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Short Review

# RIFM fragrance ingredient safety assessment, 10-undecenoic acid, heptyl ester, CAS Registry Number 68141-27-5

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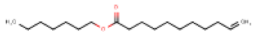
Version: 032178. This version replaces any previous versions.
**Name:** 10-Undecenoic acid, heptyl ester
**CAS Registry Number:** 68141-27-5



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**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
**DST** - Dermal Sensitization Threshold
**ECHA** - European Chemicals Agency
**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
**QRA** - Quantitative Risk Assessment
**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

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**The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits 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 use of this material under current conditions is supported by existing information.**

10-undecenoic acid, heptyl ester was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on read-across analogs heptyl alcohol (CAS # 111-70-6) and 10-undecenoic acid (CAS # 112-38-9) show that 10-undecenoic acid, heptyl ester is not expected to be genotoxic. Data show that 10-undecenoic acid, heptyl ester does not present a concern for skin sensitization. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 10-undecenoic acid, heptyl ester was found not to be a 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 $< 1$.

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**Human Health Safety Assessment**

**Genotoxicity**: Not genotoxic. (ECHA REACH Dossier: Undec-10-enoic acid; ECHA REACH Dossier: Heptan-1-ol)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** Not a concern for skin sensitization. RIFM (2003)
**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:** Screening-level: 3.01 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
**Bioaccumulation:** Screening-level: 1706 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:** Screening-level: 96-h fish LC50: 0.002 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 fish LC50: 0.002 mg/L (ECOSAR; US EPA, 2012b)
**RIFM PNEC is:** 0.0002 µg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: $< 1$

## 1. Identification

1. **Chemical Name:** 10-Undecenoic acid, heptyl ester
2. **CAS Registry Number:** 68141-27-5
3. **Synonyms:** Heptyl undec-10-enoate; Heptyl 10-undecylenate; 10-Undecenoic acid, heptyl ester
4. **Molecular Formula:** $C_{18}H_{34}O_2$
5. **Molecular Weight:** 282.47
6. **RIFM Number:** 6478
7. **Stereochemistry:** Isomer not specified. No stereocenters and 0 total stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 336.22 °C (EPI Suite)
2. **Flash Point:** 309.00 °F TCC (153.89 °C)*
3. **Log $K_{OW}$:** 7.6 (EPI Suite)
4. **Melting Point**: 71.34 °C (EPI Suite)
5. **Water Solubility:** 0.004983 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000052 mm Hg @ 20 °C (EPI Suite 4.0), 0.000102 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** colorless clear liquid (est)*

* http://www.thegoodscentscompany.com/data/rw1438271.html.

## 3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.10% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.0000063 mg/kg/day or 0.00043 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.0010 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 IV. 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).

## 4. Derivation of systemic absorption

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

## 5. 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:** Heptyl alcohol (CAS # 111-70-6); 10-Undecenoic acid (CAS # 112-38-9)
   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

## 6. Metabolism

No relevant data available for inclusion in this safety assessment.

## 7. Natural occurrence (discrete chemical) or composition (NCS)

10-Undecenoic acid, heptyl ester is not reported to occur in food by the VCF.*

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

## 8. IFRA standard

None.

## 9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 03/21/2018.

## 10. Summary

### *10.1. Human health endpoint summaries*

#### *10.1.1. Genotoxicity*

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

*10.1.1.1. Risk assessment.* 10-Undecenoic acid, heptyl ester was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). There are no studies assessing the mutagenic activity of 10-undecenoic acid, heptyl ester; however, considering the hydrolysis of the ester, the appropriate alcohol and acid parts were used to support the safety of this material. The mutagenic activity of heptyl alcohol (CAS # 111-70-6; see Section V) 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 preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with heptyl alcohol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA REACH Dossier). Under the conditions of the study, heptyl alcohol was not mutagenic in the Ames test. The mutagenic activity of 10-undecenoic acid (CAS # 112-38-9; see Section V) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were treated with 10-undecenoic acid in DMSO at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA REACH Dossier). Under the conditions of the study, 10-undecenoic acid was not mutagenic in the Ames test.

