Food and Chemical Toxicology 141 (2020) 111380

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 10-undecenoic acid, CAS Registry Number 112-38-9

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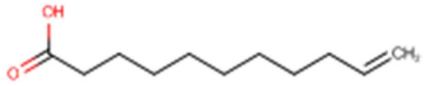
Version: 050319. This version replaces any previous versions.
Name: 10-Undecenoic acid
CAS Registry Number: 112-38-9



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

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https://doi.org/10.1016/j.fct.2020.111380
Received 5 November 2019; Received in revised form 12 February 2020; Accepted 19 April 2020
Available online 18 June 2020
0278-6915/

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.

10-Undecenoic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 10-undecenoic acid is not genotoxic. Data on 10-undecenoic acid provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 10-undecenoic acid 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 I material, and the exposure to 10-undecenoic acid is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 10-undecenoic acid 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 genotoxic. (ECHA REACH Dossier: Undec-10-enoic acid; ECHA, 2010)
Repeated Dose Toxicity: NOAEL = 60 mg/kg/day. (ECHA REACH Dossier: Undec-10-enoic acid; ECHA, 2010)
Reproductive Toxicity: NOAEL = 450 mg/kg/day. (ECHA REACH Dossier: Undec-10-enoic acid; ECHA, 2010)
Skin Sensitization: Not a concern for skin sensitization at current, declared levels of use; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 94% (OECD 301F) (ECHA REACH Dossier: Undec-10-enoic acid; ECHA, 2010)
Bioaccumulation: Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia* LC50: 7.954 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia* LC50: 7.954 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.7954 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name:** 10-Undecenoic acid
2. **CAS Registry Number:** 112-38-9
3. **Synonyms:** 10-Hendecenoic acid; Undecylenic acid; Undecenoic acid; ｱﾙｹﾆﾙﾓﾉｶﾙﾎﾞﾝ酸(C = 5～23); Undec-10-enoic acid; 10-Undecenoic acid
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.27
6. **RIFM Number:** 824
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 137 @ 2 mm Hg (Fragrance Materials Association [FMA]), 293.11 °C (EPI Suite)
2. **Flash Point:** 158 °C (Globally Harmonized System), > 200 °F; CC (FMA)
3. **Log K_{OW}:** 4.37 (EPI Suite)
4. **Melting Point**: 71.46 °C (EPI Suite)
5. **Water Solubility:** 65.84 mg/L (EPI Suite)
6. **Specific Gravity:** 0.912 (FMA), 0.9109 (Essential Oil Association, 1976 Sample 76–269)
7. **Vapor Pressure:** 0.00428 mm Hg @ 20 °C (EPI Suite v4.0), 0.002 mm Hg 20 °C (FMA), 0.00701 mm Hg @ 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Arctander Volume II 1969: Colorless leafy crystals or fused mass. The odor varies enormously in different grades of acid, from oily, mildly acid, and heavy-fruity, overall pleasant, to acrid-acrid, repulsively sour-fatty. However, for perfumery or flavor purposes, the latter type would be absolutely out of the question. A very highly refined grade of this acid has a faintly peach-like odor, accompanied by a waxy-fatty, mildly sour-sweet note which gives an overall pleasant impression. The "normal" grade, which is an industrial chemical, produced in a volume of thousands of tons, has a much inferiors color, odor, and general appearance.

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics**: 0.0045% (RIFM, 2016)
2. **Inhalation Exposure***: 0.0000021 mg/kg/day or 0.00016 mg/kg/day (RIFM, 2016)
3. **Total Systemic Exposure****: 0.000078 mg/kg/day (RIFM, 2016)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification**: Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

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**: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

8. Natural occurrence (discrete chemical) or composition (NCS)

10-Undecenoic acid is reported to occur in the following foods by the VCF*:

Milk and milk products.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 05/03/19 (ECHA, 2010).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 10-undecenoic acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 10-Undecenoic acid was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen HC is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 10-undecenoic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 10-undecenoic acid in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/mL. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2010). Under the conditions of the study, 10-undecenoic acid was not mutagenic in the Ames test.

