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RIFM fragrance ingredient safety assessment, tricyclodecenyl propionate, CAS Registry Number 17511-60-3

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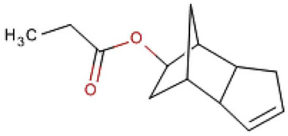
Version: 042718. This version replaces any previous versions.
Name: Tricyclodecenyl propionate
CAS Registry Number: 17511-60-3
Additional CAS Numbers*:
68912-13-0 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-indenyl propionate (mixture of isomers)
67634-24-6 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl propionate
*These materials are included in this assessment because they are isomers.



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

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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.

Tricyclodecenyl propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS# 113889-23-9) show that tricyclodecenyl propionate is not expected to be genotoxic and is not a safety concern under the current declared levels of use for skin sensitization. The local respiratory toxicity endpoint was completed using the TTC for a Cramer Class III material (0.47 mg/day). The repeated dose as well as the developmental and reproductive toxicity endpoints were completed using acetoxydihydrodicyclopentadiene (CAS# 54830-99-8) as a read-across analog, which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on tricyclodecenyl propionate. The environmental endpoints were evaluated; tricyclodecenyl propionate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not Genotoxic. (RIFM, 2000b; RIFM, 2002b)
Repeated Dose Toxicity: NOAEL = 464.1 mg/kg/day. (RIFM, 2012)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day. (RIFM, 2010)
Skin Sensitization: No safety concerns under the current, declared levels of use. (RIFM, 2001)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1981)
Local Respiratory Toxicity: No NOAEC available. Exposure below TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 21% (OECD 301B) (RIFM, 1993)
Bioaccumulation: Screening-level: 74 L/kg (EPI Suite v4.1, US EPA 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 21-day fish (Fathead minnow) NOEC: 0.8 mg/L (RIFM, 2013a)
Conclusion: Not PBT or vPvB as per the IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 21-day fish (Fathead Minnow) NOEC: 0.8 mg/L (RIFM, 2013a)
RIFM PNEC: 80 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

1. Identification

Chemical Name: Tricyclodecenyl propionate	**Chemical Name:** 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-indenyl propionate (mixture of isomers)	**Chemical Name:** 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl propionate
CAS Registry Number: 17511-60-3	**CAS Registry Number:** 68912-13-0	**CAS Registry Number:** 67634-24-6
Synonyms: Cyclaprop; 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-6-yl propionate; 4,7-Methanoindene-6-carboxylic acid, 3a,4,5,6,7,7a-hexahydro-, ethyl ester; Florocyclene; ｱﾙｶﾝ酸(C = 1 ~ 3) ﾄﾘｼｸﾛﾃﾞｾﾆﾙ; 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-6-yl propionate; Herbylpropionate; Tricyclodecenyl propionate	**Synonyms:** 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-indenyl propionate (mixture of isomers); 4,7-Methano-1H-indenol, 3a,4,5,6,7,7a-hexahydro-, propanoate; Dicyclopentadiene propionate; Tricyclo [5.2.1.02,6]dec-3-enyl propionate; Verdyl propionate; アルカン酸（C = 1 ~ 3）トリシクロデセニル	**Synonyms:** 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-5-yl propionate; 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl propionate; 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydro-, propanoate; 4,7-Methanoinden-5-ol, 3a,4,5,6,7,7a-hexahydro-, propionate; Tricyclo (5.2.1.02,6)dec-3-en-9-yl propionate
Molecular Formula: $C_{13}H_{18}O_2$	**Molecular Formula:** $C_{13}H_{18}O_2$	**Molecular Formula:** $C_{13}H_{18}O_2$
Molecular Weight: 206.29	**Molecular Weight:** 206.29	**Molecular Weight:** 206.29
RIFM Number: 856	**RIFM Number:** 5942	**RIFM Number:** 5942
Stereochemistry: Isomer not specified. 5 stereocenters and total 32 stereoisomers possible.	**Stereochemistry:**	**Stereochemistry:**

