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Short Review

RIFM fragrance ingredient safety assessment, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate, CAS registry number 67634-20-2

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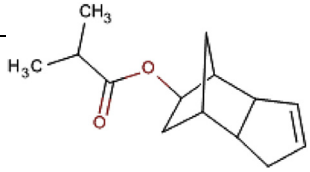
Version: 030118. This version replaces any previous versions.

Name: 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl isobutyrate
CAS Registry Number: 67634-20-2
Additional CAS Numbers
68039-39-4 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-6-yl isobutyrate
*This material was included in this assessment because the materials are isomers.



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WOE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate is not genotoxic. Data from the read-across analog butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS# 113889-23-9) show that 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate is not a safety concern under the current, declared use levels 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 repeated dose, developmental, and reproductive toxicity endpoints were completed using acetoxydihydrodicyclopentadiene (CAS# 54830-99-8) as a read-across analog, which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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, 2014b; RIFM, 2015a)

Repeated Dose Toxicity: NOAEL = 464.1 mg/kg/day. (RIFM, 2012)

Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(RIFM, 2010)
Skin Sensitization: No safety concerns under the current, declared levels of use.	(RIFM, 2001)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 32% (OECD 302C)	(RIFM, 1998)
Bioaccumulation: Screening-level: 139.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 21-day fish (Fathead Minnow) NOEC: 0.8 mg/L read-across to CAS# 17511-60-3	(RIFM, 2015c)
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 CAS# 17511-60-3	(RIFM, 2015c)
RIFM PNEC is: 80 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1	

1. Identification

Chemical Name: 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl isobutyrate	**Chemical Name**: 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-6-yl isobutyrate
CAS Registry Number: 67634-20-2	**CAS Registry Number:** 68039-39-4
Synonyms: Propanoic acid, 2-methyl-, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl ester; Tricyclo (5.2.1.02,6)dec-3-en-9-yl isobutyrate; Gardocyclene; Cyclabute; 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-5-yl 2-methylpropanoate; 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl isobutyrate	**Synonyms:** 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-6-yl 2-methylpropanoate; 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-6-yl isobutyrate; Propanoic acid, 2-methyl-, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl ester; Tricyclo (5.2.1.02,6)dec-3-en-8-yl isobutyrate
Molecular Formula: $C_{14}H_{20}O_2$	**Molecular Formula:** $C_{14}H_{20}O_2$
Molecular Weight: 220.12	**Molecular Weight:** 220.12
RIFM Number: 5828	**RIFM Number:** 5875
Stereochemistry: Isomer not specified. Five stereocenters and 32 total stereoisomers possible.	**Stereochemistry:**

2. Physical data**

1. **Boiling Point:** 273.96 °C (EPI Suite)
2. **Flash Point:** > 212.00 °F TCC (> 100.00 °C)*
3. **Log K_{ow}:** Log Pow = 4.1 (RIFM, 1997), 3.76 (EPI Suite)
4. **Melting Point**: 45.3 °C (EPI Suite)
5. **Water Solubility:** 21.27 mg/L (EPI Suite)
6. **Specific Gravity:** 1.02200 to 1.03000 @ 20.00 °C*
7. **Vapor Pressure:** 0.00279 mm Hg @ 20 °C (EPI Suite 4.0), 0.00502 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:** Pale, yellow, and clear liquid with a medium herbal, fruity, amber, chocolate, anise, and basil-like odor.*

*http://www.thegoodscentscompany.com/data/rw1001921.html, retrieved 10/4/13.

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

3. Exposure***

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.1% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0022 mg/kg/day or 0.17 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0072 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015, 2017; Safford et al., 2015, 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	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Acetoxydihydrodicyclopentadiene (CAS # 54830-99-8)
   c. **Developmental and Reproductive Toxicity:** Acetoxydihydrodicyclopentadiene (CAS # 54830-99-8)
   d. **Skin Sensitization:** Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9); 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)

Neither material included in this assessment is 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

Both materials are pre-registered for 2010; no dossier available as of 2/13/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3α,4,5,6,7,7α-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-6-yl isobutyrate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2015b). The mutagenic activity of 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl isobutyrate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl isobutyrate in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014b). Under the conditions of the study, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl isobutyrate was not mutagenic in the Ames test.