In addition, in a mammalian cell gene mutation assay conducted according to GLP regulations and OECD TG 476, Chinese hamster lung fibroblast (V79) cells were treated with 10-undecenoic acid in DMSO at concentrations up to 600 μg/mL for 3 h in the presence and absence of metabolic activation. No increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (ECHA, 2010). Under the conditions of the study, 10-undecenoic acid was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of 10-undecenoic acid 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 10% gum Arabic via oral gavage to groups of male and female CD-1 mice. Doses of 1000, 2000, or 4000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24, 48, or 72 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 (ECHA, 2010). Under the conditions of the study, 10-undecenoic acid was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 10-undecenoic acid does not present a concern for genotoxic potential.

Additional References: ECHA, 2010.

Literature Search and Risk Assessment Completed On: 06/14/19.

11.1.2. Repeated dose toxicity

The MOE for 10-undecanoic acid 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 10-undecenoic acid. In an OECD 408 and GLP-compliant subchronic toxicity study, 10 Sprague Dawley rats/sex/dose were administered undecylenic acid sodium salt (purity: 98.5%) through gavage at doses of 0 (vehicle control: water), 20, 60, and 180 mg/kg/day (180 mg/kg/day up to day 50, and 360 mg/kg/day afterwards) for 90 days. A recovery group of 10 rats/sex/day was maintained for 28 days after the end of treatment duration. No treatment-related mortality was reported during the study. No treatment-related adverse effects were observed for other tested parameters except bodyweight gain, food consumption, and cardiomyopathy. In the high-dose group, bodyweight gain and food consumption were reduced in males after increasing the dose to 360 mg/kg/day (day 50 onwards). In addition, a dose-dependent increase in severity was reported for treatment-related ptyalism, labored breathing, and poor clinical condition but the frequency was unknown. In addition, a dose-dependent increase in incidences of cardiomyopathy was observed with the increase being statistically significant only at the highest dose. Myocardial degeneration and mononuclear cell aggregation observed in the high-dose group was reversed following a recovery period. Since the study did not report any change in male bodyweight gain, food consumption, and cardiomyopathy (both sexes) following a recovery period, these changes were considered to be treatment-related adverse effects. Thus, based on the treatment-related effects of decreased bodyweight gain and food consumption in males combined with increased incidences of cardiomyopathy (in both sexes) at the high dose, the NOAEL for repeated dose toxicity was considered to be 60 mg/kg/day (ECHA, 2010).

Other studies on the target material yielding significantly higher NOAELs for the repeated dose toxicity endpoint are summarized below in Table 1.

Therefore, the MOE can be calculated by dividing the NOAEL for the sodium salt of 10-undecenoic acid by the total systemic exposure to 10-undecenoic acid, 60 mg/kg/day/0.000078 mg/kg/day or 769231.

In addition, the total systemic exposure to 10-undecanoic acid (0.078 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Tislow et al., 1950.

Literature Search and Risk Assessment Completed On: 06/10/19.

11.1.3. Reproductive toxicity

The MOE for 10-undecanoic acid is adequate for the reproductive toxicity endpoint at the current level of use.

Table 1
Additional studies on 10-undecenoic acid.

Duration in detail	GLP/Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
28–45 days	OECD 421 and GLP	Sprague Dawley rats (10/sex/group)	Oral (gavage)	0, 50, 150, and 450 mg/kg/day	NOAEL for parental toxicity: 450 mg/kg/day	Based on no effects observed up to highest dose tested	ECHA, (2010)
21 days	Non-GLP/non-guideline	Rabbit (sex and no not stated)	Dermal	2000, 4000, and 8000 mg/square feet (conversion not possible)	Derivation of NOAEL is not possible due to unavailability of systemic toxicity parameters	–	Lehman, (1955)
8 weeks	Not mentioned	Sprague Dawley male rats (7/group)	Oral (diet)	0, 0.5% undecenoic acid + 4.5% corn oil (500 mg/kg/day), 1% undecenoic acid + 4% corn oil (1000 mg/kg/day) in feed	Derived NOAEL: 500 mg/kg/day	Based on body weight reduction reported at higher concentrations	Newell et al., 1949 https://www.sciencedirect.com/science/article/pii/S0022202X1550420X

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 10-undecanoic acid that can be used to support the reproductive toxicity endpoint.