2. Physical data**

1. **Boiling Point:** 267.45 °C (EPI Suite)
2. **Flash Point:** 196 °F; CC (FMA Database)
3. **Log K_{ow}:** 3.34 (EPI Suite)
4. **Melting Point:** 45.26 °C (EPI Suite)
5. **Water Solubility:** 57.27 mg/L (EPI Suite)
6. **Specific Gravity:** 1.050 (FMA Database)
7. **Vapor Pressure:** 0.00395 mm Hg @ 20 °C (EPI Suite v4.0), 0.007 mm Hg 20 °C (FMA Database), 0.00706 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Does not significantly absorb in the region of 290–400 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$).
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium fruity herbal woody jasmine oily basil odor.*

*http://www.thegoodscentscompany.com/data/rw1011151.htmL#toorgano; retrieved 4/18/2016.

**Physical data for all materials included in this assessment are identical.

3. Exposure

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0039% (RIFM, 2013b)
3. **Inhalation Exposure*:** 0.0020 mg/kg/day or 0.15 mg/day (RIFM, 2013b)
4. **Total Systemic Exposure**:** 0.014 mg/kg/day (RIFM, 2013b)

*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).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

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 III, High (Expert Judgment)

Expert Judgment	Toxtree (v 2.6.0)	OECD QSAR Toolbox (v. 3.2)
III*	III	II

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9)
   b. **Repeated Dose Toxicity:** Acetoxydihydrodicyclopentadiene (CAS # 54830-99-8)
   c. **Developmental and Reproductive Toxicity:** Acetoxydihydrodicyclopentadiene (CAS # 54830-99-8)
   d. **Skin Sensitization:** Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9)
   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)

None of the materials included in this assessment are reported to occur in foods 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

Tricyclodecenyl propionate and 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-indenyl propionate (mixture of isomers) have dossiers available; accessed on 9/15/2017. 3a, 4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl propionate is pre-registered for 2010; no dossier available as of 4/29/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, tricyclodecenyl propionate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of tricyclodecenyl propionate 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 TA97a, TA98, TA100, TA1535, and TA102 were treated with tricyclodecenyl propionate in dimethyl sulfoxide (DMSO) at concentrations up to 1600 μg/plate, as this was the lowest toxic concentration assessed. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2000b). Under the conditions of the study, tricyclodecenyl propionate was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of tricyclodecenyl propionate; however, read-across can be made to butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9; see Section V). The clastogenicity of butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung cells were treated with butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester in DMSO at concentrations up to 2203 μg/mL for 6 h in the presence and absence of S9 metabolic activation and for 24 and 48 h in the absence of S9 metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (RIFM, 2002b). Under the conditions of the study, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to tricyclodecenyl propionate.

Based on the data available, tricyclodecenyl propionate does not present a concern for genotoxic potential.

Additional References: RIFM, 1980b.

Literature Search and Risk Assessment Completed On: 8/29/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for tricyclodecenyl 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 tricyclodecenyl propionate. Read-across material, acetoxydihydrodi cyclopentadiene (CAS # 54830-99-8; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD/GLP 408 dietary 90-day study was conducted in Sprague Dawley Crl:CD BR strain rats. Groups of 10 rats/sex/group were administered with test material, acetoxydihydrodicyclopentadiene (mixture of isomers) at doses of 0, 200, 2000, 6000, or 20000 ppm (equivalent to a mean achieved doses of 0, 15.3, 154.9, 464.1, or 1504.6 mg/kg/day, respectively). Animals of either sex treated with 20000 ppm showed reduction in overall bodyweight gain and reduction in overall food consumption. Food efficiency was also adversely affected during periods of the treatment phase at 20000 ppm in animals of either sex. Organ weight analysis revealed statistically significant increases in both absolute and relative adrenal weights among high-dose males. Microscopic examination of the adrenals showed an increase in the incidence of vacuolation of the zona fasciculata in all treated males. This was considered to be an adaptive response to stress. There was a statistically significant increase in both the absolute and relative kidney weight alterations among treated males. Microscopic examination of kidneys revealed treatment-related hyaline droplet nephropathy among all treated males. The α-2μ-globulin nature of this finding was confirmed by additional Mallory's Heidenhain staining performed on male kidneys. Kidney changes in males were consistent with documented changes of α-2μ-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992 and Lehman-McKeeman et al., 1990). Microscopic alterations in the liver included minimal centrilobular to midzonal hepatocellular hypertrophy in males treated with 2000, 6000, or 20000 ppm test material. Elevated incidences of mostly diffuse vacuolation was found in males from all treatment groups; this vacuolation did not exceed slight severity degrees. The microscopic alterations in the liver among treated males were not considered to be toxicologically relevant since there were no liver weight increases or related alterations in clinical chemistry parameters. The authors of the study concluded a NOAEL of 6000 ppm for females based on decreased body weights. However, they did not provide a NOAEL for males due to