The clastogenicity of heptyl alcohol (CAS # 111-70-6; see Section V) 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 heptyl alcohol in DMSO at concentrations up to 5000 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (ECHA REACH Dossier). Under the conditions of the study, heptyl alcohol was considered to be non-clastogenic to in the *in vitro* chromosome aberration assay. The clastogenic activity of 10-undecenoic acid (CAS # 112-38-9; see Section V) 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. 10-Undecenoic acid did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA REACH Dossier). Under the conditions of the study, 10-undecenoic acid was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available and read-across to heptyl alcohol and 10-undecenoic acid, 10-undecenoic acid, heptyl ester does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 07/26/2017.

*10.1.2. Repeated dose toxicity*

There are insufficient repeated dose toxicity data on 10-undecenoic acid, heptyl ester or any read-across materials. The total systemic exposure to 10-undecenoic acid, heptyl ester is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*10.1.2.1. Risk assessment.* There are no repeated dose toxicity data on 10-undecenoic acid, heptyl ester or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 10-undecenoic acid, heptyl ester (1.0 μg/kg/day) is below the TTC (30 μg/kg bw/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:** None.

**Literature Search and Risk Assessment Completed On:** 07/25/17.

*10.1.3. Reproductive toxicity*

There are insufficient reproductive toxicity data on 10-undecenoic acid, heptyl ester or any read-across materials. The total systemic exposure to 10-undecenoic acid, heptyl ester is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

*10.1.3.1. Risk assessment.* There are no reproductive toxicity data on 10-undecenoic acid, heptyl ester or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 10-undecenoic acid, heptyl ester (1.0 μg/kg/day) is below the TTC (30 μg/kg bw/day) (Kroes et al., 2007) 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:** 07/25/17.

*10.1.4. Skin sensitization*

Based on the existing data, 10-undecenoic acid, heptyl ester does not present a concern for skin sensitization.

*10.1.4.1. Risk assessment.* Based on the existing data, 10-undecenoic acid, heptyl ester does not present a concern for skin sensitization. The chemical structure of the material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), 10-undecenoic acid, heptyl ester was found to be negative up to a maximum tested concentration of 40% which resulted in a Stimulation Index (SI) of 0.9 (RIFM, 2003). Based on the weight of evidence from structural analysis and animal studies, 10-undecenoic acid, heptyl ester does not present a concern for skin sensitization.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 07/20/2017.

*10.1.5. Phototoxicity/photoallergenicity*

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

*10.1.5.1. Risk assessment.* There are no phototoxicity studies available for 10-undecenoic acid, heptyl ester in experimental models. UV/Vis absorption spectra indicate minor 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 lack of absorbance, 10-undecenoic acid, heptyl ester does not present a concern for phototoxicity or photoallergenicity.

*10.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor 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:** 07/12/17.

*10.1.6. Local Respiratory Toxicity*

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

*10.1.6.1. Risk assessment.* There are no inhalation data available on 10-undecenoic acid, heptyl ester. Based on the Creme RIFM Model, the inhalation exposure is 0.00043 mg/day. This exposure is 3256 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:** 08/02/2017.

*10.2. Environmental endpoint summary*

*10.2.1. Screening-level assessment*

A screening-level risk assessment of 10-undecenoic acid, heptyl ester 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, 10-undecenoic acid, heptyl ester 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 10-undecenoic acid, heptyl ester 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 ≥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.

*10.2.2. Risk assessment*

Based on current Volume of Use (2011), 10-undecenoic acid, heptyl ester presents a risk to the aquatic compartment in the screening-level assessment.

***Biodegradation:*** No data available.

***Ecotoxicity:*** No data available.

*Other available data*

10-Undecenoic acid, heptyl ester has been pre-registered for REACH with no additional data at this time.

*10.2.3. Risk assessment refinement*

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

Endpoints used to calculate PNEC are underlined.

| | (mg/L) | (Daphnia) (mg/L) | (Algae) (mg/L) | | | |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | <u>0.00512</u> | | | 1,000,000 | 5.12E-06 | |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 0.02 | <u>0.023</u> | 0.004 | | | Esters |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | <u>0.002</u> | 0.002 | 0.013 | 10,000 | 0.0002 | Neutral Organic |

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

| Exposure | Europe | North America |
|---|---|---|
| Log $K_{ow}$ Used | 7.6 | 7.6 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | < 1 | Not reported |
| **Risk Characterization: PEC/PNEC** | **< 1** | **N/A** |

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

**The RIFM PNEC is 0.0002 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:** 7/31/17.

## 11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 06/12/2018.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.11.027.