In an OECD 421/GLP study, groups of 10 Sprague Dawley rats/sex were administered the test material 10-undecanoic acid via oral gavage at doses of 0, 50, 150, or 450 mg/kg/day in corn oil. Mortality was reported among 2 high-dose males on treatment days 3 and 35; this was considered to be treatment-related though the cause of death could not be determined due to the lack of antemortem clinical signs of toxicity and no evident adverse effects were observed during macroscopic examination. Hypersalivation and respiratory difficulties were reported among the high-dose group animals. Incidences of hypersalivation were also observed among the mid- and low-dose group animals, but to a lower degree as compared to the high-dose group animals. One mid-dose male was reported to have transient loud breathing. There were no treatment-related alterations in the reproductive performance or on the development of pups at any dose level. Thus, the NOAEL for parental toxicity was considered to be 150 mg/kg/day, based on mortality and clinical signs of toxicity among the high-dose group animals. The NOAEL for fertility effects and on the development of pups was considered to be 450 mg/kg/day, the highest dose tested (ECHA, 2010).

In an OECD 414/GLP study, groups of 24 pregnant female Sprague Dawley rats/dose were administered the test material 10-undecanoic acid via oral gavage at doses of 0, 150, 450, or 750 mg/kg/day in corn oil. The animals were treated daily between days 6–21 postcoitum. Following initiation of the study, there was unexpectedly high mortality among the high-dose group animals, and thus this group was terminated. Animals of the mid-dose group exhibited hypersalivation and a statistically significant decrease in bodyweight gain when compared to the controls. There were no treatment-related alterations among the fetuses as compared to the controls. Thus, the NOAEL for maternal toxicity was considered to be 150 mg/kg/day, based on observed clinical signs of toxicity and decreased bodyweight gain among the mid-dose group dams. The NOAEL for developmental toxicity was considered to be 450 mg/kg/day since no litter was produced at the highest dose (ECHA, 2010).

Taken altogether, the NOAEL for fertility effects was considered to be 450 mg/kg/day, based on the results from the OECD 421 study. The NOAEL for developmental toxicity was considered to be 450 mg/kg/day, based on the results from both the OECD 421 and OECD 414 studies. **Therefore, the 10-undecanoic acid MOE for the reproductive toxicity endpoint can be calculated by dividing the 10-undecanoic acid NOAEL in mg/kg/day by the total systemic exposure to 10-undecanoic acid, 450/0.000078 or 5769231.**

In addition, the total systemic exposure to 10-undecanoic acid (0.078 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/07/19.

11.1.4. Skin sensitization

Based on the existing data, the Expert Panel for Fragrance Safety applied the reactive DST for 10-undecenoic acid, and it does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0 [Patlewicz et al., 2008]; OECD Toolbox v4.2 [OECD, 2018]). 10-undecenoic acid was found to be non-reactive in an *in vitro* direct peptide reactivity assay (DPRA), positive in the KeratinoSens, negative in a human cell line activation test (h-CLAT), and positive in the U-Sens (Bauch et al., 2012; Piroird et al., 2015). In a murine local lymph node assay (LLNA), 10-undecenoic acid was found to be sensitizing with an EC3 value of 19.4% (4850 μg/cm^2) (Kreiling et al., 2008). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1976). In a guinea pig maximization test, reactions indicative of skin sensitization were observed in response to 10-undecenoic acid (Kreiling et al., 2008), while no reactions indicative of skin sensitization were observed in another guinea pig maximization test (ECHA, 2010). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 2 provides the maximum acceptable concentrations for 10-undecenoic acid that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/18/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 10-undecenoic acid would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 10-undecenoic acid in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 10-undecenoic acid 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: 05/08/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 10-undecenoic acid is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 10-undecenoic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.00016 mg/day. This exposure is 8750 times lower than the Cramer Class I TTC value of 1.4 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: 06/04/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 10-undecenoic acid 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),

Table 2
Maximum acceptable concentrations for [10-undecenoic acid] that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	NRU[b]
2	Products applied to the axillae	0.0015%	0.0035%
3	Products applied to the face using fingertips	0.029%	3.6×10^{-5}%
4	Fine fragrance products	0.027%	0.0069%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	0.0040%
6	Products with oral and lip exposure	0.016%	NRU[b]
7	Products applied to the hair with some hand contact	0.056%	3.5×10^{-4}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.025%
10	Household care products with mostly hand contact	0.19%	0.0018%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	1.0%

Note: [a]For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US ECHA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in Table 3 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, 10-undecenoic acid 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) (see Table 4).

