Food and Chemical Toxicology 110 (2017) S133–S141

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

# RIFM fragrance ingredient safety assessment, isononyl propionate, CAS Registry Number 65155-45-5

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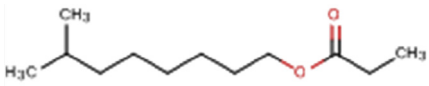
ARTICLE INFO

*Article history:*
Received 10 January 2017
Received in revised form
21 March 2017
Accepted 12 April 2017
Available online 14 April 2017

**Version: 010917. This version replaces any previous versions.**
**Name**: Isononyl propionate
**CAS Registry Number**: 65155-45-5




**Abbreviation list:**
**2-Box Model** - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor

(*continued on next page*)

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http://dx.doi.org/10.1016/j.fct.2017.04.015
0278-6915/

(*continued*)

**Creme RIFM model** - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015) 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
**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
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**TTC** - Threshold of Toxicological Concern
**UV/Vis Spectra** - Ultra Violet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use
**vPvB** - (very) Persistent, (very) Bioaccumulative
**WOE** - Weight of Evidence

**RIFM's Expert Panel* 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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

**Summary: The use of this material under current conditions is supported by existing information.**
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analogue isotridecyl acetate (CAS # 69103-23-7) show that this material is not genotoxic. Data from the suitable read across analogue 3,5,5-trimethylhexyl acetate (CAS# 58430-94-7) show that this material does not have the potential for skin sensitization and provided a MOE > 100 for the repeated dose and developmental and reproductive toxicity endpoints. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

**Human Health Safety Assessment**

| | |
|---|---|
| **Genotoxicity:** Not genotoxic. | (RIFM, 2000; RIFM, 2014b) |
| **Repeated Dose Toxicity:** NOAEL = 13.3 mg/kg/day | (RIFM, 2013) |
| **Developmental and Reproductive Toxicity:** NOAEL = 40 mg/kg/day | (RIFM, 2013) |
| **Skin Sensitization:** Not a sensitization concern. | (RIFM, 1982; RIFM, 1964; RIFM, 1973b; RIFM, 1974a; RIFM, 1973a) |
| **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: 2.89 (Biowin 3) | (EpiSuite ver 4.1) |
| **Bioaccumulation:** Screening Level: 603 L/kg | (EpiSuite ver 4.1) |
| **Ecotoxicity:** Screening Level: Fish LC50: 1.161 mg/L (RIFM Framework; Salvito et al., 2002) | (EpiSuite ver 4.1) |
| **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:** Fish LC50: 1.161 mg/L | (RIFM Framework; Salvito et al., 2002) |
| **RIFM PNEC is:** 0.001161 μg/L | |

- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America (not reported) and Europe: not Applicable; cleared at screening level

## 1. Identification

1 **Chemical Name:** Isononyl propionate
2 **CAS Registry Number**: 65155-45-5
3 **Synonyms:** Isononyl propionate; Propanoic acid, isononyl ester
4 **Molecular Formula:** $C_{12}H_{24}O_2$
5 **Molecular Weight:** 200.22
6 **RIFM Number:** 5797

## 2. Physical data

1 **Boiling Point:** 236.95 °C [EPI Suite]
2 **Flash Point:** 201.00 °F. TCC (93.89 °C)*
3 **Log $K_{OW}$**: 4.72 [EPI Suite]
4 **Melting Point**: 1.93 °C [EPI Suite]
5 **Water Solubility:** 4.064 mg/L [EPI Suite]
6 **Specific Gravity:** Not Available
7 **Vapor Pressure:** 0.035 mmHg @ 20 °C [EPI Suite 4.0], 0.0544 mm Hg @ 25 °C [EPI Suite]
8 **UV Spectra:** No significant absorbance between 290 and 700 nm; molar extinction coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9 **Appearance/Organoleptic:** A colorless clear liquid with a medium, floral, lavender, herbal, woody odor.*

* http://www.thegoodscentscompany.com/data/rw1045381.html#toorgano, retrieved 4/7/2016.

