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RIFM fragrance ingredient safety assessment, ethyl 10-undecenoate, CAS Registry Number 692-86-4

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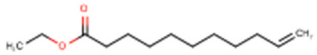
Name: Ethyl 10-undecenoate CAS Registry Number: 692-86-4



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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

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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

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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
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.

Ethyl 10-undecenoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, skin sensitization, phototoxicity/photoallergenicity, local respiratory toxicity, and environmental safety. Data from read-across analog methyl undec-10-enoate (CAS # 111-81-9) show that ethyl 10-undecenoate is not expected to be genotoxic. Data on read-across analogs ethyl alcohol (CAS # 64-17-5) and undecylenic acid (CAS # 112-38-9) provide a calculated MOE >100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog methyl undec-10-enoate (CAS # 111-81-9) show that there are no safety concerns for ethyl 10-undecenoate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; ethyl 10-undecenoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to ethyl 10-undecenoate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; ethyl 10-undecenoate 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 expected to be genotoxic.	(ECHA REACH Dossier: Methyl undec-10-enoate; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 60 mg/kg/day.	(ECHA REACH Dossier: Undec-10-enoic acid; ECHA, 2010)
Reproductive Toxicity: Developmental toxicity: 450 mg/kg/day. Fertility: 450 mg/kg/day.	(ECHA REACH Dossier: Undec-10-enoic acid; ECHA, 2010)
Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels.	(ECHA REACH Dossier: Methyl undec-10-enoate; ECHA, 2011)
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:

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Critical Measured Value: 100% (OECD 301B)	(ECHA REACH Dossier: Ethyl undec-10-enoate; ECHA, 2018)
Bioaccumulation:	
Screening-level: 48.88 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Algae EC50: 0.158 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: 0.158 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0158 μg/L	
•Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Ethyl 10-undecenoate
2. **CAS Registry Number:** 692-86-4
3. **Synonyms:** Ethyl undecylenate; 10-Undecenoic acid, ethyl ester; Ethyl undec-10-enoate; Ethyl 10-undecenoate
4. **Molecular Formula:** $C_{13}H_{24}O_2$
5. **Molecular Weight:** 212.33
6. **RIFM Number:** 969
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 264 °C (FMA), 263.64 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA), >93 °C (GHS)
3. **Log K_{OW}:** 5.15 (EPI Suite)
4. **Melting Point**: 21.98 °C (EPI Suite)
5. **Water Solubility:** 1.517 mg/L (EPI Suite)
6. **Specific Gravity:** 0.876 (FMA)
7. **Vapor Pressure:** 0.00772 mm Hg @ 20 °C (EPI Suite v4.0), 0.002 mm Hg 20 °C (FMA), 0.0125 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:** Colorless, oily liquid. Pleasant, fruity-winey odor. Oily-winey, slightly fruity taste. (Arctander, 1969)

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 v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.60% (RIFM, 2015)
2. **Inhalation Exposure*:** 0.0000049 mg/kg/day or 0.00036 mg/day (RIFM, 2015)
3. **Total Systemic Exposure**:** 0.020 mg/kg/day (RIFM, 2015)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that

include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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:** Methyl undec-10-enoate (CAS # 111-81-9)
   b. **Repeated Dose Toxicity:** Ethyl alcohol (CAS # 64-17-5) and 10-undecenoic acid (CAS # 112-38-9)
   c. **Reproductive Toxicity:** Ethyl alcohol (CAS # 64-17-5) and 10-undecenoic acid (CAS # 112-38-9)
   d. **Skin Sensitization:** Methyl undec-10-enoate (CAS # 111-81-9)
   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)

Ethyl 10-undecenoate is reported to occur in the following food by the VCF*:

Grape brandy.

*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 07/29/19 (ECHA, 2018).

