Food and Chemical Toxicology 159 (2022) 112731

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, tridecene-2-nitrile, CAS Registry Number 22629-49-8

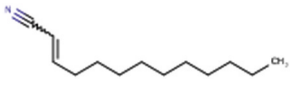
A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i],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

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel 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, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *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*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *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*
[j] *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*
[k] *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*
[l] *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*
[m] *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*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 110,121. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: Tridecene-2-nitrile CAS Registry Number: 22,629-49-8

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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., 2020)

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2021.112731
Received 1 November 2021; Accepted 27 November 2021
Available online 30 November 2021

(*continued*)

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., 2017; 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 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.

Tridecene-2-nitrile was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tridecene-2-nitrile is not expected to be genotoxic. Data provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided tridecene-2-nitrile a NESIL of 6900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV/Vis spectra; tridecene-2-nitrile is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material and the exposure to tridecene-2-nitrile is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; tridecene-2-nitrile was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2008a; RIFM, 2004)
Repeated Dose Toxicity: NOAEL = 67 mg/kg/day.	RIFM (2016b)
Reproductive Toxicity: Developmental toxicity: NOAEL = 200 mg/kg/day. Fertility: NOAEL = 200 mg/kg/day.	RIFM (2016b)
Skin Sensitization: NESIL = 6900 μg/cm^2.	RIFM (2017c)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1981a; RIFM, 1981b; RIFM, 1985b; RIFM, 1980b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 87% (OECD 301 F)	RIFM (1998a)
Bioaccumulation:	
Screening-level: 41.61 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Algae EC50: 0.079 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: 96-h Algae EC50: 0.079 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0079 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Tridecene-2-nitrile
2. **CAS Registry Number:** 22,629-49-8
3. **Synonyms:** Tridecen acid nitrile; 2-Tridecenenitrile; アルキル（又はアルケニル，C ＝ 8～18）ニトリル; Tridec-2-enenitrile; Tridecenonitrile; Ozonil; Tridecennitril; Reaction mass of (2 E)- Tridec-2-enenitrile and (2Z)- Tridec-2- enenitrile and (3 E)- Tridec-3-enenitrile and (3Z)- Tridec-3-enenitrile; Tridecene-2-nitrile
4. **Molecular Formula:** $C_{13}H_{23}N$
5. **Molecular Weight:** 193.33
6. **RIFM Number:** 1224
7. **Stereochemistry:** No stereocenter possible.

2. physical data

1. **Boiling Point:** 297.46 °C (EPI Suite), 263–286 °C at 1013 hPa (RIFM, 2015c), 280–286 °C at 1013 hPa (RIFM, 2015d)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA]), 138.0 °C (corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015e), 136.0 °C at 1013 hPa (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015f)
3. **Log K_{OW}:** 5.9/6.0 (2 minor isomers) (RIFM, 1998b), >6.0 (for the 2 major isomers) (RIFM, 1998b), 5.04 (EPI Suite), >5.9 (RIFM, 2017a)
4. **Melting Point**: 32.27 °C (EPI Suite), −37 to −42 °C at 1005 and 1014 hPa, respectively (RIFM, 2015c), −34.7 °C at 997–1005 hPa (RIFM, 2015d)
5. **Water Solubility:** 1.271 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00105 mm Hg at 20 °C (EPI Suite v4.0), 0.002 mm Hg at 20 °C (FMA), 0.00192 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. 1–10 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:** 0.013% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000054 mg/kg/day or 0.0041 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00036 mg/kg/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. Cramer classification

Class III, High

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

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification**: None

7. Metabolism

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

7.1. Additional references

None.

8. Natural occurrence

Tridecene-2-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 10/16/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for tridecene-2-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)	0.022
2	Products applied to the axillae	0.16

(continued on next page)

(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
3	Products applied to the face/body using fingertips	0.33
4	Products related to fine fragrances	3.0
5 A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.75
5 B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.60
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.75
5D	Baby cream, oil, talc	0.20
6	Products with oral and lip exposure	0.022
7	Products applied to the hair with some hand contact	1.3
8	Products with significant ano-genital exposure (tampon)	0.20
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.1
10 A	Household care products with mostly hand contact (hand dishwashing detergent)	0.022
10 B	Aerosol air freshener	8.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.20
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 tridecene-2-nitrile, the basis was the reference dose of 0.67 mg/kg/day, a predicted skin absorption value of 40%, 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, tridecene-2-nitrile does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Tridecene-2-nitrile was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. The mutagenic activity of tridecene-2-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 tridecene-2-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, 2008a). Under the conditions of the study, tridecene-2-nitrile was not mutagenic in the Ames test.