## 3. Exposure

1 Volume of Use (worldwide band): <0.1 metric tons per year (IFRA, 2011)
2 95th Percentile Concentration in Hydroalcoholics: 0.63% (RIFM, 2016)
3 Inhalation Exposure*: 0.000012 mg/kg/day or 0.00083 mg/day (RIFM, 2016)
4 Total Systemic Exposure**: 0.0077 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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).

## 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 **Analogues Selected:**
a **Genotoxicity:** Isotridecyl acetate (CAS # 69103-23-7)
b **Repeated Dose Toxicity:** 3,5,5-Trimethylhexyl acetate (CAS# 58430-94-7)
c **Developmental and Reproductive Toxicity:** 3,5,5-Trimethylhexyl acetate (CAS# 58430-94-7)
d **Skin Sensitization:** 3,5,5-Trimethylhexyl acetate (CAS# 58430-94-7)
e **Phototoxicity/Photoallergenicity:** None
f **Local Respiratory Toxicity:** None
g **Environmental Toxicity:** None
3 **Read-across Justification:** See Appendix below

## 6. Metabolism

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

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

Isononyl propionate 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, contains information on published volatile compounds which 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 2010, no dossier available as of 1/09/2017.

## 10. Summary

### *10.1. Human health endpoint summaries*

#### *10.1.1. Genotoxicity*

Based on the current existing data, isononyl propionate does not present a concern for genotoxicity.

*10.1.1.1. Risk assessment.* Isononyl propionate was assessed in the

BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2014a). There are no studies assessing the mutagenic activity of isononyl propionate however, read across can be made to isotridecyl acetate (CAS # 69103-23-7; see Section 5). The mutagenic activity of isotridecyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 were treated with isotridecyl acetate in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2000). Under the conditions of the study, isotridecyl acetate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of isononyl propionate. The clastogenic activity of read across material, isotridecyl acetate, was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with isotridecyl acetate in solvent acetone at concentrations up to 75 μg/mL in the presence and absence of metabolic activation (S9) at the 4 h and 24 h time points. Isotridecyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9 activated test systems (RIFM, 2014b). Under the conditions of the study, isotridecyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, isotridecyl acetate name does not present a concern for genotoxic potential and this can be extended to isononyl propionate.

**Additional References**: None.

**Literature Search and Risk Assessment Completed on**: 06/20/2016.

*10.1.2. Repeated dose toxicity*

The margin of exposure for isononyl propionate is adequate for the repeated dose toxicity endpoint at the current level of use.

*10.1.2.1. Risk assessment.* There are no repeated dose toxicity data on isononyl propionate. Read across material, 3,5,5-trimethylhexyl acetate (CAS# 58430-94-7; see section 5) has sufficient repeated dose toxicity data. In an OECD 422 gavage study, 10 rats/sex/group were administered 3,5,5-trimethylhexyl acetate at dose levels of 0, 40, 125 and 400 mg/kg/day. Mortality occurred in females at mid and high doses (RIFM, 2013). There was an alteration in the hematology and clinical chemistry parameters among animals in the mid and high dose groups. Adaptive histopathological alterations were reported in the liver and thyroid in females in the mid and high dose groups and in males of all treatment groups. In addition, males were reported to exhibit hyaline droplet nephropathy in all treatment groups. No other parental toxicological alterations were reported. Thus, the NOAEL was determined to be 400 mg/kg/day for males and 40 mg/kg/day for females. The most conservative NOAEL of 40 mg/kg/day was selected for the repeated dose toxicity endpoint.

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 studies. The safety factor has been approved by RIFM's Independent Expert Panel*.

Thus, the derived NOAEL for the repeated dose toxicity data is 40/3 or 13.3 mg/kg/day.