A screening-level hazard assessment using EPI Suite v4.11 (US ECHA, 2012a) did not identify 10-undecenoic acid as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for

Table 4
Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002).

Exposure	Europe	North America
Log K_{ow} Used	4.37	4.37
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Table 3
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)**	<u>2.16</u>			1000000	0.00216	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	11.254	<u>7.954</u>	14.644	10000	0.7954	Neutral organics-acid

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 (IFRA, 2015), 10-undecenoic acid presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.2. Other available data. 10-undecenoic acid has been registered for REACH with following additional data available at this time:

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 94% was observed after 28 days.

The acute fish (*Oncorhynchus mykiss*) toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value based on mean measured concentrations was reported to be 32.3 mg/L (95% CI: 15.8–47.8 mg/L).

An early-life stage fish (*Danio rerio*) toxicity test was conducted according to the OECD 210 guideline under semi-static conditions. The 35-day NOEC value based on the mean measured concentration for mortality was reported to be 0.66 mg/L.

The *Daphnia* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value was reported to be 28 mg/L (95% CI: 16–38 mg/L).

The *Daphnia magna* reproduction test was conducted according to the OECD 211 guideline under semi-static conditions. The 21-day EC10 value of 3.7 mg/L was reported for parental mortality (immobilization).

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 value based on the mean measured concentration for growth rate was reported to be 0.24 mg/L (ECHA, 2010).

11.2.3. Risk assessment refinement

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

The RIFM PNEC is 0.7954 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 06/14/19.

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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 09/30/19.

Declaration of competing interest

T 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.

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II Published by the author: Montclair, NJ (USA).

Bauch, C., Kolle, S.N., Ramirez, T., Eltze, T., Fabian, E., Mehling, A., Teubner, W., van Ravenzwaay, B., Landsiedel, R., 2012. Putting the parts together: combining in vitro methods to test for skin sensitizing potentials. Regul. Toxicol. Pharmacol. 63 (3), 489–504.

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

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

ECHA, 2010. Undec-10-enoic acid registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/10078.

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

Kreiling, R., Hollnagel, H.M., Hareng, L., Eigler, D., Lee, M.S., 2008. Comparison of the skin sensitizing potential of unsaturated compounds as assessed by the Murine Local Lymph Node Assay (LLNA) and the Guinea pig maximization test (GPMT). Food Chem. Toxicol. 46 (6), 1896–1904.

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.
Lehman, A.J., 1955. Insect repellents. Association Food Drug Officials United States 19 (2), 87–99.
Newell, G.W., Petretti, A.K., Reiner, M.D., 1949. Studies of the acute and chronic toxicity of undecylenic acid. J. Invest. Dermatol. 13 (3), 145–149. Retrieved from. https://www.sciencedirect.com/science/article/pii/S0022202X1550420X.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.
Patlewicz, G., Jeliazkova, N., Safford, R.J., Worth, A.P., Aleksiev, B., 2008. An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. SAR QSAR Environ. Res. 19 (5–6), 495–524.
Piroird, C., Ovigne, J.-M., Rousset, F., Martinozzi-Teissier, S., Gomes, C., Cotovio, J., Alepee, N., 2015. The Myeloid U937 Skin Sensitization Test (U-SENS) addresses the activation of dendritic cell event in the adverse outcome pathway for skin sensitization. Toxicol. Vitro 29 (5), 901–916.
RIFM (Research Institute for Fragrance Materials, Inc.), 1976. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1797. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of 10-undecenoic Acid in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66471. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Exposure Survey 09, January 2016.
Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.
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., 2015b. 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.
Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
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.
Tislow, R., Margolin, S., Foley, E.J., Lee, S.W., 1950. Toxicity of undercylenic. J. Pharmacol. Exp. Therapeut. 98 (1), 31–32.
US EPA, 2012. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.