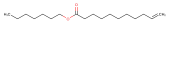
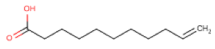
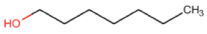
## Appendix

*Read-across Justification*

*Methods*

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 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 substance 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

| | Target Material | Read-across Material | Read-across Material |
|---|---|---|---|
| **Principal Name** | 10-Undecenoic acid, heptyl ester | 10-Undecenoic acid | Heptyl alcohol |
| **CAS No.** | 68141-27-5 | 112-38-9 | 111-70-6 |
| **Structure** |  |  |  |
| **Similarity (Tanimoto Score)** | | NA | NA |
| **Read-across Endpoint** | | • Genotoxicity | • Genotoxicity |
| **Molecular Formula** | $C_{18}H_{34}O_2$ | $C_{11}H_{20}O_2$ | $C_7H_{16}O_2$ |
| **Molecular Weight** | 282.47 | 184.28 | 116.21 |
| **Melting Point (°C, EPI Suite)** | 71.34 | 71.46 | −26.03 |
| **Boiling Point (°C, EPI Suite)** | 336.22 | 293.11 | 180.33 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 0.0136 | 0.935 | 39.8 |
| **Log Kow (KOWWIN v1.68 in EPI Suite)** | 7.6 | 3.86 | 2.62 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 0.004983 | 73.7 | 1670 |
| **$J_{max}$ (mg/cm$^2$/h, SAM)** | 0.062 | 8.003 | 173.534 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 9.16E-003 | 5.30E-001 | 2.37E+000 |
| | ***Genotoxicity*** | | |
| **DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)** | • No alert found | • No alert found | • No alert found |
| **DNA Binding (OECD QSAR Toolbox v3.4)** | • No alert found | • No alert found | • No alert found |
| **Carcinogenicity (ISS)** | • Non-carcinogen (low reliability) | • Non-carcinogen (low reliability) | • Non-carcinogen (low reliability) |
| **DNA Binding (Ames, MN, CA, OASIS v1.1)** | • No alert found | • No alert found | • No alert found |
| ***In Vitro* Mutagenicity (Ames, ISS)** | • No alert found | • No alert found | • No alert found |
| ***In Vivo* Mutagenicity (Micronucleus, ISS)** | • No alert found | • No alert found | • No alert found |
| **Oncologic Classification** | • Not classified | • Not classified | • Not classified |
| | ***Metabolism*** | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)** | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 |

## Summary

There are insufficient toxicity data on 10-undecenoic acid, heptyl ester (CAS # 68141-27-5). Hence, *in silico* evaluation was conducted to

determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 10-undecenoic acid (CAS # 112-38-9) and heptyl alcohol (CAS # 111-70-6) were identified as read-across materials with sufficient data for toxicological evaluation.

## Metabolism

Metabolism of the target material 10-undecenoic acid, heptyl ester (CAS # 68141-27-5) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is predicted to be metabolized to 10-undecenoic acid (CAS # 112-38-9) and heptyl alcohol (CAS # 111-70-6) in the first step with 0.95 probability. Hence, 10-undecenoic acid (CAS # 112-38-9) and heptyl alcohol (CAS # 111-70-6) can be used as read-across materials for the target material. Read-across analogs were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the models' domain exclusion was overridden, and justification is provided.

## Conclusions

- Read-across alcohol, heptyl alcohol (CAS # 111-70-6), and read-across acid, 10-undecenoic acid (CAS # 112-38-9), are used as read-across analogs for target ester 10-undecenoic acid, heptyl ester (CAS # 68141-27-5) for the genotoxicity endpoint.
  - 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 of the target.
  - o Structural differences between the target substance and the read-across analogs are mitigated by the fact that the target 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.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v3.4, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analogs.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analogs and the target substance.

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