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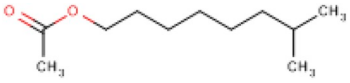
Short Review

RIFM fragrance ingredient safety assessment, isononyl acetate (isomer unspecified), CAS Registry Number 40379-24-6

A.M. Api[a], D. Belsito[b], D. Botelho[a], M. Bruze[c], G.A. Burton Jr[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], L. Jones[a], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Version: 050318. This version replaces any previous versions.
Name: Isononyl acetate (isomer unspecified)
CAS Registry Number: 40379-24-6



* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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

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.

Isononyl acetate (isomer unspecified) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that this material is not genotoxic. Data from read-across analog 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) show that this material does not have skin sensitization potential. 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 repeated dose toxicity and developmental and reproductive toxicity endpoints were completed using 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) as a read-across analog, which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2016a; RIFM, 2016b)
Repeated Dose Toxicity: NOAEL = 13.3 mg/kg/day. RIFM (2013d)
Developmental and Reproductive Toxicity: NOAEL = 40 mg/kg/day. RIFM (2013d)
Skin Sensitization: Not a sensitization concern. (RIFM, 1982; RIFM, 1964; RIFM, 1973a; RIFM, 1974a; RIFM, 1973b)
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: Critical Measured Value: 81% (OECD 301F) RIFM (1998)
Bioaccumulation: Screening-level: 186.9 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint**:** 96-h Algae EbC50: 2.1 mg/L RIFM (2013c)
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 EbC50: 2.1 mg/L RIFM (2013c)
RIFM PNEC is: 2.1 µg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe: < 1

1. Identification

1. **Chemical Name:** Isononyl acetate (isomer unspecified)
2. **CAS Registry Number:** 40379-24-6
3. **Synonyms:** Acetic acid, isononyl ester; Isononyl acetate (isomer unspecified); 7-Methyloctyl acetate
4. **Molecular Formula:** $C_{11}H_{22}O_2$
5. **Molecular Weight:** 186.95
6. **RIFM Number:** 5697

2. Physical data

1. **Boiling Point:** 218.34 °C (EPI Suite)
2. **Flash Point:** 80 °C (GHS)
3. **Log KOW:** 4.23 (EPI Suite)
4. **Melting Point:** -9.14 °C (EPI Suite)
5. **Water Solubility:** 12.56 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0943 mm Hg @ 20 °C (EPI Suite v4.0), 0.143 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1 · cm-1)
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium, herbal, sweet, cumin, woody odor.*

*http://www.thegoodscentscompany.com/data/rw1381151.html#toorgano, retrieved 4/6/2016.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.13% (RIFM, 2016c)
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or < 0.0001 mg/day (RIFM, 2016c)
4. **Total Systemic Exposure**:** 0.0051 mg/kg/day (RIFM, 2016c)

*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:** None
   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 acetate (isomer unspecified) 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

Dossier available; accessed 05/03/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, isononyl acetate (isomer unspecified) does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Isononyl acetate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2015). The mutagenic activity of isononyl 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 *Escherichia coli* strains WP2uvrA were treated with isononyl acetate in DMSO (dimethyl sulfoxide) 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, 2016a). Under the conditions of the study, isononyl acetate was not mutagenic in the Ames test.

The clastogenic activity of isononyl 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 isononyl acetate in DMSO at concentrations up to 500 μg/mL in the presence and absence of metabolic activation (S9) at the 4-h and 24-h timepoints. Isononyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016b). Under the conditions of the study, isononyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, isononyl acetate does not present a concern for genotoxic potential.

Additional References: RIFM, 2000b; RIFM, 2013e.

Literature Search and Risk Assessment Completed On: 06/16/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for isononyl acetate (isomer unspecified) 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 acetate (isomer unspecified). Read-across analog 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7; see section V) 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 the females at the mid- and high-dose levels (RIFM, 2013d). There were alterations 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 the females of the mid- and high-dose groups and in the males of all treatment groups. In addition, the 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.

The MOE for isononyl acetate is equal to the 3,5,5-trimethylhexyl acetate NOAEL divided by the total systemic exposure for isononyl acetate 13.3/0.019 or 700.

In addition, the exposure to isononyl acetate (19 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) at the current level of use.

An OECD 408, 90-day repeated dose toxicity study is planned by the SIEF on material 3,5,5-trimethylhexyl acetate to complete the ECHA REACH Dossier. The safety assessment will be reviewed when these data become available.

Additional References: None.

Literature Search and Risk Assessment Completed On: 2/10/2016.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for isononyl acetate (isomer unspecified) 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 or reproductive toxicity data on isononyl acetate (isomer unspecified). Read-across material, 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7; see section V) 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 postnatal loss reported at 125 mg/kg/day. The NOAELs for male and female reproductive toxicity were 400 and 40 mg/kg/day, respectively (RIFM, 2013d). The most conservative NOAEL of 40 mg/kg/day was selected for the developmental and reproductive toxicity endpoints. Thus the MOE for isononyl acetate can be calculated by dividing the 3,5,5-trimethylhexyl acetate NOAEL in mg/kg/day by the total systemic exposure to isononyl acetate, 40/0.019 or 2105.

