Food and Chemical Toxicology 153 (2021) 112296

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, 2-methyldecanenitrile, CAS Registry Number 69300-15-8

A.M. Api [a], D. Belsito [b], S. Biserta [a], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], S. Gadhia [a], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

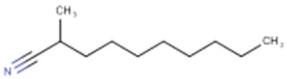
Handling Editor: Dr. Jose Luis Domingo

Keywords:
Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2021.112296
Received 29 January 2021; Received in revised form 5 April 2021; Accepted 19 May 2021
Available online 24 May 2021

Version: 012621. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available.



Name: 2-Methyldecanenitrile
CAS Registry Number: 69300-15-8

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, 2017bib_Comiskey_et_al_2015; Safford et al., 2015, 2017bib_Safford_et_al_2015bib_Safford_et_al_2017bib_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
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 as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

Summary: The existing information supports the use of this material as described in this safety assessment.

2-Methyldecanenitrile was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-methyldecanenitrile is not genotoxic. Data on read-across analog citronellyl nitrile (CAS # 51566-62-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data show that there are no safety concerns for 2-methyldecanenitrile for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-methyldecanenitrile is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to 2-methyldecanenitrile is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-methyldecanenitrile was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2009a; RIFM, 2009e)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day.	RIFM, (2008)
Reproductive Toxicity: NOAEL = 500 mg/kg/day.	RIFM, (2011)
Skin Sensitization: No safety concerns at current, declared use levels.	(RIFM, 2009f; RIFM, 2010)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV Spectra, RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 74% (OECD 301F)	RIFM, (2009c)
Bioaccumulation: Screening-level: 11.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 1.009 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: 48-h *Daphnia magna* LC50: 1.009 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.1009 μg/L

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

1. Identification

1. **Chemical Name:** 2-Methyldecanenitrile
2. **CAS Registry Number:** 69300-15-8
3. **Synonyms:** Decanenitrile, 2-methyl-; Frutonile; 2-Methyldecanonitrile; 2-Methyldecanenitrile
4. **Molecular Formula:** $C_{11}H_{21}N$
5. **Molecular Weight:** 167.96
6. **RIFM Number:** 5955
7. **Stereochemistry**: Isomer not specified. One Stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 250.43 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.2 (EPI Suite), Log P_{ow} = 4.2 (RIFM, 2009d)
4. **Melting Point**: 11.56 °C (EPI Suite)
5. **Water Solubility:** 8.892 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0266 mm Hg at 25 °C (EPI Suite), 0.0168 mm Hg at 20 °C (EPI Suite v4.0)
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:** Not Available

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0074% (RIFM, 2016e)
3. **Inhalation Exposure*:** 0.00027 mg/kg/day or 0.020 mg/day (RIFM, 2016e)
4. **Total Systemic Exposure**:** 0.00072 mg/kg/day (RIFM, 2016e)

*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 V. 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).

5. Derivation of systemic absorption

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

6. 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. **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

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

2-Methyldecanenitrile is not reported to occur in foods 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.

9. REACH dossier

Available; accessed 01/14/21.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-methyldecanenitrile does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2-methyldecanenitrile 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-methyldecanenitrile in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2009a). Under the conditions of the study, 2-methyldecanenitrile was not mutagenic in the Ames test.

The clastogenicity of 2-methyldecanenitrile was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung (V79) cells were treated with 2-methyldecanenitrile in DMSO at concentrations up to 1800 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (RIFM, 2009e). Under the conditions of the study, 2-methyldecanenitrile was considered to be non-clastogenic in the *in vitro* chromosome aberration assay. Based on the available data, 2-methyldecanenitrile does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/15/21.

11.1.2. Repeated dose toxicity

The MOE for 2-methyldecanenitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 2-methyldecanenitrile. Read-across material, citronellyl nitrile (CAS # 51566-62-2; see Section VI) 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).

Therefore, the 2-methyldecanenitrile 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 2-methyldecanenitrile, 300/0.00072 or 416667.

In addition, the total systemic exposure to 2-methyldecanenitrile (0.72 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) 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: 01/14/21.

11.1.3. Reproductive toxicity

The MOE for 2-methyldecanenitrile is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are insufficient developmental toxicity data on 2-methyldecanenitrile. Read-across material, citronellyl nitrile (CAS # 51566-62-2; see section VI) 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, 2016a). 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 fertility data on 2-methyldecanenitrile. Read-across material, citronellyl nitrile (CAS # 51566-62-2; see section V) has sufficient fertility 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 2-methyldecanenitrile 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 2-methyldecanenitrile, 500/0.00072 or 694444.

In addition, the total systemic exposure to 2-methyldecanenitrile (0.72 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) 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: 01/14/21.

11.1.4. Skin sensitization

Based on the existing data, 2-methyldecanenitrile does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, 2-methyldecanenitrile 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 v3.1.0; OECD toolbox v4.2). 2-Methyldecanenitrile was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens but positive in a human Cell Line Activation Test (h-CLAT) and U937-CD86 test (RIFM, 2016b; RIFM, 2016c; RIFM, 2016d). In a murine local lymph node assay (LLNA), 2-methyldecanenitrile was not found to be sensitizing up to 100% with a Stimulation Index (SI) of 2.7 (RIFM, 2009f). In guinea pigs, a maximization test and a Buehler test did not present reactions indicative of sensitization (RIFM, 1989; RIFM, 1982). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 2250 μg/cm^2 of 2-methyldecanenitrile in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2010). Based on weight of evidence from structural analysis and animal and human studies, 2-methyldecanenitrile 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: 01/14/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-methyldecanenitrile would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-methyldecanenitrile in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009).