The clastogenic activity of tridecene-2-nitrile 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 0, 250, 500, and 1000 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.

Based on the data available, tridecene-2-nitrile does not present a concern for genotoxic potential.

Additional references: RIFM, 1981c; RIFM, 2015g.

Literature search and risk assessment completed on: 10/02/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on tridecene-2-nitrile. A 2-week gavage, non-GLP 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/day. Mortality was reported among the animals of the high-dose group only. Alterations in the hematological and clinical chemistry parameters were reported among the high-dose females. No such alterations were reported among the mid- and low-dose animals. A decrease in body weight was reported among the high-dose animals. Ulceration of the glandular stomach was commonly observed in most of the deceased 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/day. The relative liver weight was significantly increased in the males of the 300 mg/kg/day group when compared to the control group. Based on the results of this study, the dose levels for combined repeated dose toxicity study with reproduction/developmental toxicity screening test were selected to be at 200 mg/kg/day for the high-dose level and at 20 mg/kg/day for the low-dose level. The NOAEL for the repeated dose toxicity endpoint was considered to be 20 mg/kg/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/day. 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/day, the highest dose tested. (RIFM, 2016b).

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/day.

Therefore, the tridecene-2-nitrile MOE for the repeated dose toxicity endpoint can be calculated by dividing the tridecene-2-nitrile NOAEL by the total systemic exposure to tridecene-2-nitrile, 67/0.00036, or 186,111.

In addition, the total systemic exposure to tridecene-2-nitrile (0.36 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; *Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Derivation of 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 reference dose of 0.67 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The reference dose for tridecene-2-nitrile was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 67 mg/kg/day by the uncertainty factor, 100 = 0.67 mg/kg/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: 08/13/20.

11.1.3. Reproductive toxicity

The margin of exposure for tridecene-2-nitrile is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on tridecene-2-nitrile. A gavage GLP/OECD 422 study conducted on groups of 12 Sprague Dawley Crl:CD SD strain rats/sex/group were administered test material, tridecene-2-nitrile at doses of 0 (corn oil), 20, 60, and 200 mg/kg/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/day, the highest dose tested (RIFM, 2016b). **Therefore, the tridecene-2-nitrile MOE for the reproductive toxicity endpoint can be calculated by dividing the tridecene-2-nitrile NOAEL by the total systemic exposure to tridecene-2-nitrile, 200/0.00036, or 555,556.**

In addition, the total systemic exposure to tridecene-2-nitrile (0.36 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 existing data, tridecene-2-nitrile is considered a skin sensitizer with a defined NESIL of 6900 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, tridecene-2-nitrile is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), 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 guinea pig maximization test, when 10% 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, 1985a). In a guinea pig open epicutaneous test (OET) and a Freund's complete adjuvant test (FCAT), 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 2 Confirmation of No Induction in Humans tests (CNIHs) with 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, 2017c; RIFM, 1980a).

Based on the weight of evidence (WoE) from structural analysis, animal, and human studies, tridecene-2-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 reference dose of 0.67 mg/kg/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, tridecene-2-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 phototoxicity and photoallergenicity (Henry et al., 2009). Phototoxicity studies were conducted in rabbits and guinea pigs with 10%, 0.25%, and 3% tridecene-2-nitrile and no phototoxic reactions were observed (RIFM, 1981a; RIFM, 1985b; RIFM, 1980b). Photoallergenicity studies were conducted in guinea pigs with challenge concentrations of 10% and 0.25% tridecene-2-nitrile; neither concentration resulted in photoallergenic reactions (RIFM, 1981b; RIFM, 1985b). Based on the *in vivo* study data and the lack of absorbance, tridecene-2-nitrile does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG

Table 1
Data summary for tridecene-2-nitrile.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) μg/cm^2	WoE NESIL[3] 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.

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[2] Data derived from CNIH or HMT.

