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RIFM fragrance ingredient safety assessment, myristo nitrile, CAS Registry Number 629-63-0

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

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, 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*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, 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*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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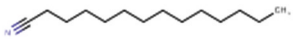

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Name: Myristo nitrile CAS Registry Number: 629-63-0

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

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

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
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.

Myristo nitrile was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog dodecanenitrile (CAS # 2437-25-4) show that myristo nitrile is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Target data and data from read-across analog octanenitrile (CAS # 124-12-9) show that there are no safety concerns for myristo nitrile for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; myristo nitrile 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; exposure is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; myristo nitrile 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.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(Intermediate ECHA REACH Dossier: Dodecanenitrile; ECHA, 2011)
Repeated Dose Toxicity: NOEL = 16.7 mg/kg/day.	(Full ECHA REACH Dossier: Dodecanenitrile; ECHA, 2017a)
Reproductive Toxicity: NOAEL = 250 mg/kg/day.	(Full ECHA REACH Dossier: Dodecanenitrile; ECHA, 2017a)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(Natsch et al., 2013)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: NOAEC not available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.95 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 121.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.059 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: 0.059 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0059 μg/L

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

1. Identification

1. **Chemical Name:** Myristo nitrile
2. **CAS Registry Number:** 629-63-0
3. **Synonyms:** LRG 1250; Tetradecanenitrile; Myristonitrile; Tetradecanonitrile; Oranile; Myristo nitrile
4. **Molecular Formula:** $C_{14}H_{27}N$
5. **Molecular Weight:** 209.37 g/mol
6. **RIFM Number:** 1223
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 286 °C (Fragrance Materials Association [FMA]), 307.52 °C (EPI Suite)
2. **Flash Point:** 148 °C (Quest), 148 °C (Globally Harmonized System)
3. **Log K_{OW}:** 5.75 (EPI Suite)
4. **Melting Point**: 52.63 °C (EPI Suite)
5. **Water Solubility:** 0.2625 mg/L (EPI Suite)
6. **Specific Gravity:** 0.828 (RIFM), 0.83 (FMA)
7. **Vapor Pressure:** 0.000787 mm Hg at 20 °C (EPI Suite v4.0), 0.00131 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance** 0.100% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000015 mg/kg/day or 0.0011 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0010 mg/kg/day (RIFM, 2021)

*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

Cramer Classification

Class III, High

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
III	III	III

Analogs Selected

a.**Genotoxicity**
Dodecanenitrile (CAS # 2437-25-4)
b.**Repeated Dose Toxicity**
Dodecanenitrile (CAS # 2437-25-4)
c.**Reproductive Toxicity**
Dodecanenitrile (CAS # 2437-25-4)
d.**Skin Sensitization**
Octanenitrile (CAS # 124-12-9)
e.**Phototoxicity/Photoallergenicity**
None
f.**Local Respiratory Toxicity**
None
g.**Environmental Toxicity**
None

Read-across Justification

See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

Myristo nitrile is reported to occur in the following foods by the VCF*:

Pork.

*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

Myristo nitrile has been pre-registered for 2010; no dossier available as of 02/28/22.

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, myristo nitrile does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Myristo nitrile was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of myristo nitrile; however, read-across can be made to dodecanenitrile (CAS # 2437-25-4; see Section VI).

The mutagenic activity of dodecanenitrile was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100, and *Escherichia coli* strain WP2uvrA were treated with dodecanenitrile in dimethyl sulfoxide (DMSO) at the concentrations up to 10000 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was observed at the

concentrations tested (ECHA, 2011). Under the conditions of the study, dodecanenitrile was considered not mutagenic in the Ames test, and this can be extended to myristo nitrile.