Based on lack of absorbance, 2-methyldecanenitrile does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The 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: 01/14/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The exposure level for 2-methyldecanenitrile is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-methyldecanenitrile. 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: RIFM, 2009b.

Literature Search and Risk Assessment Completed On: 01/14/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-methyldecanenitrile 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 ECHA, 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, 2-methyldecanenitrile 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 (EPI Suite, 2012a) did not identify 2-methyldecanenitrile as possibly being either persistent or 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.

Risk Assessment: Based on current Volume of Use (2015), 2-methyldecanenitrile presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 2009c: The ready biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. The test material at a concentration of 30 mg/L (dry weight) was incubated for 31 days. Under the conditions of the study, biodegradation of 74% was observed.

Ecotoxicity: No data available.

11.2.3. Other available data

2-Methyldecanenitrile has been registered for REACH with no additional data at this time.

11.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.2	4.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1009 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: 01/15/21.

12. Literature search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.760			1,000,000	0.002760	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.450	1.009	1.742	10,000	0.1009	Neutral organics

- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/26/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112296.

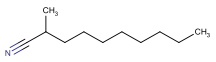
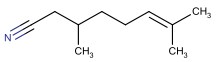
Appendix

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, 2017).

- 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	2-Methyldecanenitrile	Citronellyl nitrile
CAS No.	69300-15-8	51566-62-2
Structure		
Similarity (Tanimoto Score)		0.78
Read-across Endpoint		• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{11}H_{21}N$	$C_{10}H_{17}N$
Molecular Weight	167.30	151.25
Melting Point (°C, EPI Suite)	11.56	−8.64
Boiling Point (°C, EPI Suite)	250.43	233.15
Vapor Pressure (Pa @ 25 °C, EPI Suite)	3.55	8.84
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.20	3.55
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	8.89	37.76
J_{max} (μg/cm^2/h, SAM)	6.354	23.710
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.96E+001	3.10E+001
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Aliphatic nitriles rank B	• Aliphatic nitriles rank B
Reproductive 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 2-methyldecanenitrile (CAS # 69300-15-8). 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 2-methyldecanenitrile (CAS # for 69300-15-8) for the reproductive toxicity and the repeated dose toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic nitriles.
  - o The key difference between the target substance and the read-across analog is that the read-across analog has vinyl unsaturation while the target is completely saturated. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the aliphatic nitrile. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target substance corresponds to skin absorption $\leq$40%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$80%. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o Both the target substance and the read-across analog show a structural alert of aliphatic nitrile rank B for Repeated Dose (HESS) categorization. It is known that exposure of 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 of 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 read-across analog, the alerts are superseded by data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2017. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Letizia, C., Politano, V.T., Api, A.M., 2009. Subchronic toxicity of citronellyl nitrile in rats. Toxicologist 108 (1), 105.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1982. Guinea Pig Skin Sensitisation Test with 2-methyldecanenitrile. Unpublished report from Quest International. RIFM report number 46463. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1989. Delayed Dermal Sensitization Study of 2-methyldecanenitrile in the guinea Pig. Unpublished report from Firmenich Incorporated. RIFM report number 31689. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2008. Ninety Day Repeated Dose Oral (Gavage) Toxicity Study with Citronellyl Nitrile in the Rat. RIFM report number 54447. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2009a. Salmonella typhimurium and Escherichia coli Reverse Mutation Assay with 2-methyldecanenitrile (Frutonile). Unpublished report from Givaudan. RIFM report number 57285. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2009b. 4-Hour Acute Inhalation Toxicity Study in Rats with 2-methyldecanenitrile (Frutonile). Unpublished report from Givaudan. RIFM report number 57895. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2009c. Ready Biodegradabiity with 2-methyldecanenitrile (Frutonile). Unpublished report from Givaudan. RIFM report number 57896. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2009d. Partition Coefficient N-Octanol/water with 2-methyldecanenitrile (Frutonile). Unpublished report from Givaudan. RIFM report number 57897. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2009e. In Vitro Chromosome Aberration Test in Chinese Hamster V79 Cells with 2-methyldecanenitrile (Frutonile). Unpublished report from Givaudan. RIFM report number 58911. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2009f. Local Lymph Node Assay (LLNA) in Mice with 2-methyldecanenitrile (Frutonile). Unpublished report from Givaudan. RIFM report number 58912. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2010. Repeated Insult Patch Test with 2-methyldecanenitrile (Frutonile). Unpublished report from Givaudan. RIFM report number 57898. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2011. Oral (Gavage) One-Generation Reproduction Study of Citronellyl Nitrile in Rats, with an Evaluation through Sexual Maturity in the F1 Generation. RIFM report number 60972. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016a. Citronellyl Nitrile: Prenatal Developmental Toxicity Study in Wistar Rats Oral Administration (Gavage). Unpublished report from BASF. RIFM report number 69979. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016b. Direct Peptide Reactivity Assay (DPRA) in Fragrance Materials. RIFM report number 72225. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016c. Induction of Antioxidant-Response-Element Dependent Gene Activity and Cytotoxicity (Using MTT) in the Keratinocyte ARE-Reporter Cell Line KeratinoSens for Fragrance Materials. RIFM report number 72232. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016d. 2-Methyldecanenitrile: in Vitro Sensitization: Dendritic Cell Line Activation Assay Human Cell Line Activation Test (H-CLAT). RIFM report number 72768. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016e. Exposure Survey 11, May 2016.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.