The clastogenic activity of 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl isobutyrate 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 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl isobutyrate in ethanol at concentrations up to 2200 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-6-yl isobutyrate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in the presence or absence of S9 metabolic activation (RIFM, 2015a). Under the conditions of the study, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl isobutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl isobutyrate does not present a concern for genotoxic potential.

Additional References: RIFM, 2007.

Literature Search and Risk Assessment Completed On: 9/1/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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 data on 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate. Read-across material acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section 5) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. 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 weights 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, 2012; data also available in RIFM, 2014a). **Therefore, the 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate, 464.1/0.0072 or 64458.**

Additional References: None.

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

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate. Read-across material, acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section 5) has sufficient developmental and reproductive toxicity data to support the developmental and reproductive toxicity endpoints. An OECD 421 oral gavage reproduction and developmental toxicity screening test was conducted in Wistar Han:HsdRccHan:WIST strain rats. Groups of 10 rats/sex/dose were administered via oral gavage with test material acetoxydihydrodicyclopentadiene (mixture of isomers) at doses of 0, 100, 300, or 1000 mg/kg/day in an Arachis oil BP vehicle, for up to 43 consecutive days (including a 2-week maturation phase, pairing, gestation, and early lactation for females). There were no treatment-related developmental effects in the litter parameters evaluated or 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, 2010). **Therefore, the 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate, 1000/0.0072 or 138889.**

Additional References: None.

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

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), 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the available data and read-across material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9), 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate does not present a safety concern for skin sensitization under the current, declared levels of use. These materials are not predicted to react with skin proteins (Toxtree 2.6.13; OECD Toolbox v3.4). In guinea pig maximization studies 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate is considered a non-sensitizer according to ECETOC 87 criteria (RIFM, 1979; RIFM, 1982; ECETOC, 2003). 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, 2002d). Additionally, no reactions indicative of sensitization were observed with 5% (1550 μg/cm2) 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate in alcohol SDA 39C in a human repeat insult patch test (RIFM, 1972). In a human repeat insult patch test (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, as well as 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-inden-5-yl isobutyrate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1977.

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

10.1.5. Phototoxicity/Photoallergenicity

	Phototoxicity	Photoallergenicity
Step 1: UV benchmark ($1000\ L\ mol^{-1} \cdot cm^{-1}$)	Below	
Step 2: Study data		
Step 3: Exposure benchmark		
Step 4: Read-across		
Step 5: Generate data		

Based on the available UV/Vis spectra, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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 exposure level for 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate. Based on the Creme RIFM model, the inhalation exposure is 0.17 mg/day. This exposure is 2.8 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 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate 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.

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate presents a risk to the aquatic compartment in the screening-level assessment.

Key Studies:

Biodegradation:

RIFM, 1998: The inherent biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 302C method. The test material undergoes 32% biodegradation after 48 days in the test conditions.

RIFM, 1998; 2010: The ready biodegradability of 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate was determined by the Manometric Respirometry Test according to the OECD 301F method. After 28 days, biodegradation of 22% was observed.

Ecotoxicity: No data available.

10.2.1.1.1. Other available data. 3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl isobutyrate has been pre-registered for REACH with no additional data.

The following data is available for the read-across materials:

For Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9).

RIFM, 2002b: A 96-h acute fish (rainbow trout) toxicity test was conducted according to the OECD 203 method under “single pass” water renewal system conditions. The LC50 was reported to be 3.6 mg/L.

RIFM, 2002c: A study was performed to assess the acute toxicity of butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester to *Daphnia magna* under static conditions following the OECD 202 method. The 48-h EC50 was 4.7 mg/L.

RIFM, 2002a: A study was conducted to determine the 72-h EC50 of the test material to algae according to the OECD 201 method. Based on the time-weighted mean measured test concentrations, the EbC50 was 0.29 mg/L, and the ErC50 was 0.39 mg/L.

For Tricyclodecenyl propionate 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 one study following Council Directive 92/69/EEC, Part C Method 2 the 48-h EC50 was reported as the geometric mean of the EC0 and the EC100. The EC50 was reported as 4.6 mg/L.

