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Short Review

RIFM fragrance ingredient safety assessment, tricyclodecenyl acetate, CAS Registry Number 5413-60-5

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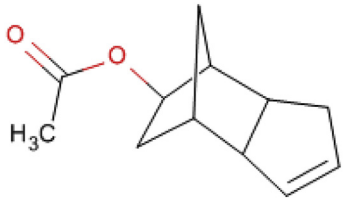
Version: 022618. This version replaces any previous versions.
Name: Tricyclodecenyl acetate
CAS Registry Number: 5413-60-5
Additional CAS Numbers*:54830-99-8 Acetoxydihydrodicyclopentadiene (mixture of isomers) 2500-83-6 Tricyclo[5.2.1.02,6]dec-4-en-8-yl acetate
*These materials were included in this assessment because the materials 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 acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that tricyclodecenyl acetate is not genotoxic and provided an MOE > 100 for the repeated dose, developmental and reproductive toxicity endpoint. Data on 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 acetate 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). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; tricyclodecenyl 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, 2016)
Repeated Dose Toxicity: NOAEL = 464.1 mg/kg/day. (RIFM, 2012a)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day. (RIFM, 2010a)
Skin Sensitization: No safety concerns under the current, declared levels of use. (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: Critical Measured Value: 17% (OECD 302C) (RIFM, 1999)
Bioaccumulation: Screening-level: 35.11 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 21-day fish (Fathead Minnow) NOEC: 0.8 mg/L read-across to Cyclaprop (CAS# 17511-60-3) (RIFM, 2013b)

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: 21-day fish (Fathead Minnow) NOEC: 0.8 mg/L read-across to Cyclaprop CAS # 17511-60-3 (RIFM, 2013b)

RIFM PNEC is: 80 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

1. Identification

Chemical Name: Tricyclodecenyl acetate	Chemical Name: Acetoxydihydrodicyclopentadiene (mixture of isomers)	Chemical Name: Tricyclo[5.2.1.02,6]dec-4-en-8-yl acetate
CAS Registry Number: 5413-60-5 **Synonyms:** Dihydro-norbicyclopentadienyl acetate; Greenylacetate; Herbaflorat; 3a,4,5,6,7,7a-Hexahydro-4,7-methanoinden-6-ylacetate; 4,7-Methano-1H-inden-6-ol, 3a,4,5,6,7,7a-hexahydro-, acetate; Tricyclodecen-4-yl 8-acetate; Verdyl acetate; Jasmacyclene; 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 acetate; Tricyclodecenyl acetate	**CAS Registry Number:** 54830-99-8 **Synonyms:** 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-1-yl acetate; 4,7-Methano-1H-indenol, 3a,4,5,6,7,7a-hexahydro-, acetate; Acetoxydihydrodicyclopentadiene (Mixture of Isomers); Cyclacet; Tricyclo[5.2.1.0(2,6)]dec-3-enyl acetate; ｱﾙｶﾝ酸（C＝1～3）ﾄﾘｼｸﾛﾃﾞｾﾆﾙ	**CAS Registry Number:** 2500-83-6 **Synonyms:** 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-5-yl acetate; 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl acetate; 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydro-, acetate; Tricyclo [5.2.1.02,6]dec-4-en-8-yl acetate; ｱﾙｶﾝ酸（C＝1～3）ﾄﾘｼｸﾛﾃﾞｾﾆﾙ
Molecular Formula: $C_{12}H_{16}O_2$ **Molecular Weight:** 192.26 **RIFM Number:** 1000 **Stereochemistry:** Isomer not specified. Five stereocenters and 32 total stereoisomers possible.	**Molecular Formula:** $C_{12}H_{16}O_2$ **Molecular Weight:** 192.26 **RIFM Number:** 1337 **Stereochemistry:**	**Molecular Formula:** $C_{12}H_{16}O_2$ **Molecular Weight:** 192.26 **RIFM Number:** 5278 **Stereochemistry:**