In addition, the total systemic exposure to isononyl acetate (19 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) at the current level of use.

An OECD 414 prenatal developmental toxicity study is planned by the SIEF on material 3,5,5-trimethylhexyl acetate to complete the ECHA REACH Dossier. The safety assessment will be reviewed when these data become available.

Additional References: None.

Literature Search and Risk Assessment Completed On: 2/10/2016.

10.1.4. Skin sensitization

Based on the existing data, isononyl acetate (isomer unspecified) does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data, isononyl acetate (isomer unspecified) does not present a concern for skin sensitization. The chemical structure of this material and read-across analog 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7; see Section V) 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, 3,5,5-trimethylhexyl acetate did not present reactions indicative of sensitization (RIFM, 1982). In a human maximization test conducted on 25 subjects with 4% 3,5,5-trimethylhexyl acetate (2760 μg/cm^2), 1 subject showed a reaction at the challenge patch removal, and the intensity of the reaction declined after 24 h (RIFM, 1973a). Due to the questionable nature of the reaction, the human maximization test was repeated 2 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, 1973b; RIFM, 1974a). Additionally, no sensitization reactions were observed in a human repeated insult patch test conducted with 2% 3,5,5-trimethylhexyl acetate in petrolatum on 52 subjects (RIFM, 1964). Based on weight of evidence from structural analysis, animal data, and human confirmatory studies, isononyl acetate (isomer unspecified) does not present a concern for skin sensitization.

Additional References: Sharp (1978); RIFM, 1974b.

Literature Search and Risk Assessment Completed On: 6/23/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, isononyl acetate (isomer unspecified) 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 acetate (isomer unspecified) 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 (Henry et al., 2009). Based on lack of absorbance, isononyl acetate (isomer unspecified) 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 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: 06/29/16.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for isononyl acetate (isomer unspecified) 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 acetate (isomer unspecified). Based on the Creme RIFM Model, the inhalation exposure is 0.84 mg/day. This exposure is 1.7 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: 6/17/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of isononyl acetate (isomer unspecified) 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, isononyl acetate (isomer unspecified) 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 v4.1 did not identify isononyl acetate (isomer unspecified) as either being possibly persistent nor 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 v4.1). 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 the current Volume of Use (2011), isononyl acetate (isomer unspecified) presents a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: For CAS # 58430-94-7.

RIFM, 1994**:** Biodegradation of the test material was evaluated by the sealed vessel test based on the OECD 301B guideline. A mineral salts medium (100 mL) inoculated with filtered activated sludge plant secondary effluent was placed in 160 mL hypovials. Following the addition of 10 mg/L of 3,5,5-trimethylhexyl acetate to the hypovials, incubation was for 28 days. The biodegradation rate was 74.5%.

RIFM, 1998**:** The Ready Biodegradability of the test material was determined by the manometric respirometry test based on OECD guideline 301F. A mineral salts medium (250 mL) inoculated with fresh activated sludge was placed in 250-mL flasks. Following the addition of 100 mg/L of 3,5,5-trimethylhexyl acetate to the flasks, incubation was conducted for 32 days. The biodegradation rate was 81% after 32 days.

RIFM, 2000a**:** Biodegradation was evaluated by the closed bottle test, which was conducted according to OECD TG 301D. Closed bottles containing 2.6 mg/L of 3,5,5-trimethylhexyl acetate and mineral medium inoculated with secondary effluent from a sewage plant were incubated for 28 days at 20° ± 1 °C. The amount of oxygen taken up by 3,5,5-trimethylhexyl acetate was measured during the 28-day period. The biodegradation rate was 3%, 9%, 16%, and 27% after 7, 14, 21, and 28 days, respectively.

Ecotoxicity: For CAS # 58430-94-7.

RIFM, 2001**:** The acute toxicity of 3,5,5-trimethylhexyl acetate on *Daphnia magna* was evaluated according to the OECD 202 part I method. The 24-h and 48-h EC0 and EC100 were 50 mg/L and > 100 mg/L, respectively.

RIFM, 2013a**:** A 96-h fathead minnow (*Pimephales promelas*) acute test was conducted according to the OECD 203 guidelines under flow-through conditions with no protocol amendments. The LC50 was reported to be 7.7 mg/L.

RIFM, 2013b**:** A *Daphnia magna* immobilization test was conducted according to the OECD 202 guidelines under flow-through conditions. The 48-h EC50 was reported to be greater than 5.4 mg/L.