The clastogenic activity of dodecanenitrile was assessed in an *in vitro* chromosome aberration assay conducted in compliance with GLP regulations and in accordance with OECD 473. Chinese hamster lung fibroblasts (V79 cells) were exposed to dodecanenitrile in acetone at the following concentrations without S9 mix, 4 h μg/mL: 1.6, 3.1, 6.3, 12.5, 25.0, 50.0 μg/mL, and with S9 mix, 4-h μg/mL: 57.8, 115.6, 231.3, 462.5, 925.0, 1850.0. In a second experiment, the concentrations were: without S9 mix, 18 h μg/mL: 0.8, 1.6, 3.1, 6.3, 12.5, 25.0; without S9 mix, 28 h μg/mL: 3.1, 6.3, 12.5, 25.0, 50.0, 75.0; with S9-mix, 4-h μg/mL: 57.8, 115.6, 231.3, 462.5, 925.0, 1850.0 μg/mL. No biologically relevant increase in the frequencies of polyploid metaphases was observed after treatment with the test material as compared to the frequencies of the controls (ECHA, 2011). Under the conditions of the study, dodecanenitrile was considered to be non-clastogenic to mammalian cells, and this can be extended to myristo nitrile.

Based on the available data, dodecanenitrile does not present a concern for genotoxic potential, and this can be extended to myristo nitrile.

Additional References: RIFM, 2008; RIFM, 2009; RIFM, 2013a.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

The MOE for myristo nitrile is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on myristo nitrile. Read-across material dodecanenitrile (CAS # 2437-25-4; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 422-compliant study, groups of 10 Wistar rats/sex/dose were administered dodecanenitrile via gavage (vehicle: 2% methylcellulose) at doses of 0, 50, 250, or 1000 mg/kg/day. Dodecanenitrile was administered to male rats for at least 28 days and to female rats for 14 days prior to pairing, through the pre-pairing, pairing, and gestation periods until the F1 generation reached day 4 postpartum. Mortality and alteration in clinical signs were reported among the high-dose group of females. Alterations in clinical signs were also reported among high-dose males and mid-dose females. Hematological alterations were reported among high-dose males; however, the significance remained unknown. During gross necropsy, the high-dose males were reported to have an enlarged liver and a reduction in thymus size. High-dose females were reported to have an enlarged liver, stomach with discolorations, crateriform retractions and foci, and enlarged adrenal glands. Secondary to the spontaneous deaths, the start of autolysis, ileum distended with gas, discoloration, incompletely collapsed lungs, urinary bladder distended, and discoloration of the liver were observed. High-dose males had a significant increase in the absolute and relative liver weights. Histopathological examination revealed minimal to moderate centrilobular to diffuse hepatocellular hypertrophy and atrophy/involution in the thymus among high-dose group males. Mid- and high-dose males showed ulceration, erosion, and mucosal necrosis in the forestomach and glandular stomach. The high-dose male kidneys showed an increase in tubular basophilia. High-dose females showed moderate, centrilobular to diffuse hepatocellular hypertrophy, along with incidences of moderate centrilobular necrosis and apoptosis. Increased incidence of ulceration, erosion, and mucosal necrosis in the forestomach and glandular stomach were reported among mid- and high-dose females. Ulceration was also reported to occur in the duodenum of high-dose females. Thus, the NOAEL was considered to be 50 mg/kg/day, based on histopathological alterations in the GI tract and liver, along with clinical signs among males and females of higher dose groups and mortality among high-dose group females (ECHA, 2017a).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 50/3, or 16.7 mg/kg/day.

Therefore, the myristo nitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the dodecanenitrile NOAEL in mg/kg/day by the total systemic exposure to myristo nitrile, 16.7/0.0010, or 16700.

In addition, the total systemic exposure to myristo nitrile (1.0 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.

*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: 09/22/21.

11.1.3. Reproductive toxicity

The MOE for myristo nitrile is adequate for the reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on myristo nitrile. Read-across material dodecanenitrile (CAS # 2437-25-4; see Section VI) has sufficient data to support the reproductive toxicity endpoints. In an OECD 422-compliant study, groups of 10 Wistar rats/sex/dose were administered dodecanenitrile via gavage (vehicle: 2% methylcellulose) at doses of 0, 50, 250, or 1000 mg/kg/day. Dodecanenitrile was administered to male rats for at least 28 days and to female rats for 14 days prior to mating, through the pre-mating, mating, and gestation periods until the F1 generation reached day 4 postpartum. At the high dose, 4 dams died spontaneously on day 1 postpartum, and 2 dams were euthanized in extremis on days 1 and 4 postpartum. Statistically significant decreases in birth and viability indices were observed at the high dose. At the high dose, pup body weight was slightly reduced on day 1 postpartum but distinctly reduced on day 4 postpartum; however, the results were based only on the data of 1 litter. Thus, the fertility NOAEL for this study was considered to be 250 mg/kg based on maternal death at the high dose. The developmental toxicity NOAEL for this study was considered to be 250 mg/kg/day based on decreased pup body weights and decreased birth and viability indices at the high dose (ECHA, 2017a).

