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RIFM fragrance ingredient safety assessment, nonen acid nitrile, CAS Registry Number 29127-83-1

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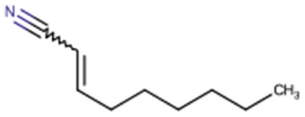
Name: Nonen acid nitrile CAS Registry Number: 29127-83-1



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
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 (Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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 Test 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.

Nonen acid nitrile was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog tridecene-2-nitrile (CAS # 22629-49-8) show that nonen acid nitrile is not expected to be genotoxic. Data on analog tridecene-2-nitrile (CAS # 22629-49-8) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints and a No Expected Sensitization Induction Level (NESIL) of 6900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; nonen acid 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; nonen acid 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.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2007; RIFM, 2004)
Repeated Dose Toxicity: NOAEL = 67 mg/kg bw/day. RIFM (2016d)
Reproductive Toxicity: Developmental toxicity: NOAEL = 200 mg/kg bw/day. Fertility: NOAEL = 200 mg/kg bw/day. RIFM (2016d)
Skin Sensitization: NESIL = 6900 μg/cm^2. RIFM (2017)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

(*continued on next page*)

(*continued*)

Persistence:	
Critical Measured Value: 69% (OECD 301F)	RIFM (2016c)
Bioaccumulation:	
Screening-level: 49.81 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 6.52 mg/L	(RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 6.52 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00652 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Nonen acid nitrile
2. **CAS Registry Number:** 29127-83-1
3. **Synonyms:** Irisnitril; Non-2-enenitrile; Orenyle; アルキル（又はアルケニル，C = 8 ~ 18）ニトリル; Nonen acid nitrile
4. **Molecular Formula:** $C_9H_{15}N$
5. **Molecular Weight:** 137.22 g/mol
6. **RIFM Number:** 1216
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 230.87 °C (EPI Suite)
2. **Flash Point:** 186 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 3.08 (EPI Suite), 3.67 (weighted average mean of 3.57 and 3.71) at 22.6 °C (RIFM, 2016b)
4. **Melting Point**: −0.46 °C (EPI Suite)
5. **Water Solubility:** 110 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0485 mm Hg at 20 °C (EPI Suite v4.0), 0.1 mm Hg at 20 °C (FMA), 0.0747 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide Band)

1. <0.1 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0003% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.0000016 mg/kg bw/day or 0.00012 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.000012 mg/kg bw/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (RIFM, 2015a; 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 (RIFM, 2015a; 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

6.1. 1. Cramer Classification: Class III, High

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

6.2. 2. Analogs Selected

Genotoxicity: Tridecene-2-nitrile (CAS # 22629-49-8)

b. **Repeated Dose Toxicity:** Tridecene-2-nitrile (CAS # 22629-49-8)
c. **Reproductive Toxicity:** Tridecene-2-nitrile (CAS # 22629-49-8)
d. **Skin Sensitization:** Tridecene-2-nitrile (CAS # 22629-49-8)
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.

Additional References: None.

8. Natural occurrence

Nonen acid nitrile 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

Pre-registered for 2010; no dossier available as of 11/01/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for nonen acid nitrile are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.19
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	0.57
4	Products related to fine fragrances	2.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.75
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.19
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.38
5D	Baby cream, oil, talc	0.063
6	Products with oral and lip exposure	0.19
7	Products applied to the hair with some hand contact	0.57
8	Products with significant ano-genital exposure (tampon)	0.063
9	Products with body and hand exposure, primarily rinse-off (bar soap)	5.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.19
10B	Aerosol air freshener	0.75
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.063
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For nonen acid nitrile, the basis was the subchronic reference dose of 0.67 mg/kg bw/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 6900 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, nonen acid nitrile does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of nonen acid nitrile has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA102 were treated with nonen acid nitrile 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 dose in the presence or absence of S9 (RIFM, 2007). Under the conditions of the study, nonen acid nitrile was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of nonen acid nitrile; however, read-across can be made to tridecene-2-nitrile (CAS # 22629-49-8; see Section VI). The clastogenic activity of read-across analog tridecene-2-nitrile (CAS # 22629-49-8) was evaluated in an in vivo micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in Arachis oil via intraperitoneal injection to groups of male mice. Doses of 1000, 500, and 250 mg/kg were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2004). Under the conditions of the study, tridecene-2-nitrile was considered to be not clastogenic in the in vivo micronucleus test, and this can be extended to nonen acid nitrile.