*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

**Therefore, the isononyl propionate MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,5,5-trimethylhexyl acetate NOAEL in mg/kg/day by the total systemic exposure for isononyl propionate 13.3/0.0077 or 1727.**

**In addition, the total systemic exposure to isononyl propionate (7.7 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the repeated dose toxicity endpoint.**

**Additional References: None**.

**Literature Search and Risk Assessment Completed on**: 02/10/2016.

*10.1.3. Developmental and reproductive toxicity*

The margin of exposure for isononyl propionate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

*10.1.3.1. Risk assessment.* There are no developmental and reproductive toxicity data on isononyl propionate. Read across material, 3,5,5-trimethylhexyl acetate (CAS# 58430-94-7; see Section 5) has sufficient developmental and reproductive toxicity data. In an OECD 422 gavage study in rats, test material, 3,5,5-trimethylhexyl acetate was administered at doses of 0, 40, 125 or 400 mg/kg/day. The NOAEL for developmental toxicity was determined to be 40 mg/kg/day due to an increase in post-implantation and post-natal loss reported at 125 mg/kg/day. The NOAEL for male and female reproductive toxicity were 400 and 40 mg/kg/day, respectively (RIFM, 2013). The most conservative NOAEL of 40 mg/kg/day was selected for the developmental and reproductive toxicity endpoints. **Therefore, the isononyl propionate MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the 3,5,5-trimethylhexyl acetate NOAEL in mg/kg/day by the total systemic exposure for isononyl propionate, 40/0.0077 or 5195.**

**In addition, the total systemic exposure to isononyl propionate (7.7 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoints.**

**Additional References:** None.

**Literature Search and Risk Assessment Completed on**: 02/10/2016.

*10.1.4. Skin sensitization*

Based on the data for read across material 3,5,5-trimethylhexyl acetate (CAS# 58430-94-7), isononyl propionate does not present a concern for skin sensitization.

*10.1.4.1. Risk assessment.* Based on the existing data and read across material 3,5,5-trimethylhexyl acetate (CAS# 58430-94-7; see Section 5), isotridecyl acetate does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Toxtree 2.6.13; OECD toolbox v3.3). In a guinea pig maximization test, read across material 3,5,5-trimethylhexyl acetate did not present reactions indicative of sensitization (RIFM, 1982). No confirmatory human studies are available for isononyl propionate. In a human maximization test conducted on 25 subjects with 4%

3,5,5-trimethylhexyl acetate (2760 μg/cm$^2$, one subject showed reaction at patch removal and the intensity of the reaction declined after 24 h (RIFM, 1973b). Due to the questionable nature of the reaction, the human maximization test was repeated two more times on separate panels of individuals (a total of 50 subjects) with 4% 3,5,5-trimethylhexyl acetate (2760 μg/cm$^2$) and no reactions were observed in any of the subjects tested (RIFM, 1973a; RIFM, 1974a). Additionally, no sensitization reactions were observed in a human repeated insult patch test conducted with 2% of 3,5,5-trimethylhexyl acetate in petrolatum on 52 subjects (RIFM, 1964). Based on read across data, isononyl propionate does not present a concern for skin sensitization.

**Additional References**: RIFM, 1968; Sharp, 1978; RIFM, 1974b.

Literature Search and Risk Assessment Completed on: 06/23/2016.

*10.1.5. Phototoxicity/photoallergenicity*

Based on available UV/Vis spectra, isononyl propionate 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 isononyl propionate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol$^{-1}$ · cm$^{-1}$ (Henry et al., 2009). Based on the lack of absorbance, isononyl propionate does not present a concern for phototoxicity or photoallergenicity.

**Additional References**: None.

**Literature Search and Risk Assessment Completed on**: 06/29/2016.

*10.1.6. Local respiratory toxicity*

The margin of exposure could not be calculated due to the lack of appropriate data. The material, isononyl propionate, exposure level 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 isononyl propionate. Based on the Creme RIFM model, the inhalation exposure is 0.00083 mg/day. This exposure is 1686.7 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References**: None.

**Literature Search and Risk Assessment Completed on**: 06/17/2016.

*10.2. . environmental endpoint summary*

*10.2.1. Screening-level assessment*

A screening level risk assessment of isononyl propionate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of s creening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, isononyl propionate 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 EPISUITE ver 4.1 did not identify isononyl propionate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

*10.2.2. Risk assessment*

Based on the current Volume of Use (2011), isononyl propionate does not present a risk to the aquatic compartment in the screening level assessment.