treatment-related alterations in the kidney. Since the alterations in the kidney were consistent with α-2μ-globulin nephropathy, and due to the absence of such effects among treated females, these changes were not considered to be adverse. Thus, the NOAEL for males was also considered to be 6000 ppm based on decreased body weights among high-dose group animals. A NOAEL of 6000 ppm or 464.1 mg/kg/day was considered for this study (RIFM, 2012; data also available in RIFM, 2014).

Therefore, the tricyclodecenyl propionate MOE for the repeated dose toxicity endpoint can be calculated by dividing the acetoxydihydrodicyclopentadiene NOAEL in mg/kg/day by the total systemic exposure to tricyclodecenyl propionate, 464.1/0.014 or 33150.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for tricyclodecenyl 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 or reproductive toxicity data on tricyclodecenyl propionate. Read-across material acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section V) has sufficient developmental and reproductive toxicity data to support the developmental and reproductive toxicity endpoints. An OECD 421 oral gavage reproduction and developmental toxicity screening test was conducted in Wistar Han:HsdRccHan:WIST strain rats. Groups of 10 rats/sex/dose were administered via oral gavage with test material acetoxydihydrodicyclopentadiene (mixture of isomers) at doses of 0, 100, 300, or 1000 mg/kg/day in an Arachis oil BP vehicle for up to 43 consecutive days (including a 2-week maturation phase, pairing, gestation, and early lactation for females). There were no treatment-related developmental effects in the litter parameters evaluated or any reproductive effects. Thus, the NOAEL for developmental and reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010).

Therefore, the tricyclodecenyl propionate MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the acetoxydihydrodicyclopentadiene NOAEL in mg/kg/day by the total systemic exposure to tricyclodecenyl propionate, 1000/0.014 or 71429.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/17.

10.1.4. Skin sensitization

Based on the available material-specific data and read-across material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 1113889-23-9), tricyclodecenyl propionate does not present a safety concern for skin sensitization under the current declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for tricyclodecenyl propionate. Based on the existing data and read-across material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9; see Section V), tricyclodecenyl propionate does not present a safety concern for skin sensitization under the current declared levels of use. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test no sensitization reactions were observed with read-across butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (RIFM, 2002c). In a human maximization test with 8% (5520 μg/cm^2) tricyclodecenyl propionate, 1 reaction was observed. However, the authors of the study report considered this study inconclusive due to strong reactions observed with other materials tested concurrently on the same subjects (RIFM, 1980a). In another human maximization test, 20% (13800 μg/cm^2) tricyclodecenyl propionate did not result in skin reactions in any of the subjects tested (RIFM, 1976). In a confirmatory human repeat insult patch test with 5% or (1550 μg/cm^2) read-across material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester, no reactions indicative of skin sensitization were observed (RIFM, 2001).