Therefore, the myristo nitrile MOE for the reproductive toxicity endpoint can be calculated by dividing the dodecanenitrile NOAEL in mg/kg/day by the total systemic exposure to myristo nitrile, 250/0.0010, or 250000.

In addition, the total systemic exposure to myristo nitrile (1.0 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: 09/22/21.

11.1.4. Skin sensitization

Based on the existing data and read-across material octanenitrile (CAS # 124-12-9), myristo nitrile does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for myristo nitrile. Based on the existing data and read-across material octanenitrile (CAS # 124-12-9; see Section VI), myristo nitrile does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material octanenitrile was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and U-SENS test (Natsch et al., 2013). In guinea pig sensitization studies, no reactions indicative of sensitization were observed with myristo nitrile (RIFM, 1975a; RIFM, 1975d). Additionally, in a Buehler test, read-across material octanenitrile did not present reactions indicative of sensitization (RIFM, 1989). A human maximization test on 30 subjects with 2% or 1380 μg/cm^2 myristo nitrile in petrolatum did not result in sensitization reactions in any of the subjects tested (RIFM, 1982).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across octanenitrile, myristo nitrile does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1975c; RIFM, 1975b.

Literature Search and Risk Assessment Completed On: 10/12/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, myristo nitrile 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 myristo nitrile in experimental models. UV/Vis absorption spectra indicate no 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 the lack of absorbance, myristo nitrile 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 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: 09/28/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are limited inhalation data available on myristo nitrile. Based on the Creme RIFM Model, the inhalation exposure is 0.0011 mg/day. This exposure is 427.3 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, 2018.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of myristo nitrile 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, myristo nitrile was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify myristo nitrile as possibly 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), myristo nitrile presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

Other available data

Myristo nitrile has been pre-registered for REACH with no additional data at this time.

11.2.3. 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)**	0.154			1000000	0.000154	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.074	0.059	0.185	10000	0.0059	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.75	5.75
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<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 0.0059 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 VoU.

Literature Search and Risk Assessment Completed On: 10/06/21.

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
- **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 02/28/22.

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.2022.112928.

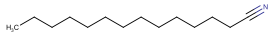
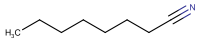
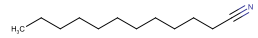
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

- 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 material and the read-across analogs were calculated using EPI Suite (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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Myristo nitrile	Octanenitrile	Dodecanenitrile
CAS No.	629-63-0	124-12-9	2437-25-4
Structure			
Similarity (Tanimoto Score)		1.00	1.00
SMILES	CCCCCCCCCCCCCC#N	CCCCCCCC#N	CCCCCCCCCCCC#N
Endpoint		Skin sensitization	Genotoxicity Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{14}H_{27}N$	$C_8H_{15}N$	$C_{12}H_{23}N$
Molecular Weight (g/mol)	209.377	125.215	181.323
Melting Point (°C, EPI Suite)	19.00	−45.60	4.00
Boiling Point (°C, EPI Suite)	307.52	205.20	277.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.75E-01	5.20E+01	3.15E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.63E-01	2.34E+02	2.51E+00
Log KOW	5.75	2.75	4.77
J_{max} (μg/cm^2/h, SAM)	0.04	23.66	0.42
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.28E+01	1.69E+01	5.26E+01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found		No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found		No alert found
Carcinogenicity (ISS)	No alert found		No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found		No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found		No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found		No alert found
Oncologic Classification	Not classified		Not classified
Repeated Dose Toxicity			
Repeated Dose (HESS)	Aliphatic nitriles (Hepatotoxicity) Rank B		Aliphatic nitriles (Hepatotoxicity) Rank B
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Non-toxicant (low reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	
Protein Binding (OECD)	No alert found	No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified.	No skin sensitization reactivity domain alerts were identified.	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on the target material, myristo nitrile (CAS # 629-63-0). Hence *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, octanenitrile (CAS # 124-12-9) and dodecanenitrile (CAS # 2437-25-4) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusions