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

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

Other available data:

Isononyl propionate 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.**

| | LC50 (Fish) | EC50 (Daphnia) | EC50 (Algae) | AF | PNEC | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening Level **(Tier 1)** | <u>1.161</u> mg/L | | | 1,000,000 | 0.001161 μg/L | |

Exposure information and PEC Calculation (following RIFM Framework; Salvito et al., 2002)

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ used | 4.72 | 4.72 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | <1 | Not reported |
| **Risk Characterization: PEC/PNEC** | **<1** | **NA** |

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

**The RIFM PNEC is 0.001161 μg/L. The revised PEC/PNECs for EU and NA:** Not applicable; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed on**: 02/10/2016.

## Literature search*

- **RIFM database**: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR,SIDS
- **ECHA**http://echa.europa.eu/
- **NTP**http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor**http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS**http://www.epa.gov/hpv/hpvis/index.html
- **US EPARobust Summary**http://cfpub.epa.gov/hpv-s/
- **Japanese NITE**http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base**http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google**https://www.google.com/webhp?tab%3dww%26ei%3dKMSoUpiQK-arsQS324GwBg%26ved%3d0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.04.015.

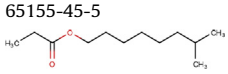
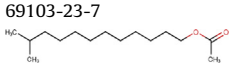
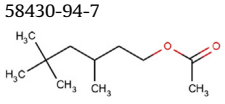
## Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.04.015.

## Appendix

*Methods:*

- The identified read across analogue were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints. (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analogue were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- $J_{max}$ were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogues were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Strategies on finding and utilizing read across are highlighted in Schultz et al., 2015.

| | Target | Read Across | |
|---|---|---|---|
| Principal Name | Isononyl propionate | Isotridecyl acetate | 3,5,5-Trimethylhexyl acetate |
| CAS No. | 65155-45-5 | 69103-23-7 | 58430-94-7 |
| Structure |  |  |  |
| Similarity (Tanimoto score) | 1 | 0.83721 | 0.75895 |
| Read across endpoint | | • Genotoxicity | • Repeated dose<br>• Developmental and reproductive<br>• Skin sensitization |
| Molecular Formula | $C_{12}H_{24}O_2$ | $C_{15}H_{30}O_2$ | C11H22O2 |
| Molecular Weight | 200.32 | 242.41 | 186.30 |
| Melting Point (°C, EPISUITE) | 1.93 | 23.27 | −13.62 |
| Boiling Point (°C, EPISUITE) | 236.95 | 287.35 | 198.85 |

(*continued*)

