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Short Review

RIFM fragrance ingredient safety assessment, tricyclodecanyl acetate, CAS Registry Number 64001-15-6

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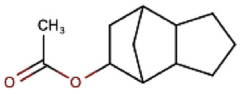

Abbreviation/Definition List:

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

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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: Existing data support the use of this material.

Tricyclodecanyl acetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog acetoxydihydrodicyclopentadiene (mixture of isomers; CAS# 54830-99-8) show that tricyclodecanyl acetate is not expected to be genotoxic. Data from read-across analog butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl butanoate; CAS# 113889-23-9) show that this material is not a safety concern under the current declared levels of use for the skin sensitization endpoint. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.47 mg/day). Data from read-across analog butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl butanoate; CAS# 113889-23-9), which provided an MOE > 100 for the repeated dose toxicity endpoint. Read-across analog acetoxydihydrodicyclopentadiene (mixture of isomers; CAS# 54830-99-8) provided an MOE > 100 for the developmental and reproductive toxicity endpoints. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; tricyclodecanyl acetate 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, 2007; RIFM, 2016b)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(RIFM, 2002d)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(RIFM, 2010; RIFM, 2012)
Skin Sensitization: No safety concerns under the current, declared levels of use.	(RIFM, 2002c; RIFM, 2001)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.91 (BIOWIN 3)	(EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 48.68 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 4.156 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Algae 96-h EC50: 4.156 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.4156 µg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1 **Chemical Name:** Tricyclodecanyl acetate
2 **CAS Registry Number:** 64001-15-6
3 **Synonyms:** Dihydrocyclacet; 4,7-Methano-1H-inden-5-ol, octahydro-, acetate; Octahydro-4,7-methano-1H-indene-5-yl acetate; Octahydro-1H-4,7-methanoinden-5-yl acetate; Tricyclodecanyl acetate
4 **Molecular Formula:** $C_{12}H_{18}O_2$
5 **Molecular Weight:** 194.27
6 **RIFM Number:** 1278
7. **Stereochemistry:** Isomer not specified. Three stereocenters and 8 total stereoisomers possible.

2. Physical data

1 **Boiling Point:** 248.12 °C (EPI Suite)
2 **Flash Point:** > 212.00 °F TCC (> 100.00 °C)*
3 **Log K_{OW}:** 3.06 (EPI Suite)
4 **Melting Point:** 33.6 °C (EPI Suite)
5 **Water Solubility:** 113.5 mg/L (EPI Suite)
6 **Specific Gravity:** 1.04600 to 1.05400 @ 25.00 °C*
7 **Vapor Pressure:** 0.008 mm Hg 20C, 0.0141 mm Hg @ 20 °C (EPI Suite 4.0), 0.0245 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a medium herbal, green, fruity, and basil odor*

*http://www.thegoodscentscompany.com/data/rw1044461.html, retrieved 10/2/13.

3. Exposure

1 **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2 **95th Percentile Concentration in Hydroalcoholics:** 0.071% (RIFM, 2016a)
3 . **Inhalation Exposure*:** 0.0015 mg/kg/day or 0.12 mg/day (RIFM, 2016a)
4 . **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2016a)

*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 III, High (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
III*	II	II

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

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

No relevant data available for inclusion in this safety assessment.

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

Tricyclodecanyl 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 that 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

Available; accessed 07/31/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Tricyclodecanyl acetate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of tricyclodecanyl acetate. However, read-across can be made to acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8; see Section V). The mutagenic activity of acetoxydihydrodicyclopentadiene (mixture of isomers) 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/preincubation method. *Salmonella typhimurium* strains TA97a, TA98, TA100, TA1535, and *Escherichia coli* strain WP2uvrA were treated with acetoxydihydrodicyclopentadiene (mixture of isomers) in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2007). Under the conditions of the study, acetoxydihydrodicyclopentadiene (mixture of isomers) was not mutagenic in the Ames test, and this can be extended to tricyclodecanyl acetate.

There are no studies assessing the clastogenic activity of tricyclodecanyl acetate. However, read-across can be made to acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8; see Section V). The clastogenic activity of acetoxydihydrodicyclopentadiene (mixture of isomers) 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 acetoxydihydrodicyclopentadiene (mixture of isomers) in DMSO at concentrations up to 1900 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Acetoxydihydrodicyclopentadiene (mixture of isomers) 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, acetoxydihydrodicyclopentadiene (mixture of isomers) was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to tricyclodecanyl acetate.

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

Additional References: RIFM, 2002b.