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, ethyl 10-undecenoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Ethyl 10-undecenoate was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: <80% relative cell density) and 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. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic activity of ethyl 10-undecenoate; however, read-across can be made to methyl undec-10-enoate (CAS # 111-81-9; see Section VI). The mutagenic activity of methyl undec-10-enoate 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 and pre-incubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with methyl undec-10-enoate in dimethyl sulfoxide or ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, methyl undec-10-enoate was not mutagenic in the Ames test, and this can be extended to ethyl 10-undecenoate.

There are no studies assessing the clastogenic activity of ethyl 10-undecenoate. However, read-across can be made to methyl undec-10-enoate (CAS # 111-81-9; see Section VI). The clastogenicity of methyl undec-10-enoate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with methyl undec-10-enoate in ethanol at concentrations up to 10 mM for 3 h in the presence and absence of exogenous metabolic activation (S9) and for 20 h and 44 h in the absence of metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2011). Under the conditions of the study, methyl undec-10-enoate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to ethyl 10-undecenoate.

Based on the data available, methyl undec-10-enoate does not present a concern for genotoxic potential, and this can be extended to ethyl 10-undecenoate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/14/19.

11.1.2. Repeated dose toxicity

The MOE for ethyl 10-undecenoate 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 ethyl 10-undecenoate. However, ethyl 10-undecenoate is expected to be hydrolyzed to ethyl alcohol (CAS # 64-17-5; see Section VI) and 10-undecenoic acid (112-38-9; see Section VI). There are sufficient toxicity data on ethyl alcohol (ethanol) and 10-undecenoic acid (undecylenic acid) to support the safety assessment of ethyl 10-undecenoate.

Repeated dose toxicity data available on ethanol have been reviewed by the OECD (2004) and NICNAS (2014). In a 90-day repeated dose toxicity study on Sprague Dawley rats, rats of both sexes were administered ethanol orally (in liquid diet) at concentrations of 1%, 2%, 3%, 4%, 5%, and 10% (equivalent to 1200, 2400, 3600, 4800, 6000, and 12000 mg/kg/day). No treatment-related mortality was reported during the study. At 3600 mg/kg/day, adverse liver effects were reported, including dose-related hepatic yellowing, centrilobular steatosis, increased frequency and severity of Mallory bodies (hyaline), and acidophilic degeneration and necrosis. At higher doses, male rats showed minor changes to organ weights and hematology/biochemistry,

and female rats showed minor biochemistry changes and increased estrous cycle length, along with the presence of liver nodules. Based on the adverse liver effects seen at 3600 mg/kg/day, the NOAEL from this study was concluded to be 2400 mg/kg/day.

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 ethyl 10-undecenoate, 60/0.020, or 3000.

In addition, the total systemic exposure to ethyl 10-undecenoate (20 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: 10/24/19.

11.1.3. Reproductive toxicity

The MOE for ethyl 10-undecenoate 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 ethyl 10-undecenoate. However, ethyl 10-undecenoate is expected to be hydrolyzed to ethyl alcohol (CAS # 64-17-5; see Section VI) and 10-undecenoic acid (112-38-9; see Section VI). There are sufficient toxicity data on ethanol and undecylenic acid to support the safety assessment of ethyl 10-undecenoate.

Reproductive toxicity data available on ethanol have been reviewed by the OECD (2004) and NICNAS (2014). Although ethanol can elicit adverse effects on the reproductive system, it can only be achieved by deliberate oral consumption of alcoholic beverages. It was concluded in the OECD SIDS review for ethanol that blood ethanol concentrations resulting from ethanol exposure at doses relevant to occupational exposure and the use of consumer products containing ethanol are unlikely to produce reproductive toxicity. Daily ethanol formation has been estimated to be 40–80 mg/kg/day (EFSA, 2009). Hence, endogenous formation in humans is of considerably larger amounts, and ethanol formation from hydrolysis of ethyl 10-undecenoate is not considered to affect the safety assessment of ethyl 10-undecenoate for the reproductive toxicity endpoint.

