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Short Review

RIFM fragrance ingredient safety assessment, 9-decenoic acid, CAS Registry Number 14436-32-9

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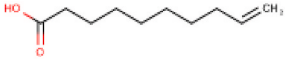

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

(*continued on next page*)

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(*continued*)

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
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, 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.
9-Decenoic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 10-undecenoic acid (CAS # 112-38-9) show that 9-decenoic acid is not expected to be genotoxic and 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; 9-decenoic 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 9-decenoic acid is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 9-decenoic 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.

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Human Health Safety Assessment	
Genotoxicity: Not expected to be 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 use levels; 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:	
Screening-level: 3.18 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 3.16 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 5.31 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 5.31 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.00531 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name**: 9-Decenoic acid
2. **CAS Registry Number**: 14436-32-9
3. **Synonyms**: Dec-9-enoic acid; 9-Decenoic acid
4. **Molecular Formula:** $C_{10}H_{18}O_2$
5. **Molecular Weight**: 170.25
6. **RIFM Number**: 549
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 277.55 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.88 (EPI Suite)
4. **Melting Point**: 68.27 °C (EPI Suite)
5. **Water Solubility:** 74.1 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0025 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} · 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 v1.0)

1.95th Percentile Concentration in Shampoo: 0.008%	RIFM (2017) (No reported use in hydroalcoholics)
2. Inhalation Exposure*: <0.0001 mg/kg/day or <0.0001 mg/day	RIFM (2017)
3. Total Systemic Exposure**: 0.00015 mg/kg/day	RIFM (2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015a, 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, 2015, 2017; Safford, 2015a, 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:** 10-Undecenoic acid (CAS # 112-38-9)
   b. **Repeated Dose Toxicity:** 10-Undecenoic acid (CAS # 112-38-9)
   c. **Reproductive Toxicity:** 10-Undecenoic acid (CAS # 112-38-9)
   d. **Skin Sensitization:** 10-Undecenoic acid (CAS # 112-38-9)
   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)

9-Decenoic acid is reported to occur in the following foods by the VCF*:

Beer	Cheeses, various types
Blue cheeses	Milk and milk products
Cheddar cheese	Wine

*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 2013; no dossier available as of 05/03/19.

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, 9-decenoic acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of 9-decenoic acid; however, read-across can be made to 10-undecenoic acid (CAS # 112-38-9; see Section VI).

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, and this can be extended to 9-decenoic acid.

In addition, 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*, and this can be extended to 9-decenoic acid.

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 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, and this can be extended to 9-decenoic acid.

Based on the available data, 10-undecenoic acid does not present a concern for genotoxic potential, and this can be extended to 9-decenoic acid.

Additional References: ECHA, 2010.

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

11.1.2. Repeated dose toxicity

The MOE for 9-decenoic acid 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 9-decenoic acid. Read-across material 10-undecenoic acid (CAS # 112-38-9; see Section VI) has sufficient data that can be used to support the repeated dose toxicity endpoint. In an OECD 408 and GLP-compliant subchronic toxicity study, 10 Sprague Dawley rats/sex/dose were orally 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 were 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 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 9-decenoic acid, 60/0.00015 or 400000.

In addition, the total systemic exposure to 10-undecanoic acid (0.15 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Tislow, (1950).

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

11.1.3. Reproductive toxicity

The MOE for 9-decenoic acid 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 9-decenoic acid. Read-across material 10-undecenoic acid (CAS # 112-38-9; see Section VI) has sufficient reproductive toxicity data 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 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 9-decenoic 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 9-decenoic acid, 450/0.00015, or 3000000.**

In addition, the total systemic exposure to 10-undecanoic acid (0.15 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 06/10/19.

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

Table 2
Maximum acceptable concentrations for 9-decenoic 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%	NRU[b]
3	Products applied to the face using fingertips	0.029%	NRU[b]
4	Fine fragrance products	0.027%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	NRU[b]
6	Products with oral and lip exposure	0.016%	NRU[b]
7	Products applied to the hair with some hand contact	0.056%	NRU[b]
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.0080%
10	Household care products with mostly hand contact	0.19%	NRU[b]
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	NRU[b]

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.

11.1.4. Skin sensitization

Based on the existing data and the read-across material 10-undecenoic acid (CAS # 112-38-9), the Expert Panel for Fragrance Safety applied the reactive DST for 9-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. No skin sensitization studies are available for 9-decenoic acid and limited data are available for its read-across material, 10-undecenoic acid (CAS # 112-38-9; see Section VI). The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.2). The read-across material 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, 2012; Piroird, 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, 2008). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1976). In a guinea pig maximization test with 10-undecenoic acid, reactions indicative of skin sensitization were observed (Kreiling, 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 on the target material and the read-across material, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). 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 9-undecenoic acid that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent the maximum acceptable concentrations based on the DST approach. However, additional studies may show that 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, 9-decenoic 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 9-decenoic 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, 2009). Based on the lack of absorbance, 9-decenoic 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, 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 9-decenoic 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 9-decenoic acid. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 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 9-decenoic acid was performed following the RIFM Environmental Framework (Salvito, 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, 9-decenoic acid 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 9-decenoic 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 9-decenoic acid presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. No data available.

11.2.3. Ecotoxicity

No data available.

11.2.3.1. Other available data. 9-Decenoic acid has been registered for REACH with no additional data available at this time.

11.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.88	3.88
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.00531 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: 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
- **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 09/30/19.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5.31			1000000	0.00531	

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111541.

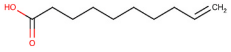
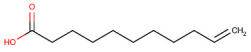
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox 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).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- 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	9-Decenoic acid	10-Undecenoic acid
CAS No.	14436-32-9	112-38-9
Structure		
Similarity (Tanimoto Score)		1.00
Read-across Endpoint		• Genotoxicity • Reproductive Toxicity • Skin Sensitization • Repeated Dose Toxicity
Molecular Formula	$C_{10}H_{18}O_2$	$C_{11}H_{20}O_2$
Molecular Weight	170.25	184.27
Melting Point (°C, EPI Suite)	68.27	24.50
Boiling Point (°C, EPI Suite)	277.55	275.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.33	0.12
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.88	3.86
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	7.41E+01	7.37E+01
J_{max} (μg/cm^2/h, SAM)	9.69	8.00
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.99E-01	5.30E-01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• No alert found	• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)	• Non-toxicant (moderate reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No skin sensitization reactivity domain alerts identified	• No skin sensitization reactivity domain alerts identified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 9-decenoic acid (CAS # 14436-32-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 10-undecenoic acid (CAS # 112-38-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 10-Undecenoic acid (CAS # 112-38-9) was used as a read-across analog for the target material 9-decenoic acid (CAS # 14436-32-9) for the skin sensitization, repeated dose toxicity, genotoxicity, and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of straight-chain unsaturated carboxylic acids.
  - o The target material and the read-across analog share a terminal vinyl group.
  - o The key difference between the target material and the read-across analog is that the target material is a C10 unsaturated carboxylic acid, whereas the read-across analog is a C11 unsaturated carboxylic acid. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - 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.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no toxicological alerts for the target material as well as for the read-across analog. Data are consistent with *in silico* alerts.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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