Literature Search and Risk Assessment Completed On: 08/02/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for tricyclodecanyl acetate 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 tricyclodecanyl acetate. Read-across material butanoic acid 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl butanoate; CAS # 113889-23-9; see Section V) has an OECD 407 28-day oral gavage repeated dose toxicity study conducted in Sprague Dawley Crl:CD(SD) IGS BR strain rats. Groups of 5 rats/sex/dose were administered daily via gavage with test material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (cyclobutanate) at doses of 0, 15, 150, or 1000 mg/kg/day in Arachis oil BP for 28 days. Additional groups of 5 rats/sex were assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups. At 150 and 1000 mg/kg/day, male rats were observed to have a greater incidence of accumulations of eosinophilic material in the tubular epithelium of the kidney, which have regressed for the high-dose recovery group of male rats. These kidney changes in males were consistent with documented changes of alpha-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). There were no treatment-related adverse effects observed up to the highest dose tested, thus the NOAEL for the repeated dose toxicity endpoint was considered to be 1000 mg/kg/day (RIFM, 2002d).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study. The safety factor has been approved by the Expert Panel for Fragrance Safety.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the tricyclodecanyl acetate MOE can be calculated by dividing the butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester NOAEL in mg/kg/day divided by the total systemic exposure to tricyclodecanyl acetate, 333/0.0016 or 208125.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/11/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for tricyclodecanyl acetate 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 toxicity data on tricyclodecanyl acetate. Read-across material acetoxydihydrodicyclopentadiene (mixture of isomers; CAS # 54830-99-8; see Section V) has an OECD/GLP 421 oral gavage reproduction and developmental toxicity screening test conducted in Wistar Han:HsdRccHan:WIST strain rats. Groups of 10 rats/sex/dose were administered via 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. Thus, the NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010).

Therefore, the tricyclodecanyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the acetoxydihydrodicyclopentadiene NOAEL in mg/kg/day by the total systemic

exposure to tricyclodecanyl acetate, 1000/0.0016 or 625000.

There are no reproductive toxicity data on tricyclodecanyl acetate. Read-across material acetoxydihydrodicyclopentadiene (mixture of isomers; CAS # 54830-99-8; see Section V) has an OECD/GLP 421 oral gavage reproduction and developmental toxicity screening test conducted in Wistar Han:HsdRccHan:WIST strain rats. Groups of 10 rats/sex/dose were administered via 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 reproductive effects on the mating, fertility and gestation lengths. Thus, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010). An OECD/GLP 408 dietary subchronic toxicity study was conducted with Sprague Dawley Crl:CD BR strain rats for 90 consecutive days. Groups of 10 rats/sex/dose were administered feeds containing test material acetoxydihydrodicyclopentadiene (mixture of isomers) at concentrations of 0, 200, 2000, 6000, or 20000 ppm (equivalent to a mean achieved dose of 0, 15.3, 154.9, 464.1, or 1504.6 mg/kg/day, respectively). In addition to the systemic toxicity parameters, the reproductive organs including estrous cycling and sperm assessments were also conducted on all animals. No treatment-related effects on the concentration, motility, or morphology of the epididymal sperm in males and the female estrous cycles were observed. Thus, the NOAEL for reproductive toxicity was considered to be 20000 ppm or 1504.6 mg/kg/day, the highest dose tested (RIFM, 2012). The most conservative NOAEL from the OECD 421 study was selected for the reproductive toxicity endpoint.

Therefore, the tricyclodecanyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the acetoxydihydrodicyclopentadiene NOAEL in mg/kg/day by the total systemic exposure to tricyclodecanyl acetate, 1000/0.0016 or 625000.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/11/17.

10.1.4. Skin sensitization

Based on the limited available data and read-across to 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9), tricyclodecanyl acetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the limited available data and read-across to 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl butanoate; CAS # 113889-23-9; see Section V), tricyclodecanyl acetate would not be expected to present a safety concern for skin sensitization. These materials are not predicted to react with skin proteins (OECD Toolbox V3.4; Roberts and Natsch, 2009; Toxtree 2.6.13). No predictive sensitization tests are available for tricyclodecanyl acetate. However, read-across 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester was found to be negative in a guinea pig maximization test (RIFM, 2002c). Additionally, in a human repeated insult patch test no reactions indicative of sensitization were observed with 6.25% or 4845 μg/cm^2 tricyclodecanyl acetate in 75% alcohol in any of the 41 volunteers (RIFM, 1971). Similarly, no reactions were observed when 5% 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester in any of the 114 volunteers (RIFM, 2001). Based on the weight of evidence from structural analysis, human data, and read-across to 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester, tricyclodecanyl acetate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/20/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, tricyclodecanyl acetate 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 tricyclodecanyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, tricyclodecanyl acetate 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: 07/06/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material tricyclodecanyl acetate exposure level 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 tricyclodecanyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.12 mg/day. This exposure is 3.92 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.

