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Short Review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester, CAS Registry Number 113889-23-9

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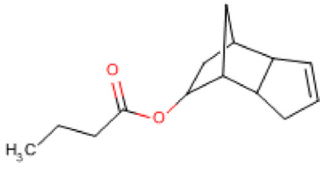
Name: Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester
CAS Registry Number: 113889-23-9



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.

Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester is not genotoxic and 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 repeated dose, developmental and reproductive toxicity endpoints were completed using acetoxydihydrodicyclopentadiene (CAS# 54830-99-8) as a read-across analog, which provided an acceptable MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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, 2001b; RIFM, 2002g)
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, 2002h; RIFM, 2001a)
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: 34% BOD, 100% GC (OECD 301C) (RIFM, 2015)
Bioaccumulation: Screening-level: 156.1 L/kg (EPI Suite v4.1, US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h algae EbC50: 0.29 mg/L (RIFM, 2002c)
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: 48-h algae EbC50: 0.29 mg/L (RIFM, 2002c)
RIFM PNEC is: 0.29 μg/L
•Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1

1. Identification

1. **Chemical Name:** Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester
2. **CAS Registry Number:** 113889-23-9
3. **Synonyms:** Cyclobutanate; Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester
4. **Molecular Formula:** $C_{14}H_{20}O_2$
5. **Molecular Weight:** 220.31
6. **RIFM Number:** 6498
7. **Stereochemistry:** Isomer not specified. Five stereocenters and 32 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 548 ± 0.5 K (RIFM, 2002a)
2. **Flash Point:** 134 °C (GHS), 6.17 × 10-7 @ pH 9 (RIFM, 2002d), 134 ± 2 °C (RIFM, 2001c)
3. **Log K_{OW}:** 4.48 (RIFM, 2002a)
4. **Melting Point**: 253 ± 0.5 K (RIFM, 2002a)
5. **Water Solubility:** Insoluble*
6. **Specific Gravity:** 1.03 @ 20.0 ± 0.5 C (RIFM, 2002d)
7. **Vapor Pressure:** 0.002000 mm/Hg @ 25.00 °C*
8. **UV Spectra:** No significant absorption between 290 and 700 nm; molar absorption coefficient is below the benchmark of concern ($1000\ L\ mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless to pale yellow clear liquid with a medium fruity, green, peach, orchid, balsam, woody odor.*

*http://www.thegoodscentscompany.com/data/rw1573161.html#toorgano, retrieved 12/1/2015.

3. Exposure

1 **Volume of Use (worldwide band)**: 10–100 metric tons per year (IFRA, 2015)
2 **95th Percentile Concentration in Hydroalcoholics**: 0.02% (RIFM, 2014a)
3 **Inhalation Exposure***: 0.0027 mg/kg/day or 0.19 mg/day (RIFM, 2014a)
4 **Total Systemic Exposure****: 0.012 mg/kg/day (RIFM, 2014a)

*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 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, 2017; Safford et al., 2015, 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High (Expert Judgment)

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

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

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**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification**: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester is not reported to occur in food by the VCF*.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database that 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

Available, accessed 09/15/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2001b). Under the conditions of the study, butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester was not mutagenic in the Ames test.

The clastogenicity of butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung cells were treated with butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester in DMSO at concentrations up to 2203 μg/mL for 6 h in the presence and absence of S9 metabolic activation and for 24 and 48 h in the absence of S9 metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (RIFM, 2002g). Under the conditions of the study, butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester does not present a concern for genotoxic potential.

Additional References: None.

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

10.1.2. Repeated dose toxicity

The margin of exposure for butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester. An OECD 407 oral gavage 28-day subchronic toxicity study was conducted in Sprague Dawley Crl:CD (SD) IGS BR strain rats. Groups of 5 rats/sex/group were administered via oral gavage daily with test material butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (cyclobutanate) at doses of 0, 15, 150, or 1000 mg/kg/day in Arachis oil BP for 28 days. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups. Clinical signs of salivation were observed immediately after the administration of the test material among animals of the high-dose group. This finding was short-lived and regressed in the recovery group animals. It was considered to be due to the unpleasant taste or locally irritant formulation of the test material and not the systemic toxicity of the test material. There were higher incidences of globular accumulations of eosinophilic material in the tubular epithelium of the kidneys among males of the mid- and high-dose groups, with no significant kidney weight changes. These kidney changes in males were consistent with documented changes of alpha-2μ-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman and Caudil, 1992; and Lehman-McKeeman et al., 1990). Furthermore, the condition was observed to have regressed after the 14-day treatment-free recovery period for high-dose males. Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2002i).

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

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33 mg/kg/day.

Read-across material acetoxydihydrodicyclopentadiene (CAS# 54830-99-8; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD/GLP 408 dietary 90-day study was conducted in Sprague Dawley Crl:CD BR strain rats. Groups of 10 rats/sex/group were administered with test material acetoxydihydrodicyclopentadiene (mixture of isomers) at doses of 0, 200, 2000, 6000, or 20,000 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 20,000 ppm. Animals of either sex treated with 20,000 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-2u-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 20,000 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 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. 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. Thus, the NOAEL for males was also considered to be 6000 ppm, based on decreased body weights among high-dose group animals. A NOAEL of 6000 ppm or 464.1 mg/kg/day was considered for this study (RIFM, 2012; data also available in RIFM, 2014).

