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Short review

RIFM fragrance ingredient safety assessment, isotridecyl acetate, CAS registry number 69103-23-7

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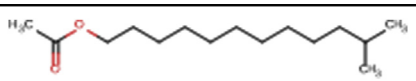

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Abbreviation list:
2-Box Model-a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF-Assessment Factor
BCF-Bioconcentration Factor
Creme RIFM model-The Creme RIFM model uses probabilistic (Monte Carlo) 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

(*continued*)

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 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 has no skin sensitization potential and provided a MOE > 100 for the repeated dose, 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, 2014)
Repeated Dose Toxicity: NOAEL = 13.3 mg/kg/day (RIFM, 2013a)
Developmental and Reproductive Toxicity: NOAEL = 40 mg/kg/day (RIFM, 2013a)
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: Critical Measured Value: 38% (OECD 301F) (RIFM, 2001a,b,c)
Bioaccumulation: Screening Level: 239 mg/l (EpiSuite ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48 h *Daphnia magna* EC0 >1 mg/l. (RIFM, 2001a,b,c)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-Level: PEC/PNEC (RIFM Framework; Salvito et al., 2002) (North America and Europe) > 1
Critical Ecotoxicity (RIFM, 2001a,b,c)
Endpoint: 48 h *Daphnia magna* EC0 >1 mg/l
RIFM PNEC is: 0.2 μg/L
- Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe: <1

1. Identification

1. **Chemical Name:** Isotridecyl acetate
2. **CAS Registry Number:** 69103-23-7
3. **Synonyms:** Acetic acid, isotridecyl ester; Isotridecyl acetate
4. **Molecular Formula:** $C_{15}H_{30}O_2$
5. **Molecular Weight:** 242.03
6. **RIFM Number:** 5952

2. Physical data

1. **Boiling Point:** 287.35 °C [EPI Suite]
2. **Flash Point:** >93 °C [GHS]
3. **Log K_{OW}:**6.19 [EPI Suite]
4. **Melting Point**: 23.27 °C [EPI Suite]
5. **Water Solubility:** 0.134 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00381 mm Hg @ 25 °C [EPI Suite], 0.00235 mmHg @ 20 °C [EPI Suite 4.0]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid.*

*http://www.thegoodscentscompany.com/data/rw1045631.html#toorgano, retrieved 4/6/2016.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA , 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.06% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00032 mg/kg/day or 0.021 mg/day (RIFM, 2016)
4. **Total Systemic Exposure****: 0.0055 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:** 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)

Isotridecyl acetate 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, isotridecyl acetate does not present a concern for genotoxicity.

10.1.2. Risk assessment

Isotridecyl acetate was assessed in the BlueScreen assay and was found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013b). The mutagenic activity of isotridecyl acetate (CAS # 69103-23-7) 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.

The clastogenic activity of 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, 2014). 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 does not present a concern for genotoxic potential.

Additional References: None.

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

10.1.3. Repeated Dose Toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on isotridecyl acetate. 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, 2013a). 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 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 isotridecyl acetate 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 to isotridecyl acetate, 13.3/0.0055 or 2418.

In addition, the total systemic exposure to isotridecyl acetate (5.5 μg/kg/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.

10.1.5. Developmental and reproductive toxicity

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

10.1.6. Risk assessment

There are no developmental or reproductive toxicity data on isotridecyl acetate. 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 dose levels 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 NOAEL for male and female reproductive toxicity were 400 and 40 mg/kg/day, respectively (RIFM, 2013a). The most conservative NOAEL of 40 mg/kg/day was selected for the developmental and reproductive toxicity endpoints. **Therefore, the isotridecyl acetate 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 to isotridecyl acetate, 40/0.0055 or 7273.**

In addition, the total systemic exposure to isotridecyl acetate (5.5 μg/kg/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.

10.1.7. Skin sensitization

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

10.1.8. Risk assessment

Limited skin sensitization studies are available on isotridecyl acetate. 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 open epicutaneous test (OET), no sensitization reactions were observed with isotridecyl acetate (RIFM, 1986). Similarly, 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 isotridecyl acetate. 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/cm²) 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% 3,5,5-trimethylhexyl acetate in petrolatum on 52 subjects (RIFM, 1964). Based on existing data and read across material, isotridecyl acetate does not present a concern for skin sensitization.

