence of an α-hydrogen atom, and the position of the double bond are important determinants for the extent of metabolism of aliphatic nitriles to cyanide. For rank B chemicals, the toxicity mechanism is well known but it is not validated because RDT data for enough compounds are not available. The data described for the read-across analog in the sections above show that the margin of exposure is adequate at the current level of use for the read-across analog. Based on the structural similarity and the data for the read-across analog, the alerts are superseded by data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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