- Dodecanenitrile (CAS # 2437-25-4) was used as a read-across analog for the target material myristo nitrile (CAS # 629-63-0) for the genotoxicity, reproductive toxicity, and repeated dose toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to the structural class of aliphatic saturated nitriles.
  - The target material and the read-across analog share a decanenitrile substructure.
  - The key difference between the target material and the read-across analog is the length of the aliphatic chain, which differs by only 2 carbons. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox, structural alerts for toxic endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are categorized as aliphatic nitriles Rank B with hepatotoxicity alert by HESS categorization for repeated dose toxicity. The data described in the repeated dose toxicity section shows that the MOE for the read-across analog is adequate at the current level of use. Therefore, this alert will be superseded by the availability of the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural differences between the target material and the read-across analog do not affect consideration of the toxic endpoints.
- Octanenitrile (CAS # 124-12-9) was used as a read-across analog for the target material myristo nitrile (CAS # 629-63-0) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of aliphatic saturated nitriles.
  - The target material and the read-across analog share a decanenitrile substructure.
  - The key difference between the target material and the read-across analog is the length of the aliphatic chain, which differs by only 1 or 2 carbons. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq$80% skin absorption for the target material, while it translates to $\leq$40% absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target material and the appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - According to the QSAR OECD Toolbox, structural alerts for toxic endpoints are consistent between the target material and the read-across analog.
  - There are no *in silico* alerts for the target material or the read-across analog, which is consistent with data.
  - The target material and the read-across analog are predicted to be sensitizers by the CAESAR model for skin sensitization. There are no other protein binding alerts for both of the substances related to the skin sensitization endpoint. The data described in the skin sensitization section show that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, this prediction will be superseded by the availability of the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural differences between the target material and the read-across analog do not affect consideration of the toxic endpoints.

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, 2011. Intermediate Registration Dossier Dodecanenitrile. Retrieved from. https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/2083/1/2.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017a. Full Registration Dossier Dodecanenitrile. Retrieved from. https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/20698/1/2.

ECHA, 2017b. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

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.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

Natsch, A., Ryan, C.A., Foertsch, L., Emter, R., Jaworska, J., Gerberick, F., Kern, P., 2013. A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation. J. Appl. Toxicol. 33 (11), 1337–1352.

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, 1975a. Skin Irritation and Capacity for Allergic Sensitization of Myristonitrile Determined by the Open Epicutaneous Test (OET) on guinea Pigs. Unpublished Report from Roure, Inc. RIFM Report Number 1654. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1975b. Capacity for Allergic Sensitization Determined by the Maximization Test (MT) of Myristonitrile on guinea Pigs. Unpublished Report from Roure, Inc. RIFM Report Number 1655. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1975c. Capacity for Allergic Sensitization Determined by the Draize Test (DT) on guinea Pigs. Unpublished Report from Roure, Inc. RIFM Report Number 1656. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1975d. Capacity of Allergic Sensitization Determined by the Intradermal Test of Myristonitrile with Freund's Complete Adjuvant (FCAT) in guinea Pigs. Unpublished Report from Roure, Inc. RIFM Report Number 1657. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1982. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1643. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1989. Delayed Dermal Sensitisation Study in the guinea Pig with Octanenitrile. Unpublished Report from Firmenich SA. RIFM Report Number 38769. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2008. In Vitro Chromosome Aberration Test in Chinese Hamster V79 Cells with Dodecanenitrile. RIFM Report Number 54625. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2009. Battery of Genotoxicity Studies Conducted on a Group of Structurally Related Nitriles. RIFM Report Number 56493. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2013a. Evaluation of Genotoxicity of Nitrile Fragrance Ingredients Using in Vitro and Invivo Assays. RIFM Report Number 66369. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2013b. Report on the Testing of Myristo Nitrile in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66145. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2018. Myristo Nitrile (Oranile): Acute Inhalation Toxicity (Acute Toxic Class Method) in Rats. Unpublished Report from Givaudan. RIFM Report Number 77736. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2020. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM Report Number 76272. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2021. Exposure Survey 30, January 2021.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
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, v2.0. United States Environmental Protection Agency, Washington, DC, USA.