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

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

10.1.9. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, isotridecyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for isotridecyl acetate 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, isotridecyl acetate does not present a concern for phototoxicity or photoallergenicity.

There are no studies available on isotridecyl acetate in experimental models.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/03/2016.

10.1.11. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, isotridecyl acetate, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.12. Risk assessment

There are no inhalation data available on isotridecyl acetate. Based on the Creme RIFM model, the inhalation exposure is 0.021 mg/day. This exposure is 66.7 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 isotridecyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening 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, isotridecyl acetate 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 EPISUITE ver 4.1 did not identify isotridecyl acetate 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 bio-accumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate 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), isotridecyl acetate presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Biodegradation

RIFM, 2001a: The test material was tested for ready biodegradability according to OECD 301D Closed Bottle Test. Under the conditions of the study, biodegradation of 7% was observed.

RIFM, 2001b: The biodegradation potential of the test material was measured using a manometric respirometer according to the OECD 301F method. Under the conditions of the study, 38% biodegradation was observed after 28 days.

10.2.4. Ecotoxicity

RIFM, 2001a,b,c: A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 part I method (limit test) in a static system. Under the conditions of the study, no immobilization was observed after 24 or 48 h exposure at 1 mg/l.

10.2.5. Other available data

Isotridecyl acetate has been pre-registered for REACH with no additional data at this time.

10.2.6. 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)**	0.0738 mg/L			1,000,000	7.38E-05 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.115 mg/L	0.153 mg/L	0.034 mg/L			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.034 mg/L	0.029 mg/L	0.105 mg/L	10,000	0.0029 μg/L	Neutral Organic SAR (Baseline toxicity)

Tier 3: Measured Data (including REACH data)

	LC50	EC50	NOEC	AF	PNEC	Comments
Fish						
Daphnia		1.0 mg/L		5,000	0.2 μg/L	
Algae						

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	6.19	6.19
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.2 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: 02/10/2016.

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/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 EPA Robust 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=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*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.2017.03.003.

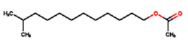
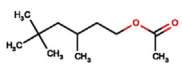
Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.003.

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).
- Jmax 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).

	Target material	Read across material
Principal Name	Isotridecyl acetate	3,5,5-Trimethylhexyl acetate
CAS No.	69103-23-7	58430-94-7
Structure		
Similarity (Tanimoto score)	1	0.56873
Read across endpoint		• Repeated dose • Developmental and reproductive • Skin sensitization
Molecular Formula	$C_{15}H_{30}O_2$	$C_{11}H_{22}O_2$
Molecular Weight	242.41	186.30
Melting Point (°C, EPISUITE)	23.27	−13.62
Boiling Point (°C, EPISUITE)	287.35	198.85
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.508	50.9
Log Kow (KOWWIN v1.68 in EPISUITE)	6.19	4.12
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	0.134	15.62
J_{max} (mg/cm^2/h, SAM)	0.021209	1.971154
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	5.32E+002	1.71E+002
Genotoxicity		
DNA binding (OASIS v 1.1 QSAR Toolbox 3.1)	• AN2, SN1, SN2	• AN2, SN1, SN2

(*continued on next page*)

(*continued*)

	Target material	Read across material
DNA binding by OECD QSAR Toolbox (3.1)	• 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 (3.1)	• Non binder, non cyclic structure	• Non binder, non cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• Non Toxicant (moderate reliability)	• Non Toxicant (low reliability)
Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism		
OECD QSAR Toolbox (3.1)	See Supplemental Data 1	See Supplemental Data 2
Rat liver S9 metabolism simulator	• 5 metabolites from Rat S9 simulator. • Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.	• 5 metabolites from Rat S9 simulator. • Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.

Summary

There are insufficient toxicity data on Isotridecyl acetate (CAS # 69103-23-7). Hence, *in-silico* evaluation was conducted to determine suitable read across analogues for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogue 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) was identified as a proper read across material with data for its respective toxicity endpoints.

12. Conclusion/rationale

- Read across material 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) could be used as structurally similar read across analogue for the target material isotridecyl acetate (CAS # 69103-23-7) for repeated dose, developmental, reproductive, and skin sensitization toxicological 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 has 11-methyldodecyl group while the read across has 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 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 the 3,5,5-trimethylhexyl 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 repeated dose, developmental, reproductive, and skin sensitization endpoints.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for repeated dose, developmental, reproductive, 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, developmental, reproductive, 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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