2. Physical data

CAS# 5413-60-5	CAS# 54830-99-8	CAS# 2500-83-6
Boiling Point: 250.43 °C (EPI Suite) **Flash Point:** > 200 °F; CC (FMA Database) **Log K_{ow}:** 3.8 at 25 °C (RIFM, 1996c), 2.85 (EPI Suite), Log Pow = 3.4 and 3.5 (RIFM, 2010e)	**Boiling Point:** 253.97 °C (EPI Suite) **Flash Point:** 94 °C (GHS, IFF) **Log K_{ow}:** 7.93 × 10(3), log10 Pow 3.90 (RIFM, 2012b), 7.93 × 10(3), Log10 Pow = 3.90 (RIFM, 2010b), 2.98 (EPI Suite)	**Boiling Point:** 250.43 °C (EPI Suite) **Flash Point:** > 93 °C (GHS) **Log K_{ow}:** 2.85 (EPI Suite), Log Pow = 3.4 and 3.5 (RIFM, 2010e)
Melting Point: 34.66 °C (EPI Suite) **Water Solubility:** 177.4 mg/L (EPI Suite)	**Melting Point**: 44.07 °C (EPI Suite) **Water Solubility:** 137.4 mg/L (EPI Suite)	**Melting Point**: 34.66 °C (EPI Suite) **Water Solubility:** 177.4 mg/L (EPI Suite)
Specific Gravity: 1.0735 (EOA, 1974 Sample 74–253), 1.072 (FMA Database)	**Specific Gravity:** 1.07000 to 1.07800 @ 20 °C*	**Specific Gravity:** N/A
Vapor Pressure: 0.0123 mm Hg @ 20 °C (EPI Suite 4.0), 0.0213 mm Hg @ 25 °C (EPI Suite)	**Vapor Pressure:** 0.00828 mm Hg @ 20 °C(EPI Suite 4.0), 0.0145 mm Hg @ 25 °C (EPI Suite)	**Vapor Pressure:** 0.0123 mm Hg @ 20 °C (EPI Suite 4.0), 0.0213 mm Hg @ 25 °C (EPI Suite)
UV Spectra: No significant absorbance in the range of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)		
Appearance/Organoleptic: A colorless to pale yellow clear viscous liquid with a medium floral, green, soapy, cedar pine, and woody odor.*	**Appearance/Organoleptic:** A clear, colorless liquid with a green and woody odor.	**Appearance/Organoleptic:** A colorless to pale yellow clear liquid with a medium floral, green, herbal odor.*

*http://www.thegoodscentscompany.com, retrieved 9/15/2017.

3. Exposure***

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.60% (RIFM, 2013a)
3. **Inhalation Exposure*:** 0.0029 mg/kg/day or 0.21 mg/day (RIFM, 2013a)
4. **Total Systemic Exposure**:** 0.017 mg/kg/day (RIFM, 2013a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM 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	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: None
   b. Repeated Dose Toxicity: None
   c. Developmental and Reproductive Toxicity: None
   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: Tricyclodecenyl propionate: CAS # 17511-60-3
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 in this safety assessment are 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 contains 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

Dossiers available for tricyclodecenyl acetate and acetoxydihydrodicyclopentadiene (mixture of isomers) (reaction mass). Acetoxydihydrodicyclopentadiene (mixture of isomers) and tricyclo [5.2.1.02,6]dec-4-en-8-yl acetate are pre-registered for 2010; no dossiers available as of 2/13/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenic activity of acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA97a, TA98, TA100, and TA1535, and *Escherichia coli* strain WP2uvrA were treated with acetoxydihydrodicyclopentadiene (mixture of isomers) in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate with and without S9 metabolic activation. No increases in the number of revertant colonies were observed in the tester strains at any of the concentrations assessed (RIFM, 2007). Under the conditions of this study, there was no evidence of mutagenic activity detected for acetoxydihydrodicyclopentadiene (mixture of isomers) in the Ames test.

The clastogenic activity of acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) 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 at any concentration in either non-activated or S9-activated test systems (RIFM, 2016). Under the conditions of the study, acetoxydihydrodicyclopentadiene (mixture of isomers) was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, acetoxydihydrodicyclopentadiene (mixture of isomers) does not present a concern for genotoxic potential.

Additional References: RIFM, 2009; RIFM, 1980b; Symrise, 2009.

Literature Search and Risk Assessment Completed On: 08/28/2017.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 1 of the combined materials, acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section I). An OECD 408/GLP 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). A reduction in overall bodyweight gain was detected in animals of either sex treated with 20000 ppm. Animals of either sex treated with 20000 ppm showed a reduction in overall food consumption, and food efficiency was also adversely affected during periods of the treatment phase. 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 alpha-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 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). 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 were 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 kidney were consistent with alpha-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, 2012a; data also available in RIFM, 2014). **Therefore, the tricyclodecenyl acetate 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 acetate, 464.1/0.017 or 27300.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/2017.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on 1 of the combined material, acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section I). 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 two-week maturation phase, pairing, gestation and early lactation for females). There were no treatment-related developmental effects in the litter parameters evaluated or on any reproductive effects. Thus, the NOAEL for developmental and reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010a). **Therefore, the tricyclodecenyl acetate 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 acetate, 1000/0.017 or 58824.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/2017.