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

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

10.2.1.2. 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.

RIFM Framework Screening-level **(Tier 1)**	4.42			1,000,000	0.00442	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.779	4.786	1.542	10,000	0.1542	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.796	3.202	4.663			Neutral Organic
Tier 3: Measured Data including read-across						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	3.6		0.8	10	80	
Daphnia		4.7	0.83			
Algae		0.29	1.8			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.1	4.1
Biodegradation Factor Used	0.1	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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.2018.08.015.

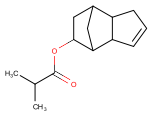
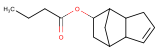
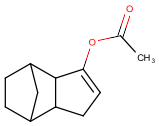
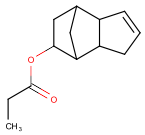
Appendix

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 were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US 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	3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl isobutyrate	Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester	Acetoxydihydrodicyclopentadiene (Mixture of Isomers)	Tricyclodecenyl propionate
CAS No.	**67634-20-2,** 68039-39-4	113889-23-9	54830-99-8	17511-60-3
Structure				
Similarity (Tanimoto Score)		0.92	0.80	0.92
Read-across Endpoint		• Skin sensitization • Environmental toxicity	• Repeated dose toxicity • Reproductive and developmental toxicity	• Environmental toxicity
Molecular Formula	$C_{14}H_{20}O_2$	$C_{14}H_{20}O_2$	$C_{12}H_{16}O_2$	$C_{13}H_{18}O_2$
Molecular Weight	220.31	220.31	192.26	206.29
Melting Point (°C, EPI Suite)	45.30	55.60	44.07	45.26
Boiling Point (°C, EPI Suite)	273.96	283.56	253.97	267.45
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.67	0.323	1.94	0.941
Log Kow (KOWWIN v1.68 in EPI Suite)	3.76	3.83	2.98	3.34
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	21.27	18.41	137.4	57.27
J_{max} (mg/cm^2/h, SAM)	10.515	9.472	22.988	14.620
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.02E+001	3.02E+001	1.36E+002	2.28E+001
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 (low reliability)		• Toxicant (good reliability)	
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found	• SN2 reaction		
Protein Binding (OECD)	• Acylation	• Acylation		
Protein Binding Potency	• Not possible to classify	• Not possible to classify		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• SN2 reaction		
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found		
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate (CAS # 67634-20-2). 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), acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8), 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 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate (CAS # 67634-20-2) for the skin sensitization endpoint.

- ○ The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
- ○ The target substance and the read-across analog share an unsaturated tricyclic alcohol fragment.
- ○ The key difference between the target substance and the read-across analog is that the target substance has an isopropyl 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.
- ○ The target substance and the read-across analog have several protein-binding alerts like SN2 reaction and acylation. The data described in the skin sensitization section shows that the read-across analog does not pose a concern for the skin sensitization endpoint under the current, declared levels of use. Therefore, the alert will be superseded by the availability of the data.
- ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9) was used as a read-across analog for the target material 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate (CAS # 67634-20-2) for the environmental toxicity 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 isopropyl moiety as an acid fragment, and the read-across analog has propyl moiety as an acid fragment. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated tricyclic alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target substance and $\leq 40\%$ for the read-across analog. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) was used as a read-across analog for the target material 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate (CAS # 67634-20-2) for repeated dose, reproductive, and developmental toxicity endpoints.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of cyclic esters.
  - ○ The target substance and the read-across analog share an unsaturated tricyclic alcohol fragment.
  - ○ The key difference between the target substance and the read-across analog is that the target substance has a propyl moiety as an acid fragment and the read-across analog has acetyl moiety as an acid fragment. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated tricyclic alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ The target substance and the read-across analog are predicted to be a toxicant by the CAESAR model for developmental toxicity. The data described in the developmental toxicity section above shows that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Tricyclodecenyl propionate (CAS # 17511-60-3) was used as a read-across analog for the target material 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl isobutyrate (CAS # 67634-20-2) for the environmental toxicity 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 isopropyl moiety as an 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.

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