Sufficient fertility and developmental toxicity data are available on undecylenic acid. In an OECD 421/GLP gavage study, groups of 10 Sprague Dawley rats/sex/dose were administered test material undecylenic acid at doses of 0 (corn oil), 50, 150, and 450 mg/kg/day. The females were administered the test material 2 weeks before mating, during mating (2 weeks), during pregnancy, during lactation until day 4 post-partum. Mortality was reported among 2 high-dose males (day 3 and 35). There were no antemortem clinical signs reported among these animals, and no evidence of the cause of death could be determined following macroscopic examination. There were no treatment-related effects on testes or epididymis weights at necropsy, and no effects were reported during the microscopic examination of the testes, epididymis, or ovaries among treated animals. With respect to developmental toxicity, no mortality, body weight changes, sexual maturation, or any gross pathology findings were observed in pups. The NOAEL for fertility and developmental toxicity was considered to be 450 mg/kg/day, the highest dose tested (ECHA, 2010).

In an OECD 414/GLP gavage study, groups of 24 pregnant Sprague Dawley rats were administered undecylenic acid daily between days 6–21 post coitum at doses of 0 (corn oil), 150, 450, or 750 mg/kg/day. Mortality was reported among high-dose animals, which led to discontinuation of dosing for this dose group. With respect to developmental toxicity, no mortality, body weight changes, sexual maturation, or any gross pathology findings were observed in pups. The NOAEL for developmental toxicity was considered to be 450 mg/kg/day, based on absence of developmental effects in this mid dose group. (ECHA, 2010).

Thus, overall, the NOAEL for fertility and developmental toxicity endpoint for undecylenic acid was considered to be 450 mg/kg/day.

Therefore, the ethyl 10-undecenoate MOE for the fertility and developmental toxicity endpoint can be calculated by dividing the undecylenic acid NOAEL in mg/kg/day by the total systemic exposure to ethyl 10-undecenoate, 450/0.020, or 22500.

In addition, the total systemic exposure to ethyl 10-undecenoate (20 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007;

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

Laufersweiler et al., 2012) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/16/19.

11.1.4. Skin sensitization

Based on the existing data and read-across material methyl undec-10-enoate (CAS # 111-81-9), ethyl 10-undecenoate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for ethyl 10-undecenoate. Based on the existing data and read-across material methyl undec-10-enoate (CAS # 111-81-9; see Section VI), ethyl 10-undecenoate is not considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, no reactions indicative of sensitization were observed with read-across material methyl undec-10-enoate (ECHA, 2011). In a human maximization test, no skin sensitization reactions were observed with ethyl 10-undecenoate (RIFM, 1977).

Based on WoE from structural analysis, animal and human studies, and read-across material methyl undec-10-enoate, ethyl 10-undecenoate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/07/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl 10-undecenoate 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 ethyl 10-undecenoate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, ethyl 10-undecenoate 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: 08/13/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for ethyl 10-undecenoate 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 ethyl 10-undecenoate. Based on the Creme RIFM Model, the inhalation exposure is 0.00036 mg/day. This exposure is 3889 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: 09/11/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl 10-undecenoate 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, ethyl 10-undecenoate 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 ethyl 10-undecenoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), ethyl 10-undecenoate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Ethyl 10-undecenoate has been registered for REACH with following additional data available at this time:

The ready biodegradability of the test material was evaluated using

the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 100% was observed after 28 days.

The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 91.4% was observed after 28 days.

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 67% was observed after 28 days (ECHA, 2018).

11.2.2. Risk assessment refinement

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

Endpoints used to calculate PNEC are highlighted.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	5.15	5.15
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	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 0.0158 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: 10/17/19.

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 01/31/20.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.52			1000000	0.00052	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.412	0.611	0.158	10000	0.0158	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.260	0.197	0.489			Neutral Organics

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.2020.111655.