10.1.4. Skin sensitization

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), tricyclodecenyl acetate 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 acetate. 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 V), tricyclodecenyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicates 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 material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (RIFM, 2002b). In a human maximization test, no skin sensitization reactions were observed with tricyclodecenyl acetate (RIFM, 1974; RIFM, 1977). In a confirmatory human repeat insult patch test (HRIPT) with 3500 μg/cm2 of tricyclodecenyl acetate, no reactions indicative of sensitization were observed in any of the 53 volunteers (RIFM, 1980a). Additionally, in a confirmatory HRIPT with 1550 μg/cm2 of tricyclodecenyl acetate, no reactions indicative of sensitization were observed in any of the 41 volunteers (RIFM, 1971). In an HRIPT from the read-across material, no reactions indicative of sensitization were observed in 112 subjects with 5% (1550 μg/cm2) butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (RIFM, 2001).

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

Additional References: RIFM, 1960a; RIFM, 1960b.

Literature Search and Risk Assessment Completed On: 09/07/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, tricyclodecenyl 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 tricyclodecenyl 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, tricyclodecenyl 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: 08/11/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, tricyclodecenyl 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 tricyclodecenyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.21 mg/day. This exposure is 2.2 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: 09/11/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of tricyclodecenyl 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, tricyclodecenyl 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 tricyclodecenyl 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 v4.11). 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 acetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. For CAS # 5413-60-5.

RIFM, 1997: Inherent biodegradability of the test material was evaluated in a modified SCAS Test according to the OECD 302A method. The average extent of mineralization of the test material in the sealed vessel test using acclimatized inoculum was 12.5%.

RIFM, 1993b: The inherent biodegradability of the test material was evaluated using a modified sealed vessel test according to the OECD 301B guidelines. After 56 days the average percentage of biodegradation was 13.8%.

RIFM, 1996a: A study was conducted to determine the ready and ultimate biodegradability of the test material using the OECD 301B method. No biodegradation was observed.

RIFM, 1999: The Inherent Biodegradability of the test material was determined by the Respirometric Method according to the OECD 302C guidelines. Test material underwent 17% biodegradation after 31 days in the test conditions.

RIFM, 1996b: The Ready Biodegradability of the test material was determined by the Manometric Respirometry following the 301F method. The test material undergoes only 10% biodegradation after 28 days in the test conditions.

RIFM, 2010f: The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test following the 301F method. The test material undergoes 14% biodegradation after 28 days (16% biodegradation after 60 days, 16% biodegradation after 61 days) in the test conditions.

10.2.2.2. Ecotoxicity. For CAS # 5413-60-5.

RIFM, 1993a: A 96-h acute toxicity study was conducted with zebrafish. The geometric mean of LC0/LC100 was reported to be 15.8 mg/L.

For CAS # 54830-99-8.

RIFM, 2010c: A 48-h *Daphnia magna* acute toxicity test was conducted according to the OECD 202 method. The calculated EC50 was reported to be 25 mg/L.

RIFM, 2010d: An algae inhibition test was conducted according to the OECD 201 method. The 72-h ErC50 (inhibition of growth rate) was 25 mg/L, and the EyC50 (inhibition of yield) was 9.2 mg/L.

10.2.2.3. Other available data. Tricyclodecenyl acetate has been registered under REACH with no additional data at this time.

The following additional data are available for the read-across material cyclaprop CAS# 17511-60-3:

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, 2000: There are 2 *Daphnia magna* immobilization studies reported. In 1 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, 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, 2013b**:** A *Daphnia magna* reproduction test following OECD TG 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**:** 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).

10.2.3. 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)**	7.045			1,000,000	0.00704	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	8.229	15.62	5.814	10,000	0.5814	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	27.40	16.82	17.31			Neutral Organic
Tier 3: Measured Data including read-across						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	15.8		0.8	10	80	
Daphnia		25	0.83			
Algae		9.2	1.8			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.8	3.8
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 < 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: 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:** 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.2017.09.035.