| | Target | Read Across | |
|---|---|---|---|
| Vapor Pressure(Pa @ 25 °C, EPISUITE) | 7.25 | 0.508 | 50.9 |
| Log Kow (KOWWIN v1.68 in EPISUITE) | 4.72 | 6.19 | 4.12 |
| Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE) | 4.064 | 0.134 | 15.62 |
| $J_{max}$ (mg/cm$^2$/h, SAM) | 0.596292 | 0.021209 | 1.971154 |
| Henry's Law (Pa·m$^3$/mol, Bond Method, EPISUITE) | 2.28E+002 | 5.32E+002 | 1.71E+002 |
| Genotoxicity | | | |
| DNA binding (OASIS v 1.1 QSAR Toolbox 3.1) | • No alert found | • AN2, SN1, SN2 | • AN2, SN1, SN2 |
| DNA binding by OECD QSAR Toolbox (3.1) | • No alert found | • No alert found | • No alert found |
| Carcinogenicity (genotox and non-genotox) alerts (ISS) | • No alert found | • No alert found | • No alert found |
| DNA alerts for Ames, MN, CA by OASIS v 1.1 | • No alert found | • No alert found | • No alert found |
| In-vitro Mutagenicity (Ames test) alerts by ISS | • No alert found | • No alert found | • No alert found |
| In-vivo mutagenicity (Micronucleus) alerts by ISS | • No alert found | • No alert found | • No alert found |
| Oncologic Classification | • Not classified | • Not classified | • Not classified |
| Repeated dose toxicity | | | |
| Repeated Dose (HESS) | • Not categorized | • Not categorized | • Not categorized |
| Reproductive and developmental toxicity | | | |
| ER Binding by OECD QSAR Tool Box (3.1) | • Non binder, non cyclic structure | • Non binder, non cyclic structure | • Non binder, non cyclic structure |
| Developmental Toxicity Model by CAESAR v2.1.6 | • NON-Toxicant (low reliability) | • NON-Toxicant (moderate reliability) | • NON-Toxicant (low reliability) |
| Sensitization | | | |
| Protein binding by OASIS v1.1 | • No alert found | • No alert found | • No alert found |
| Protein binding by OECD | • No alert found | • 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) | • Not possible to classify according to these rules (GSH) |
| Protein binding alerts for skin sensitization by OASIS v1.1 | • No alert found | • No alert found | • No alert found |
| Skin Sensitization model (CAESAR) (version 2.1.6) | • Sensitizer (good reliability) | • Sensitizer (good reliability) | • Sensitizer (good reliability) |
| Metabolism | | | |
| OECD QSAR Toolbox (3.1) | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 |
| Rat liver S9 metabolism simulator | • 5 metabolites from Rat S9 simulator.<br>• Aldehydes, anionic surfactants, esters, Schiff base formation. | • 5 metabolites from Rat S9 simulator.<br>• Aldehydes, esters, AN2, SN1, SN2, Schiff base formation. | • 5 metabolites from Rat S9 simulator.<br>• Aldehydes, esters, AN2, SN1, SN2, Schiff base formation. |

*Summary*

There are insufficient toxicity data on isononyl propionate (CAS # 65155-45-5). Hence *in-silico* evaluation was conducted by determining suitable read across analogues for this material. Based on structural similarity, reactivity, metabolism data, physico-chemical properties and expert judgment, suitable analogues isotridecyl acetate (CAS # 69103-23-7) and 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) were identified as proper read across materials with data for their respective toxicity endpoints.

*Conclusion/Rationale*

- Read across material isotridecyl acetate (CAS # 69103-23-7) could be used as structurally similar read across analogue for the target material isononyl propionate (CAS # 65155-45-5) for the genotoxicity endpoint.

- The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
- The key difference between the target substance and the read across analogue is that the target has a 7-methyloctyl group while the read across has 11-methyl dodecyl group. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
- The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by terpene fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevent from a toxic endpoint perspective.
- The target substance and the read across analogue have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for genotoxicity endpoints.
- According to the QSAR OECD Toolbox (V3.4), structural alerts for genotoxicity endpoint are consistent between the target substance and the read across analogue as seen in the above table.
- The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
- The structural alerts for genotoxicity endpoint are consistent between the metabolites of the read across analogue and the target substance.
- The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

- Read across material 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) could be used as structurally similar read across analogue for target material isononyl propionate (CAS # 65155-45-5) for the repeated dose toxicity, developmental and reproductive toxicity and skin sensitization endpoints.
  - The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - The key difference between the target substance and the read across analogue is that the target have 7-methyloctyl group while the read across have 3,5,5-trimethylhexyl group. The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the differences in structure are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analogue have a Tanimoto score as mentioned in the table above. The Tanimoto score is mainly driven by the isononyl fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevent from a toxicological endpoint perspective.
  - The target substance and the read across analogue have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for repeated dose toxicity, developmental and reproductive toxicity and skin sensitization endpoints.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for repeated dose toxicity, developmental and reproductive toxicity and skin sensitization endpoints are consistent between the target substance and the read across analogue as seen in the table above.
  - The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
  - The structural alerts for repeated dose toxicity, developmental and reproductive toxicity and skin sensitization endpoints are consistent between the metabolites of the read across analogue and the target substance.
  - The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

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