Based on the weight of evidence from structural analysis, human studies, and read-across material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester, tricyclodecenyl propionate does not present a safety concern for skin sensitization under the current declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/10/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra and data, tricyclodecenyl propionate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV absorption spectra indicate no significant absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In a rat phototoxicity study, application of 30% tricyclodecenyl propionate in ethanol did not result in phototoxic reactions (RIFM, 1981). Based on lack of absorbance and the *in vivo* study data, tricyclodecenyl propionate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level of tricyclodecenyl propionate is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on tricyclodecenyl propionate. Based on the Creme RIFM model, the inhalation exposure is 0.15 mg/day. This exposure is 3.1 times lower than the Cramer Class III TTC value of 0.47 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: 04/03/13; revised 06/09/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of tricyclodecenyl propionate 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, tricyclodecenyl propionate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify tricyclodecenyl propionate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2015), tricyclodecenyl propionate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 1996a: A study was conducted following OECD Guideline 301B. 10 mg/L of the test substance was incubated for 28 days. At the end of the study, 14.1% biodegradation was observed.

RIFM, 1993: A study was conducted following OECD Guideline 301B. 10 mg/L of the test substance was incubated for 56 days. At the end of the study, 21.2% biodegradation was observed.

RIFM, 1997: A study was conducted following OECD Guideline 302A. 10.5 mg/L of the test substance was incubated for 29 days. At the end of the study, 17% biodegradation was observed.

RIFM, 1996b: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 15% was observed.

RIFM, 1999: The inherent biodegradability of the test material was determined by the respirometric method following the OECD 302C method. Under the conditions of the study, biodegradation of 20% was observed.

10.2.2.2. Ecotoxicity. RIFM, 2011c: An algae growth inhibition study was conducted following OECD Guideline 201. The growth rate (r) and yield (y) of *Desmodesmus subspicatus* were affected by the presence of the test material over the 72-h period. The 72-h ErC50 was reported to be 2.5 mg/L. The 72-h EyC50 (0–72 h) of the test material was reported to be 3.3 mg/L. The No Observed Effect Concentration (NOEC) for growth rate and yield was 1.8 mg/L, and the Lowest Observed Effect Concentration (LOEC) for growth rate and yield was 4.0 mg/L (RIFM, 2011c).

RIFM, 2000a: There are 2 *Daphnia magna* immobilization studies reported. In one study following Council Directive 92/69/EEC, Part C Method 2, the 48-h EC50 was reported as the geometric mean of the EC0 and the EC100. The EC50 was reported as 4.6 mg/L (RIFM, 2000a).

RIFM, 2011b: A *Daphnia magna* immobilization test was conducted according to the OECD 202 guidelines under flow-through conditions. The reported EC50 was > 14 mg/L.

RIFM, 2011a: An acute fish toxicity study following OECD Test Guideline 203 under flow-through conditions using *Pimephales promelas* reported a 96-h LC50 of 6.7 mg/L.

RIFM, 2013a: A *Daphnia magna* reproduction test following OECD Test Guideline 211 was performed. This was a 21-day study performed under flow-through conditions. The reported NOEC was 0.83 mg/L (mean measured concentration) for reproduction and growth (total length). The EC50 for immobility was 1.5 mg/L and for reproduction was 2.1 mg/L.

RIFM, 2015: A fish (Fathead minnow) early-life stage toxicity test was conducted according to the OECD 210 method under flow-through conditions. Based on mean measured concentrations, the 21-day NOEC was reported to be 0.8 mg/L (growth).

10.2.2.3. Other available data. This material has been registered under REACH with 2 related materials (CAS # 68912-13-0, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl propionate (mixture of isomers) and CAS # 67634-24-6 3a, 4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl propionate) 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)**	19			1,000,000	0.019	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.55	8.19	2.82	10,000	0.282	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	10.61	6.82	8.46			Neutral Organics
Tier 3: Measured Data						
	LC50 (mg/L)	EC50 (mg/L)	NOEC (mg/L)	AF	PNEC (µg/L)	Comments
Fish	6.7		0.8	10	80	
Daphnia		>14	0.83			
Algae		2.5	1.8			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.34	3.34
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	> 1000*	> 1000*

Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Combined regional Volume of Use.