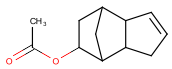
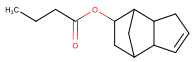
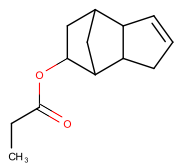
Appendix

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	
Principal Name	Tricyclodecenyl acetate	Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester	Tricyclodecenyl propionate
CAS No.	**5413–60–5**, 54830-99-8, and 2500-83-6	113889-23-9	17511-60-3
Structure			
Similarity (Tanimoto Score)		0.94	0.96
Read-across Endpoint		• Skin sensitization	• Environmental
Molecular Formula	$C_{12}H_{16}O_2$	$C_{14}H_{20}O_2$	$C_{13}H_{18}O_2$
Molecular Weight	192.26	220.31	206.29
Melting Point (°C, EPI Suite)	34.66	55.60	45.26
Boiling Point (°C, EPI Suite)	250.43	283.56	267.45
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.84	0.323	0.941
Log Kow (KOWWIN v1.68 in EPI Suite)	2.85	3.83	3.34
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	177.4	18.41	57.27
J_{max} (mg/cm^2/h, SAM)	22.988	9.472	14.620

Henry's Law ($Pa \cdot m^3$/mol, Bond Method, EPI Suite)	1.72E + 001	3.02E + 001	2.28E + 001
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 acetate (CAS # 5413-60-5). 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 tricyclodecenyl propionate (CAS # 17511-60-3) 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 acetate (CAS # 5413-60-5) for 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 methyl 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. The data described in the skin sensitization section shows that the read-across analog does not pose a concern for skin sensitization under the current, declared levels 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.
- Tricyclodecenyl propionate (CAS # 17511-60-3) was used as a read-across analog for the target material tricyclodecenyl acetate (CAS # 5413-60-5) for the environmental 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 acetyl acid fragment and the read-across analog has an ethyl 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 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 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)

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research institute for fragrance materials, inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. European Chemical Agency Read-across Assessment Framework. ECHA Read-across Assessment Framework. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Lehman-McKeeman, L.D., Rivera-Torres, M.I., Caudill, D., 1990. Lysosomal degradation of alpha2u-globulin and alpha2u-globulin-xenobiotic conjugates. Toxicol. Appl. Pharmacol. 103 (3), 539–548.

Lehman-McKeeman, L.D., Caudill, D., 1992. a-2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. Toxicol. Appl. Pharmacol. 116 (2), 170–176.

OECD, 2012. The OECD QSAR Toolbox, V 3.4. http://www.qsartoolbox.org/.