Based on the data available, nonen acid nitrile does not present a concern for genotoxic potential.

Additional References: RIFM, 1981; RIFM, 2008; RIFM, 2015c.

Literature Search and Risk Assessment Completed On: 10/02/20.

11.1.2. Repeated dose toxicity

The MOE for nonen acid 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 nonen acid nitrile. Read-across material, tridecene-2-nitrile (CAS # 22629-49-8; see Section VI), has sufficient repeated dose toxicity data. A 2-week gavage, non-GLP dose range finding (DRF) study was conducted on groups of 5 Sprague Dawley Crl:CD BR strain rats/sex/group to determine the dose for an OECD 422 study. The animals were treated with test material tridecene-2-nitrile at doses of 0 (corn oil), 100, 300, and 1000 mg/kg bw/day. Mortality was reported among the animals of the high-dose group only. Alterations in the hematological and clinical chemistry parameters were reported among the high-dose females. Hematological alterations included low values in erythrocyte count, hemoglobin, hematocrit, and leukocyte counts among 2 moribund high-dose females. High values in alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, total cholesterol, and triglycerides were noted in 1 high-dose moribund female. No such alterations were reported among the mid- and low-dose animals. A decrease in body weight was reported among the high-dose animals. Ulceration of the glandular stomach was commonly observed in most of the dead or moribund males. The focus of the glandular stomach and thickening/perforation of the forestomach were noted in most of the dead or moribund females. No other treatment-related macroscopic alteration was reported among the animals of the mid- and low-dose groups. The absolute and relative liver weights were prominently increased in 1 moribund male and 1 moribund female at 1000 mg/kg bw/day. The relative liver weight was significantly increased in the males of the 300 mg/kg bw/day group when compared to the control group. Based on the result of this study, the dose levels for the combined repeated dose toxicity study with a reproduction/developmental toxicity screening test were selected to be at 200 mg/kg bw/day for the high-dose level and at 20 mg/kg bw/day for the low-dose level. Thus, the NOAEL for the repeated dose toxicity endpoint was considered to be 20 mg/kg bw/day (RIFM, 2016a).

A gavage GLP/OECD 422 study was conducted on groups of 5 Sprague Dawley Crl:CD SD strain rats/sex/group where the test material tridecene-2-nitrile was administered at doses of 0 (corn oil), 20, 60, and 200 mg/kg bw/day. There were no alterations in body weight or clinical signs, food consumption, estrous cycles (females), reproductive function and pup examinations, sensory and motor activities among parental animals, urinalysis, hematology, clinical chemistry, and thyroid hormone analysis. Local effects on the stomach were reported among a few of the control and treated animals. Macroscopic alterations included a

focus on the mucosa of the glandular stomach in 1 high-dose male, 1 control female, and mid- and low-dose females, along with polyp/thickening of mucosa in the forestomach in 1 high-dose female. Microscopic alterations included epithelial hyperplasia/hyperkeratosis with inflammatory cell infiltration in the forestomach submucosa in 1 high-dose female. This finding corresponded to macroscopically observed polyp/thickening of the forestomach. Erosion of the mucosa in the glandular stomach was observed in 1 high-dose male and mid- and high-dose females. This finding was in concordance with macroscopically observed focus on the mucosa of the glandular stomach. At the end of the recovery period, these findings were not observed in any animals indicating that these effects were reversible. The effects on the stomach were considered to be local effects and reversible, hence not considered towards deriving a NOAEL. Thus, the NOAEL for the repeated dose toxicity was considered to be 200 mg/kg bw/day, the highest dose tested (RIFM, 2016d).

A default safety factor of 3 was used when deriving a NOAEL from the 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 200/3 or 67 mg/kg bw/day.

Therefore, the nonen acid nitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the tridecene-2-nitrile NOAEL by the total systemic exposure to nonen acid nitrile, 67/0.000012, or 5583333.

In addition, the total systemic exposure to nonen acid nitrile (0.012 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Derivation of subchronic reference dose (RfD)

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic RfD of 0.67 mg/kg bw/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for nonen acid nitrile was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 67 mg/kg bw/day by the uncertainty factor, 100 = 0.67 mg/kg bw/day.

*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: 10/01/20.