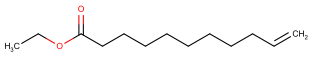
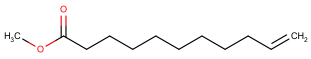
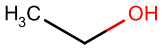
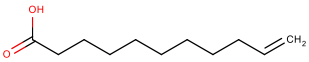
Appendix

Read-across Justification

Methods

The read-across analogs were 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	Read-across Material	Read-across Material
Principal Name	Ethyl 10-undecenoate	Methyl undec-10-enoate	Ethyl alcohol	10-Undecenoic acid
CAS No.	692-86-4	111-81-9	64-17-5	112-38-9
Structure				
Similarity (Tanimoto Score)		0.88	0.10	0.72
Read-across Endpoint		• Genotoxicity • Skin Sensitization	• Repeated Dose Toxicity • Reproductive Toxicity	• Repeated Dose Toxicity • Reproductive
Molecular Formula	$C_{13}H_{24}O_2$	$C_{12}H_{22}O_2$	C_2H_6O	$C_{11}H_{20}O_2$
Molecular Weight	212.33	198.30	46.06	184.27
Melting Point (°C, EPI Suite)	−38.00	−27.50	−114.1	24.5
Boiling Point (°C, EPI Suite)	264.50	248.00	78.2	275.0
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.667	4.040	7.91E+003	1.25E-001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.15	4.66	−0.31	3.86
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.517	4.709	1e+006	73.70
J_{max} (μg/cm^2/h, SAM)	4.076	8.575	7192.05	8.003
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.25E+02	1.69E+02	5.07E-001	5.30E-001
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found		
	• No alert found	• No alert found		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
DNA Binding (OECD QSAR Toolbox v4.2)				
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		• Ethanol (Hepatotoxicity) Alert	• Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure		• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (good reliability)		• Toxicant (experimental value)	• Non-toxicant (moderate reliability)
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on ethyl 10-undecenoate (CAS # 692-86-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, methyl undec-10-enoate (CAS # 111-81-9), ethyl alcohol (CAS # 64-17-5), and 10-undecenoic acid (CAS # 112-38-9) were identified as a read-across analogs with sufficient data for toxicological evaluation.

Metabolism

The metabolism of the target material ethyl 10-undecenoate (CAS # 692-86-4) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to ethyl alcohol (CAS # 64-17-5) and 10-undecenoic acid (CAS # 112-38-9) in the first step with 0.95 probability. Hence, ethyl alcohol (CAS # 64-17-5) and 10-undecenoic acid (CAS # 112-38-9) can be used as read-across analogs for the target material. Read-across analogs ethyl alcohol (CAS # 64-17-5) and 10-undecenoic acid (CAS # 112-38-9) were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion has been overridden, and a justification is provided.

Conclusions

- Methyl undec-10-enoate (CAS # 111-81-9) was used as a read-across analog for the target material methyl undec-10-enoate (CAS # 111-81-9) for the skin sensitization and genotoxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of straight-chain unsaturated esters.
  - o The target material and the read-across analog share a 10-undecenoic acid moiety.
  - o The key difference between the target material and the read-across analog is that the target material ester has an ethanol moiety, whereas the read-across analog has a methanol moiety. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - 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 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.
- The read-across alcohol ethyl alcohol (CAS # 64-17-5) and the read-across acid 10-undecenoic acid (CAS # 112-38-9) are used as read-across analogs for the target ester ethyl 10-undecenoate (CAS # 692-86-4) for the reproductive toxicity and repeated dose toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.

- Structural differences between the target material and the read-across analogs are mitigated by the fact that the target material could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
- The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
- Read-across ethyl alcohol (CAS # 64-17-5) presents an alert for the repeated dose (HESS) classification scheme as hepatotoxic as well as a developmental toxicity (CAESAR) alert as a toxicant. Ethyl alcohol is quickly excreted from the body, so it does not pose any health concern at the reported levels of use. The predictions are superseded by the data.
- According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
- 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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