RIFM, 2013c**:** An algae (*Pseudokirchneriella subcapitata*) growth inhibition test was conducted according to the OECD 201 guidelines. The 96-h EbC50 and ErC50 were reported to be 2.1 mg/L and 7.7 mg/L, respectively.

Other available data: Isononyl acetate (isomer unspecified) CAS # 58430-94-7 has been registered under 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	1.379			1,000,000	0.001379	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.445	2.394	0.729	10,000	0.0729	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.920	1.325	2.216			Neutral Organic SAR (Baseline toxicity)
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	7.7					
Daphnia		>5.4				
Algae		2.1		1000	2.1	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.6	4.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10-100*	10-100*
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Volumes for both CAS # have been combined.

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

The RIFM PNEC is 2.1 μg/L. The revised PEC/PNECs for EU and NA are < 1 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: 6/29/2016.

11. 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
- 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.

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.2018.11.029.

Appendix

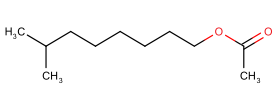
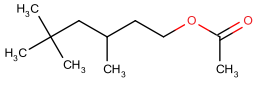
Supplemental Data 1 Supplemental Data 2

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, 2012) and the European Chemical Agency read-across assessment framework (ECHA, 2012).

- 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 (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
Principal Name	Isononyl acetate (isomer unspecified)	3,5,5-Trimethylhexyl acetate
CAS No.	40379-24-6	58430-94-7
Structure		
Similarity (Tanimoto score)	1.0	0.76
Read-across endpoint		• Repeated dose • Reproductive and Developmental toxicity • Skin sensitization
Molecular Formula	$C_{11}H_{22}O_2$	$C_{11}H_{22}O_2$
Molecular Weight	186.30	186.30
Melting Point (°C, EPI Suite)	−9.14	−13.62
Boiling Point (°C, EPI Suite)	218.34	198.85
Vapor Pressure (Pa @ 25 °C, EPI Suite)	19	50.9
Log Kow (KOWWIN v1.68 in EPI Suite)	3.8	3.5
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	182.789	183.687
J_{max} (mg/cm^2/h, SAM)	18.377	14.139
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.69e-003	1.69e-003
	Genotoxicity	
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• AN2 Schiff's base formation • SN1 nucleophilic attack • SN2 Acylation	• AN2 Schiff's base formation • SN1 nucleophilic attack • SN2 Acylation
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
	Repeated dose toxicity	
Repeated Dose (HESS)	• Not categorized	• Not categorized
	Reproductive and developmental toxicity	
ER Binding by OECD QSAR Tool Box (3.4) Developmental Toxicity Model by CAESAR v2.1.6	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
	Skin Sensitization	
Protein binding by OASIS v1.1	• Not classified	• Not classified
Protein binding by OECD	• Not classified	• Not classified
Protein binding potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)

	Respiratory	
Respiratory sensitization OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
	Metabolism	
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2
Rat liver S9 metabolism simulator	• 5 metabolites from rat S9 simulator. • AN2 Schiff's base formation SN1 nucleophilic attack SN2 Acylation • No metabolites observed in Rat or mammalian metabolism.	• 5 metabolites from rat S9 simulator. • AN2 Schiff's base formation SN1 nucleophilic attack SN2 Acylation • No metabolites observed in Rat or mammalian.

Summary

There are insufficient toxicity data on isononyl acetate (isomer unspecified) (CAS # 40379-24-6). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusion

- 3,5,5-Trimethylhexyl acetate (CAS # 58430-94-7) was used as structurally similar read-across analog for isononyl acetate (isomer unspecified) (CAS # 40379-24-6) for the reproductive and developmental toxicity and repeated dose toxicity endpoints.
  - o The target and the read-across analog are structurally similar and belong to a class of esters.
  - o The target and the read-across material have an acetate fragment in common.
  - o The key difference between the target material and the read-across material is that the target has an isononyl fragment while the read-across material has a 3,5,5-trimethylhexyl fragment.
  - o The target and read-across analog have a Tanimoto score of 0.76, which is mainly driven by alkane and acetate groups. The differences in the structure that are responsible for a Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
  - o The physical–chemical properties of the target and the read-across analog are similar.
  - o The structural alerts for toxicological endpoints are consistent between the target as well as the read-across material.
  - o The structural alerts show that the read-across material is slightly more reactive for the reproductive and developmental toxicity and repeated dose endpoints than the target material.
  - o The structural alerts show that the predicted metabolites of the read-across material are equally reactive as compared to the target material or its predicted metabolites.
  - o The target and analog are expected to be metabolized similarly as shown by a metabolism simulator. All of the read-across metabolites show similar structural alerts for the reproductive and developmental toxicity and repeated dose toxicity endpoints.
  - o The structural differences between the target material and the read-across analog appear to be toxicologically insignificant.

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