11.1.3. Reproductive toxicity

The MOE for nonen acid nitrile is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on nonen acid nitrile. Read-across material tridecene-2-nitrile (CAS # 22629-49-8; see Section VI) has sufficient reproductive toxicity data. A gavage GLP/OECD 422 study conducted on groups of 5 Sprague Dawley Crl:CD SD strain rats/sex/group were administered the test material, tridecene-2-nitrile at doses of 0 (corn oil), 20, 60, and 200 mg/kg bw/day. There were no alterations in body weight, clinical signs, food consumption, estrous cycles (females), reproductive function, pup examinations, sensory and motor activities among parental animals, urinalysis, hematology, clinical chemistry, and thyroid hormone analysis. The NOAEL for reproductive toxicity was considered to be 200 mg/kg bw/day, the highest dose tested (RIFM, 2016d).

Therefore, the nonen acid nitrile MOE for the reproductive toxicity endpoint can be calculated by dividing the tridecene-2-nitrile NOAEL by the total systemic exposure to nonen acid nitrile, 200/0.000012, or 16666667.

In addition, the total systemic exposure to nonen acid nitrile (0.012 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/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: 10/01/20.

11.1.4. Skin sensitization

Based on the existing data and read-across analog tridecene-2-nitrile (CAS # 22629-49-8), nonen acid nitrile is considered a skin sensitizer with a defined NESIL of 6900 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for nonen acid nitrile. Based on the existing data and read-across tridecene-2-nitrile (CAS # 22629-49-8; see Section VI), nonen acid nitrile is considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Toxtree v3.1.0; OECD Toolbox v4.2). In a Buehler test, no reactions were observed with nonen acid nitrile (RIFM, 1984a). In a GLP-compliant murine local lymph node assay (LLNA), read-across material tridecene-2-nitrile was found to be sensitizing with an EC3 value of 28% (7000 μg/cm^2) (RIFM, 2015b). Similarly, skin sensitization reactions were observed in a GLP-compliant guinea pig maximization test, when 10% read-across tridecene-2-nitrile was used for both intradermal and topical induction (RIFM, 1982). However, skin sensitization reactions were not observed in another guinea pig maximization test when 0.5% and 1% tridecene-2-nitrile were used for intradermal and topical induction, respectively (RIFM, 1985). In a guinea pig open epicutaneous test (OET) and a Freund's complete adjuvant test (FCAT), read-across material tridecene-2-nitrile presented reactions indicative of sensitization (RIFM, 1977). However, in a human maximization test, no skin sensitization reactions were observed with tridecene-2-nitrile (RIFM, 1986). In a Confirmation of No Induction in Humans test (CNIH), no reactions indicative of sensitization were observed when 0.125% or 97 μg/cm^2 nonen acid nitrile in ethanol was used for induction and challenge in any of the 40 volunteers (RIFM, 1965). Additionally, in 2 CNIHs with read-across material, tridecene-2-nitrile, 5.9% or 6967 μg/cm^2 in 1:3 ethanol:diethyl phthalate (EtOH:DEP) and 2% or 2000 μg/cm^2 in dimethyl phthalate (DMP), no reactions indicative of sensitization were observed in any of the 108 and 48 volunteers, respectively (RIFM, 2017; RIFM, 1980).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and data on the read-across material tridecene-2-nitrile, nonen acid nitrile is a weak sensitizer with a WoE NESIL of 6900 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a subchronic RfD of 0.67 mg/kg bw/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/03/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, nonen acid nitrile would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for

Table 1
Data summary for tridecene-2-nitrile as read-across material for nonen acid nitrile.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
7000 [1]	Weak	6967	690	NA	6900

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = Lowest observed effect level; NA = Not Available.
[a] Based on animal data (LLNA) using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

phototoxicity and photoallergenicity (Henry et al., 2009). In *in vivo* guinea pig phototoxicity and photoallergenicity studies, 0.5% nonen acid nitrile did not result in skin reactions (RIFM, 1984b; RIFM, 1984c). These studies did not, however, deliver an appropriate dose of UV. Based on the lack of absorbance, nonen acid 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 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: 09/21/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to the lack of appropriate data. The exposure level for nonen acid nitrile 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 nonen acid nitrile. Based on the Creme RIFM Model, the inhalation exposure is 0.00012 mg/day. This exposure is 3916.7 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/30/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of nonen acid 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, nonen acid nitrile was identified as a fragrance material with no 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 nonen acid nitrile as either 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 $\geq$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.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), nonen acid nitrile presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 2016c: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to OECD 301F and GLP guidelines. Biodegradation of 69% was observed after 28 days.