The most conservative NOAEL of 333 mg/kg/day from the OECD 407 study was selected for the repeated dose toxicity endpoint. **Therefore, the butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester MOE for the repeated dose toxicity endpoint can be calculated by dividing the butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester NOAEL in mg/kg/day by the total systemic exposure to butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester, 333/0.012 or 27,750.**

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester. Read-across material acetoxydihydrodicyclopentadiene (CAS # 54830-99-8; see Section V) has sufficient developmental and reproductive toxicity data to support the developmental and reproductive toxicity endpoints. An OECD 421 oral gavage reproduction and developmental toxicity screening test was conducted in Wistar Han:HsdRccHan:WIST strain rats. Groups of 10 rats/sex/dose were administered via oral gavage with test material acetoxydihydrodicyclopentadiene (mixture of isomers) at doses of 0, 100, 300, or 1000 mg/kg/day in an Arachis oil BP vehicle, for up to 43 consecutive days (including a 2-week maturation phase, pairing, gestation and early lactation for females). There were no treatment-related developmental effects in the litter parameters evaluated or 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester, 1000/0.012 or 83,333.**

10.1.4. Skin sensitization

Based on the existing data, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 existing data, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test no sensitization reactions were observed with butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (RIFM, 2002h). In a human confirmatory repeat insult patch test (HRIPT) no reactions indicative of sensitization were observed in 112 subjects with 5% or (1550 μg/cm2) butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (RIFM, 2001c).

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/05/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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, butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester. Based on the Creme RIFM model, the inhalation exposure is 0.19 mg/day. This exposure is 2.5 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: 06/09/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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, butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester 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 butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (IFRA, 2015), butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2002d: Biodegradation of the test material was evaluated by a sealed vessel test according to the OECD 301B guidelines. Under conditions of the study, the test material attained 38% degradation after 28 days.

RIFM, 2015: Ready biodegradability of the test material was evaluated according to the OECD 301C method. After 28 days, biodegradation was 34% and 100% by BOD and GC, respectively.

10.2.2.2. Ecotoxicity. RIFM, 2002c: An algae growth inhibition test was conducted according to the OECD 201 method, and analyzed at 0, 24, 48, and 72 h by a gas chromatographic and mass spectrometric method. Based on the time-weighted mean measured butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester concentrations, the 72-hour E(*b*)C50 was 0.29 mg/L, and the E(r)C50 value was 0.39 mg/L.

RIFM, 2002e: A 96-hour rainbow trout (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method. The 96-h LC50 based on the time-weighted mean measured test concentrations was 3.6 mg/L.

RIFM, 2002f: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method. The 48-hour EC50 for butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester to *Daphnia magna* based on the mean measured test concentrations was 4.7 mg/L.

10.2.2.3. Other available data. Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester has been registered under REACH with no additional data.

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)**	2.067			1,000,000	0.002067	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.517	4.302	1.370	10,000	0.1370	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.119	2.769	4.147			Neutral Organic SAR (Baseline toxicity)
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	3.6					
Daphnia		4.7				
Algae		0.29		1,000	0.29	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.48	4.48
Biodegradation Factor Used	0.1	0.1
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 further assessment is necessary.

The RIFM PNEC is 0.29 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to theaquatic 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 http://dx.doi.org/10.1016/j.fct.2018.06.041.

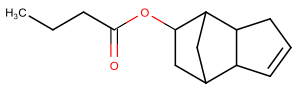
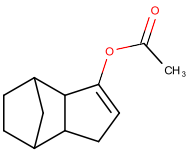
Appendix

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 physicochemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US ECHA, 2012).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox 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	Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester	Acetoxydihydrodicyclopentadiene (Mixture of Isomers)
CAS No.	113889-23-9	54830-99-8
Structure		
Similarity (Tanimoto Score)		0.80
Read-across Endpoint		• Repeated dose toxicity • Reproductive and developmental toxicity
Molecular Formula	$C_{14}H_{20}O_2$	$C_{12}H_{16}O_2$
Molecular Weight	220.31	192.26
Melting Point (°C, EPI Suite)	55.60	44.07
Boiling Point (°C, EPI Suite)	283.56	253.97
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.323	1.94
Log Kow (KOWWIN v1.68 in EPI Suite)	3.83	2.98
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	18.41	137.4
J_{max} (mg/cm^2/h, SAM)	9.472	22.988
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.02E + 001	1.36E + 002
Repeated Dose Toxicity		
Repeated Dose (HESS)	•Not categorized	•Not categorized
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v3.4)	•Non-binder, without OH or NH2 group	•Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	•Toxicant (good reliability)	•Toxicant (good reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

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

Conclusions

- Acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) was used as a read-across analog for the target material butanoic acid, 3a, 4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9) for repeated dose and reproductive and developmental 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 propyl moiety as an acid fragment and the read-across analog has acetyl moiety as an acid fragment. This structural difference is toxicologically insignificant.
- The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated tricyclic alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physicochemical 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. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ 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 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.

Explanation of cramer classification

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

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