OECD, 2015. Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1960. Schwartz Patch Test Study with Tricyclodecenyl Acetate in Human Subjects. Unpublished report from Givaudan Corporation. RIFM report number 14936. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1960. Repeat Insult Patch Test in Human Subjects with Fragrance Materials. Unpublished report from Givaudan Corporation. RIFM report number 15107. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1971. Repeated Insult Patch Test with Acetoxydihydrodicyclopentadiene. Unpublished report from International Flavors and Fragrances. RIFM report number 48341. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1801. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1691. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Evaluation of Potential Hazards by Dermal Contact of Fragrance Materials in Human Subjects. Unpublished report from International Flavors and Fragrances. RIFM report number 1982. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Ames Metabolic Aactivation Test to Assess the Potential Mutagenic Effect of Tricyclodecenyl Acetate. Unpublished report from Quest International. RIFM report number 46286. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1993. Acute Fish Toxicity of Tricyclodecenyl Acetate. Unpublished report from Haarmann & Reimer GmbH. RIFM report number 41113. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1993. The Inherent Biodegradability of Base Perfumes in the Sealed Vessel Test. Unpublished report from Quest International. RIFM report number 49449. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1996. The Ultimate Biodegradability of Base Perfumes in the Sealed Vessel Test. Unpublished report from Quest International. RIFM report number 49697. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1996. Ready Biodegradability of Tricyclodecenyl Acetate (Verdyl Acetate). Unpublished report from Givaudan. RIFM report number 51517. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1996. Partition Coefficient N-octanol/water of Tricyclodecenyl Acetate (Verdyl Acetate). Unpublished report from Givaudan. RIFM report number 51518. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997. Assessment of the Inherent Biodegradability of Tricyclodecenyl Acetate in a Sealed Vessel CO2 Production Test Using Acclimatised Effluent from a Modified Semi-continuous Activated Sludge Test. Unpublished report from Quest International. RIFM report number 46283. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Inherent Biodegradability of Tricyclodecenyl Acetate (Verdyl Acetate). Unpublished report from Givaudan. RIFM report number 51516. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000. Tricyclodecenyl Propionate (Herbylpropionat): Acute Daphnia Toxicity. Unpublished report from Symrise. RIFM report number 53647. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Repeated Insult Patch Test with Butanoic Acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl Ester. Unpublished report from International Flavors and Fragrances. RIFM report number 48571. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Butanoic Acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl Ester: Skin Sensitisation in the guinea Pig - Magnusson and Kligman Maximisation Method. Unpublished report from IFF Incorporated. RIFM report number 47519. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Acetoxydihydrodicyclopentadiene: Bacterial Reverse Mutation Test. Unpublished Report from International Flavors and Fragrances. RIFM Report Number 53436. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Evaluation of Acetoxydihydrodicyclopentadiene (Mixture of Isomers)(cyclacet) in the L5178Y TK +/- Mouse Lymphoma Mutagenesis Assay with colony Size Evaluation in the Presence and Absence of Induced Rat Liver S-9 with a Confirmatory Study. Unpublished report from International Flavors and Fragrances. RIFM report number 57765. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Acetoxydihydrodicyclopentadiene (Mixture of Isomers) (Cyclacet): Oral (Gavage) Reproduction/developmental Toxicity Screening Test in the Rat. Unpublished report from International Flavors and Fragrances. RIFM report number 59511. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Acetoxydihydrodicyclopentadiene (Mixture of Isomers) (Cyclacet): Determination of Partition Coefficient and Auto-ignition Temperature (Liquids and Gases). Unpublished report from International Flavors and Fragrances. RIFM report number 59512. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Acetoxydihydrodicyclopentadiene (Mixture of Isomers) (Cyclacet): Acute Toxicity to Daphnia magna. Unpublished report from International Flavors and Fragrances. RIFM report number 59514. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Acetoxydihydrodicyclopentadiene (Mixture of Isomers) (Cyclacet): Algal Growth Inhibition Test. Unpublished report from International Flavors and Fragrances. RIFM report number 59515. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Partition coefficient n-octanol/water of tricyclodecenyl acetate and tricyclo[5.2.1.02,6]dec-4-en-8-yl acetate (jasmacyclene). Unpublished report from Givaudan. RIFM report number 59955. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Ready Biodegradability of Tricyclodecenyl Acetate (Jasmacyclene). Unpublished report from Givaudan. RIFM report number 57800. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2011. Tricyclodecenyl Propionate: a 96- Hour Flow-through Acute Toxicity Test with the Fathead Minnow (Pimephales promelas). RIFM report number 61644. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2011. Tricyclodecenyl Propionate: a 48-hour Flow-through Acute Toxicity Test with the Cladoceran (Daphnia magna). RIFM report number 61645. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2011. Tricyclodecenyl Propionate (Cyclaprop): Algal Growth Inhibition Test. Unpublished report from International Flavors and Fragrances. RIFM report number 63364. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. Acetoxydihydrodicyclopentadiene (Mixture of Isomers): Ninety Day Repeated Dose Oral (Dietary) Toxicity Study in the Rat. RIFM report number 64051. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. 3,5,5-Trimethylhexyl Acetate (Neononylacetate): Determination of Vapor Pressure Using the Vapor Pressure Balance Method. Unpublished report from Symrise. RIFM report number 65187. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Exposure Survey 02, November 2013.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Tricyclodecenyl Propionate (Cyclaprop): a Flow-through Life-cycle Toxicity Test with the Cladoceran (Daphnia magna). RIFM report number 64342. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Evaluation of the Subchronic Toxicity of Acetoxydihydrodicylopentadiene. RIFM report number 66954. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Cyclaprop, 4,7-methano-1H-inden-6-ol,3a,4,5,6,7,7a-hexahydro: Propionate; an Early Life-stage Toxicity Test with the Fathead Minnow (Cyclaprop): Pimephales promelas). RIFM report number 70180. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Acetoxydihydrodicyclopentadiene (Mixture of Isomers): in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 70986. RIFM, Woodcliff Lake, NJ, USA.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Symrise, 2009. 4,7-Methano-1H-inden-6-ol, 3a,4,5,6,7,7a-hexahydro-,acetate (Herbaflorat): Mutagenicity Study with Salmonella typhimurium/mammalian Microsome Reverse Mutation Assay (Ames Test). (ua. Unpublished).
US EPA, 2012. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.