[3] WoE NESIL limited to 2 significant figures.

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

11.1.6.1. Risk assessment. There is insufficient inhalation data available on tridecene-2-nitrile. Based on the Creme RIFM Model, the inhalation exposure is 0.0041 mg/day. This exposure is 114.6 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, 1989.

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 tridecene-2-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, tridecene-2-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 tridecene-2-nitrile as being 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). 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), tridecene-2-nitrile presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies.

Biodegradation

RIFM, 1996a: Biodegradation was evaluated by the sealed vessel test according to the OECD 301 B method. 10 mg/L of tridecene-2-nitrile was incubated with filtered activated sludge at 20 °C for 28 days. The rate of degradation after 28 days was 81.2%.

RIFM, 1998a: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301 F method. Under the conditions of the test, biodegradation of 87% was observed after 28 days.

RIFM, 1996b: The biodegradability of the test material was evaluated using the biochemical oxygen demand (BOD) test for insoluble substances (BODIS). The extent of biodegradation was calculated as the cumulative BOD related to the theoretical oxygen demand. The average degradation rate after 28 days was 49.5%.

RIFM, 2000: The ready biodegradability of the test material was assessed in a closed bottle test according to the OECD 301D method. Under the conditions of this study, biodegradation of 10% was observed.

Ecotoxicity

RIFM, 2001: A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under static conditions. The 48-h EC0/EC100 based on mean measured concentrations was reported to be 0.02 mg/L.

RIFM, 2008b: A 96-h fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. Based on the mean measured concentrations, the LC50 was reported to be 0.164 mg/L.

RIFM, 2017a: A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 value based on mean measured concentrations was reported to be 0.0108 mg/L.

RIFM, 2017b: An algae growth inhibition test was conducted according to the OECD 201 guideline, under static conditions. The 72-h EC50 values based on measured test concentration for growth rate and yield were reported to be 106 mg/L (95% CI: 100–112 mg/L) and 65.6 mg/L (95% CI: 58.4–127 mg/L).

Other available data

Tridecene-2-nitrile has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since tridecene-2-nitrile has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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)**	0.106			1,000,000	0.000106	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.104	0.195	0.079	10,000	0.0079	Vinyl/Allyl Nitriles
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.295	0.222	0.527			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.9	5.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.0079 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: 10/03/20.

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 08/17/21.

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.

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.