Key studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/02/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of tricyclodecanyl acetate 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, tricyclodecanyl 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 EPI Suite v4.1 (US EPA, 2012a) did not identify tricyclodecanyl acetate as possibly being either 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 v4.1). 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 (2015), tricyclodecanyl acetate does present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. Not data available.

10.2.4. Other available data

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

10.2.5. 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)**	31.34			1,000,000	0.003134	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.227	11.554	4.156	10,000	0.42	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	17.75	11.12	12.42			Neutral Organic

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.06	3.06
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is > 1. Additional assessment is necessary.

The RIFM PNEC is 0.42 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: 8/2/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.074.

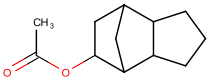
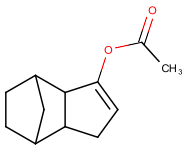
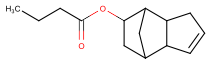
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material
Principal Name	Tricyclodecanyl acetate	Acetoxydihydrodicyclopentadiene (mixture of isomers)	Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl butanoate)
CAS No.	64001-15-6	54830-99-8	113889-23-9
Structure			
Similarity (Tanimoto Score)		0.83	0.85
Read-across Endpoint		• Genotoxicity • Reproductive and developmental toxicity	• Skin sensitization • Repeated dose toxicity
Molecular Formula	$C_{12}H_{18}O_2$	$C_{12}H_{16}O_2$	$C_{14}H_{20}O_2$
Molecular Weight	194.28	192.26	220.31
Melting Point (°C, EPI Suite)	33.60	44.07	55.60
Boiling Point (°C, EPI Suite)	248.12	253.97	283.56
Vapor Pressure (Pa @ 25 °C, EPI Suite)	3.27	1.94	0.323
Log KOW(KOWWIN v1.68 in EPI Suite)	3.06	2.98	3.83
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	113.5	137.4	18.41
J_{max} (mg/cm^2/h, SAM)	20.475	22.988	9.472
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.95E + 001	1.36E + 002	3.02E + 001
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• Schiff base formation • Nucleophilic attack • Acylation	• Schiff base formation • Nucleophilic attack • Acylation	

DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• Schiff base formation • Nucleophilic attack • Acylation	
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)	64001-15-6.pdf	54830-99-8.pdf	113889-23-9.pdf

Summary

There are insufficient toxicity data on Tricyclodecanyl acetate (CAS # 64001-15-6). 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, Acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) and butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl butanoate; CAS # 113889-23-9) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) was used as a read-across analog for the target material tricyclodecanyl acetate (CAS # 64001-15-6) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
  - o The target substance and the read-across analog share a cyclic secondary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a saturated alcohol fragment attached to the acetyl moiety and the read-across analog has an unsaturated alcohol fragment attached to the acetyl moiety. This structural difference is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic secondary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have a Schiff base formation alert by DNA binding model by OECD. The read-across analog also has the same alert by OASIS. This shows that the read-across analog is predicted to have comparable reactivity with the target substance. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alert will be superseded by the availability of the data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o 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 tricyclodecanyl acetate (CAS # 64001-15-6) for reproductive and developmental toxicity.

- o The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
- o The target substance and the read-across analog share a cyclic secondary alcohol fragment.
- o The key difference between the target substance and the read-across analog is that the target substance has a saturated alcohol fragment attached to the acetyl moiety, and the read-across analog has an unsaturated alcohol fragment attached to the acetyl moiety. This structural difference is toxicologically insignificant.
- o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic secondary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- o The target substance and the read-across analog are predicted to be toxicants by developmental toxicity model by CAESAR. The data described in developmental and reproductive toxicity section above show that the margin of exposure of the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by the availability of the data.
- o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o 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 tricyclodecanyl acetate (CAS # 64001-15-6) for repeated dose toxicity.
  - o The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
  - o The target substance and the read-across analog share a cyclic secondary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a saturated alcohol fragment attached to the acetyl moiety, and the read-across analog has an unsaturated alcohol fragment attached to the butyrate moiety. This structural difference is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic secondary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o 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.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o 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 (3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl butanoate; CAS # 113889-23-9) was used as a read-across analog for the target material tricyclodecanyl acetate (CAS # 64001-15-6) for skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
  - o The target substance and the read-across analog share a cyclic secondary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a saturated alcohol fragment attached to the acetyl moiety, and the read-across analog has an unsaturated alcohol fragment attached to the butyrate moiety. This structural difference is toxicologically insignificant.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic secondary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o 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.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The read-across analog has an SN2 protein binding alert by OASIS. The target substance does not have any protein binding alert. According to these predictions, the read-across analog is expected to be more reactive compared to the target substance. Data superseded predictions in this case.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o 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

Due to potential discrepancies between 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.

Q1. A 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. A common component of food? No
Q33. Has a 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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