RIFM, 2011: The ready biodegradability of the test material was evaluated using the closed bottle test according to OECD 301D and GLP guidelines. Biodegradation of 54% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Nonen acid 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.67	3.67
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	6.52			1000000	0.00652	

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

The RIFM PNEC is 0.00652 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 10/02/20.

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 11/01/21.

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 B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2022.112915.

Appendix

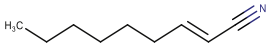
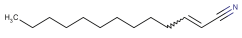
Read-across Justification

Methods

Read-across analogs are 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 Chemical 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 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).

	Target Material	Read-across Material
Principal Name	Nonen acid nitrile	Tridecene-2-nitrile
CAS No.	29127-83-1	22629-49-8
Structure		
Similarity (Tanimoto Score)		0.92
Read-across Endpoint		• Genotoxicity • Repeated dose toxicity • Reproductive toxicity • Skin sensitization
Molecular Formula	$C_9H_{15}N$	$C_{13}H_{23}N$
Molecular Weight (g/mol)	137.23	193.34
Melting Point (°C, EPI Suite)	−0.46	32.27
Boiling Point (°C, EPI Suite)	230.87	297.46
Vapor Pressure (Pa @ 25°C, EPI Suite)	9.96	0.256
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.67	5.04
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	110	0.27
J_{max} (μg/cm^2/h, SAM)	31.08	0.047
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.89E-004	2.76E-003
Genotoxicity		
DNA Binding (OASIS v 1.4 QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding by OECD QSAR Toolbox (v4.2)	• No alert found	• No alert found
Carcinogenicity (Genotox and Non-genotox) Alerts (ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate reliability)
DNA Alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames Test) alerts by ISS**	• No alert found	• No alert found
***In vivo* Mutagenicity (Micronucleus) Alerts by ISS**	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Aliphatic nitriles (Hepatotoxicity) alert	• Aliphatic nitriles (Hepatotoxicity) alert
Reproductive Toxicity		
ER Binding by OECD QSAR Tool Box (v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding by OASIS v1.1	• AN2 • Michael addition	• Michael addition
Protein Binding by OECD	• Michael addition	• Michael addition
Protein Binding Potency	• Slightly reactive (GSH)	• Slightly reactive
Protein Binding Alerts for Skin Sensitization by OASIS v1.1	• No alert found	• AN2 – Michael addition
Skin Sensitization Model (CAESAR) (v2.1.6)	• Non-sensitizer (low reliability)	• Sensitizer (low reliability)
Metabolism		
OECD QSAR Toolbox (v4.2) Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on the target material nonen acid nitrile (CAS 29127-83-1). 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, tridecene-2-nitrile (CAS # 22629-49-8) was identified as read-across material with data for their respective toxicity endpoints.

Conclusion

- For the target material nonen acid nitrile (CAS # 29127-83-1), tridecene-2-nitrile (CAS # 22629-49-8) was used as a read-across analog for the genotoxicity, reproductive toxicity, repeated dose toxicity, and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of α,β-unsaturated aliphatic nitriles.
  - o The target material and the read-across analog share an α,β-unsaturated nitrile group.
  - o The key difference between the target material and the read-across analog is that the target material has an 8 carbon long straight chain, whereas the read-across analog has 2, 6-nonadienenitrile has the same length with additional vinylene group at 5 position, and the read-across analog

tridecene-2-nitrile has 12 carbon long straight chain. This structure difference between the target material and the read-across analog does not affect consideration of the toxicity endpoint.

- o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. The differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
- o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to 80% skin absorption for the target material, 80% absorption for 2, 6-nonadienenitrile, and 10% absorption for tridecene-2-nitrile. While percentage skin absorption estimated from J_{max} values indicate exposure to 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.
- o According to the QSAR OECD Toolbox (V3.4), structural alerts for toxic endpoints are consistent between the target material and the read-across analog.
- o According to HESS categorization, the target material, as well as the read-across analogs, are categorized as aliphatic nitriles with hepatotoxicity alert. The data described in the repeated dose section show that the MOE is adequate at the current level of use.
- o The target material and the read-across analog have several protein binding alerts. According to these predictions, the target material and the read-across analog have comparable reactivities. The read-across analog is predicted to be a sensitizer by the CAESAR model for skin sensitization, while the target material is predicted to be a non-sensitizer. The *in silico* alerts are consistent with the data described in the skin sensitization section above.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.

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