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

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

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.
RIFM (Research Institute for Fragrance Materials, Inc), 1977. Skin Irritation and Capacity of Allergenic Sensitization of Tridecene-2-Nitrile (Tridecenonitrile) Determined by the Open Epicutaneous Test on guinea Pigs. Unpublished Report from Givaudan. RIFM Report Number 55962. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980a. Clinical Safety Evaluation of Tridecene-2-Nitrile (Tridecenonitrile). Repeated Insult Patch Test of Tridecene-2-Nitrile (Tridecenonitrile). Unpublished Report from Givaudan-Roure Corporation. RIFM Report Number 31616. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980b. Tridecene-2-nitrile (Tridecenonitrile): Determination of Phototoxicity in guinea Pigs. Unpublished Report from Givaudan. RIFM Report Number 55961. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1981a. Primary Skin Irritation, Eye Irritation and Phototoxicity Test with Tridecene-2-Nitrile in Albino Rabbits. Unpublished Report from Naarden International. RIFM Report Number 1925. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1981b. Photosensitization Test with Tridecene-2-Nitrile in guinea Pigs. Unpublished Report from Naarden International. RIFM Report Number 1927. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1981c. Evaluation of Tridecene-2-Nitrile in the Salmonella/microsome Mutagenicity Test. Unpublished Report from Naarden International. RIFM Report Number 1928. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1982. Sensitization Test with Tridecene-2-Nitrile in guinea Pigs (Maximization Test). Unpublished Report from Naarden International. RIFM Report Number 1926. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1985a. Delayed Contact Hypersensitivity of Tridecene-2-Nitril in guinea-pigs Modified by Magnusson and Kligman. Unpublished Report from Dragoco Gerberding & Co. GmbH. RIFM Report Number 31873. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1985b. An Assessment of the Phototoxicity & Photosensitization Potential of Tridecene-2-Nitrile 1% in Petrolatum in the guinea Pig. Unpublished Report from Dragoco Gerberding & Co. GmbH. RIFM Report Number 31874. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1986. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 3100. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1989. Acute Inhalation Toxicity Study of Tridecene-2-Nitrile Vapor in Rats. Unpublished Report from Quest International Ltd. RIFM Report Number 32107. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1996a. The Ultimate Biodegradability of Base Perfumes in the Sealed Vessel Test. Unpublished Report from Quest International. RIFM Report Number 49435. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1996b. Assessment of the Biodegradability of Tridecene-2-Nitrile (Ozonil) with the BOD Test for Insoluble Substances (BODIS). Unpublished Report from Symrise. RIFM Report Number 58139. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1998a. Ready Biodegradability of Tridecene-2-Nitrile (Tridecenonitrile). Unpublished Report from Givaudan. RIFM Report Number 51001. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1998b. Partition Coefficient N-Octanol/water of Tridecene-2-Nitrile (Tridecenonitrile). Unpublished Report from Givaudan. RIFM Report Number 51002. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2000. Biodegradation of Tridecene-2-Nitrile (Ozolin). Unpublished Report from Symrise. RIFM Report Number 58140. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2001. Tridecene-2-nitrile (Ozonil): Acute Daphnia Toxicity. Unpublished Report from Symrise. RIFM Report Number 58141. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2004. Tridecene-2-nitrile: Micronucleus Test in the Mouse. Unpublished Report from Quest International. RIFM Report Number 45023. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008a. Tridecene-2-nitrile (Ozonil): Reverse Mutation Assay "Ames Test" Using Salmonella Typhimuium. Unpublished Report from Symrise. RIFM Report Number 58142. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2008b. Tridecene-2-nitrile (Ozonil): Fish (Zebrafish), Acute Toxicity Test, Semi-static, 96 Hours. Unpublished Report from Symrise. RIFM Report Number 58143. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of Tridecene-2-Nitrile in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65499. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015a. Novel Database for Exposure to Fragrance Ingredients in Cosmetics and Personal Care Products. RIFM Report Number 68681. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015b. Tridecene-2-nitrile (Ozonil): Skin Sensitization: Local Lymph Node Assay in Mice. Unpublished Report from Murphy, V.A. RIFM Report Number 69581. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015c. Tridecene-2-nitrile (Ozonil): Determination of Physico-Chemical Properties Melting Point and Boiling Point. Unpublished Report from Symrise. RIFM Report Number 70548. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015d. Tridecene-2-nitrile (Tridecennitril): Determination of Physico-Chemical Properties Melting Point and Boiling Point. Unpublished Report from Symrise. RIFM Report Number 70744. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015e. Tridecene-2-nitrile (Tridecennitril): Determination of Physico-Chemical Properties Flash Point. Unpublished Report from Symrise. RIFM Report Number 70747. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015f. Tridecene-2-nitrile (Ozonil): Determination of Physico-Chemical Properties Flash Point. Unpublished Report from Symrise. RIFM Report Number 70751. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015g. Tridecene-2-nitrile (Ozonil): Gene Mutation Assay in Chinese Hamster V79 Cells in Vitro (V79/HPRT). Unpublished Report from Symrise. RIFM Report Number 70756. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016a. Tridecene-2-nitrile (Ozonil): Two-Week Repeated Oral Dose Range Finding Study of Ozonil in Sprague-Dawley Rats. Unpublished Report from Symrise. RIFM Report Number 70757. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016b. Combined Repeated Oral Dose Toxicity Study with the Reproduction/developmental Toxicity Screening Test of Tridecene-2-Nitrile (Ozonil) in SD Rats. Unpublished Report from RIFM Report Number 71190. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017a. Tridecene-2-nitrile (Ozonil): Acute Immobilisation Test to Daphnia Magna, Semi-static, 48 Hours, in a Closed System without Headspace. Unpublished Report from RIFM Report Number 72148. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017b. Tridecene-2-nitrile (Ozonil): Alga, Growth Inhibition Test with Pseudokirchneriella Subcapitata, 72 Hours. Unpublished Report from Symrise. RIFM Report Number 72637. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2017c. Tridecene-2-nitrile: Repeated Insult Patch Test (RIPT). RIFM Report Number 72879. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. 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.
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.
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.