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

The RIFM PNEC is 80 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/24/17.

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.2018.10.017.

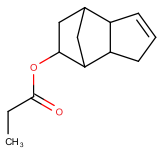
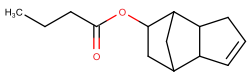
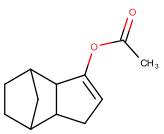
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US ECHA, 2012).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (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 v4.2 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2012).

	Target Material	Read-across Material	
Principal Name	Tricyclodecenyl propionate	Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester	Acetoxydihydrodicyclopentadiene (Mixture of Isomers)
CAS No.	**17511-60-3**, 68912-13-0, 67634-24-6	113889-23-9	54830-99-8
Structure			
Similarity (Tanimoto Score)		0.97	0.81
Read-across Endpoint		• Genotoxicity • Skin sensitization	• Repeated dose toxicity • Reproductive and developmental toxicity

Molecular Formula	$C_{13}H_{18}O_2$	$C_{14}H_{20}O_2$	$C_{12}H_{16}O_2$
Molecular Weight	206.29	220.31	192.26
Melting Point (°C, EPI Suite)	45.26	55.60	44.07
Boiling Point (°C, EPI Suite)	267.45	283.56	253.97
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.941	0.323	1.94
Log Kow (KOWWIN v1.68 in EPI Suite)	3.34	3.83	2.98
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	57.27	18.41	137.4
J_{max} (mg/cm^2/h, SAM)	14.620	9.472	22.988
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.28E + 001	3.02E + 001	1.36E + 002
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized		• Not categorized
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without Oh or NH2 group		• Non-binder, without Oh or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)		• Toxicant (good reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• SN2 reaction	
Protein Binding (OECD)	• Acylation	• Acylation	
Protein Binding Potency	• Not possible to classify	• Not possible to classify	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• SN2 reaction	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on tricyclodecenyl propionate (CAS # 17511-60-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9) and acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9) was used as a read-across analog for the target material tricyclodecenyl propionate (CAS # 17511-60-3) for the genotoxicity endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
  - ○ The target substance and the read-across analog share an unsaturated tricyclic alcohol fragment.
  - ○ The key difference between the target substance and the read-across analog is that the target substance has an ethyl moiety as an acid fragment and the read-across analog has propyl moiety as an acid fragment. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated tricyclic alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target substance and $\leq 40\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the

read-across analog.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9) was used as a read-across analog for the target material tricyclodecenyl propionate (CAS # 17511-60-3) for the skin sensitization endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
  - ○ The target substance and the read-across analog share an unsaturated tricyclic alcohol fragment.
  - ○ The key difference between the target substance and the read-across analog is that the target substance has an ethyl moiety as an acid fragment and the read-across analog has propyl moiety as an acid fragment. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated tricyclic alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target substance and $\leq 40\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ The target substance and the read-across analog have several protein binding alerts like SN2 reaction and acylation. The data described in the skin sensitization section show that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alert will be superseded by the availability of the data.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) was used as a read-across analog for the target material tricyclodecenyl propionate (CAS # 17511-60-3) for the repeated dose and reproductive and developmental toxicity endpoints.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
  - ○ The target substance and the read-across analog share an unsaturated tricyclic alcohol fragment.
  - ○ The key difference between the target substance and the read-across analog is that the target substance has an ethyl moiety as an acid fragment and the read-across analog has acetyl moiety as an acid fragment. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated tricyclic alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ The target substance and the read-across analog are predicted to be a toxicant by the CAESAR model for developmental toxicity. The data described in the developmental toxicity section above show that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of cramer classification:

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? No
Q22. Common component of food? No
Q33. Has sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulfonate or sulfamate? No, Class III (High Class).

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