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Short Review

RIFM fragrance ingredient safety assessment, 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene, CAS Registry Number 53018-24-9

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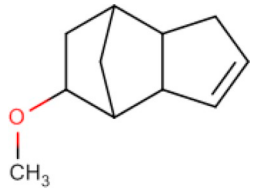

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Abbreviation/Definition List:

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., 2015a, 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 as 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 two-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 existing information supports the use of this material as described in this safety assessment.

3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene is not genotoxic. The skin sensitization endpoint was completed using DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. Data from read-across analog acetoxydihydrodicyclopentadiene (CAS # 54830-99-8) provide a calculated MOE > 100 for the repeated dose and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material and the exposure to 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene is below the TTC (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was evaluated based on UV spectra; 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene was found not to be a PBT as per the IFRA Environmental Standards, and its risk quotients, based on its screening-level (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1985a; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 464.1 mg/kg/day. RIFM (2012)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day. RIFM (2010)
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 0.3% (OECD 301B) RIFM (1996)
Bioaccumulation: Screening-level: 22.5 L/kg (EPI Suite, v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 74.99 mg/L (RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 74.99 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.07499 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene
2. **CAS Registry Number:** 53018-24-9
3. **Synonyms:** 8,9-Dihydro-9-methoxydicyclopentadiene; 4,7-Methano-1H-indene, 3a,4,5,6,7,7a-hexahydro-5-methoxy-; 5-Methoxy-3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indene; Verdalia A; 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-5-yl methyl ether; 3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene
4. **Molecular Formula:** $C_{11}H_{16}O$
5. **Molecular Weight:** 164.24
6. **RIFM Number:** 5721
7. **Stereochemistry:** Isomer not specified. Five stereocenters and 32 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 209.47 °C (US EPA, 2012a)
2. **Flash Point:** 84 °C (GHS)
3. **Log K_{OW}:** 2.54 (US EPA, 2012a)
4. **Melting Point**: 7.01 °C (US EPA, 2012a)
5. **Water Solubility:** 442.4 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 1.00600 to 1.01400 @ 25.00 °C*
7. **Vapor Pressure:** 0.224 mm Hg @ 20 °C (US EPA, 2012a), 0.329 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm (RIFM Database); molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless clear liquid (est) with a fruity, sweet, green, herbal, and melon-like odor.*

*http://www.thegoodscentscompany.com/data/rw1044501.html.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.056% (RIFM, 2014b)
3. **Inhalation Exposure*:** 0.00055 mg/kg/day or 0.040 mg/day (RIFM, 2014b)
4. **Total Systemic Exposure**:** 0.0020 mg/kg/day (RIFM, 2014b)

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8)
   c. **Reproductive Toxicity:** Acetoxydihydrodicyclopentadiene (mixture of isomers) (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

No relevant data available for inclusion in this safety assessment.

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

3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene is not reported to occur in foods by the VCF.*

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 07/30/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through alterations in gene expressions in a human cell line. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

The mutagenic activity of 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent with OECD TG 471 using the standard plate incorporation/pre-incubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene 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

concentration in the presence or absence of S9 (RIFM, 1985a). Under the conditions of the study, 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene was not mutagenic in the Ames test.

The clastogenic activity of 3a,4,5,6,7,7a-hexahydromethoxy-4,7-methano-1H-indene (isomer unspecified) 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-hexahydromethoxy-4,7-methano-1H-indene (isomer unspecified) in DMSO at concentrations up to 164.3 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h of 3a,4,5,6,7,7a-hexahydromethoxy-4,7-methano-1H-indene (isomer unspecified) did not induce binucleated cells with micronuclei when tested up to cytotoxic levels concentration, in either the presence or absence of an S9 activation system (RIFM, 2017). Under the conditions of the study, of 3a,4,5,6,7,7a hexahydromethoxy-4,7-methano-1H-indene (isomer unspecified) was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/27/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene. Read-across material, acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. 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 also showed 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 α-2u-globulin nature of this finding was confirmed by additional Mallory's Heidenhain staining performed on male kidneys. Kidney changes in males were consistent with documented changes of α-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 20000 ppm test material. Elevated incidences of mostly diffuse vacuolation was found in males from all treatment groups; this vacuolation did not exceed slight severity degrees. The 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 weights 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, 2014a).

Therefore, the 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene 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-5-methoxy-4,7-methano-1H-indene, 464.1/0.002 or 232050.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/27/17.

10.1.3. Reproductive toxicity

The margin of exposure for 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene. Read-across material, acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8; see Section V) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. 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 toxicity and fertility was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010).

Therefore, the 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene (mixture of isomers) MOE for the reproductive 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-5-methoxy-4,7-methano-1H-indene, 1000/0.002 or 500000.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/27/17.

10.1.4. Skin sensitization

Based on the existing data, 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In guinea pigs, a maximization test did not present reactions indicative of sensitization (RIFM, 1985b).

Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentrations for 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the

Table 1
Acceptable concentrations for 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Concentration in Finished Products
1	Products applied to the lips	0.07%	0.00%
2	Products applied to the axillae	0.02%	0.01%
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.06%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.02%
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.01%
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.01%
10	Household care products with mostly hand contact	2.70%	0.10%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	4.61%

Note:
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/02/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene 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 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. 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-5-methoxy-4,7-methano-1H-indene 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, $1000\,L\,mol^{-1}\cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene, 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 3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene. Based on the Creme RIFM model, the inhalation exposure is 0.040 mg/day. This exposure is 11.8 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: 12/1/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene 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-5-methoxy-4,7-methano-1H-indene was identified as a fragrance material with no 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-5-methoxy-4,7-methano-1H-indene as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially

bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μ/L)	Chemical Class
RIFM Framework Screening-level (**Tier 1**)	74.99			1,000,000	0.07499	

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 1997: A Semi-Continuous Activated Sludge (SCAS) test was conducted according to OECD 302A guidelines and EEC Directive 67/548/EEC Part C. 3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-5-yl methyl ether was added directly at a concentration of 10.1 mg/L to the sealed vessel and was aerated with activated sludge for 23 h in a SCAS aeration unit after which the supernatant liquor was removed. The aeration was restarted after settled domestic sewage and test substance were added to the settled sludge. This cycle was repeated for up to 3 months to ensure acclimatization of the microbes to the test substance. The biodegradability of 3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-5-yl methyl ether could not be determined under the conditions of the test due to the volatile characteristics of the test material.

RIFM, 1997**:** The assessment of the inherent biodegradability of 3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-5-yl methyl ether in a sealed vessel CO_2 test using acclimatized effluent from a modified SCAS test was conducted according to OECD 301B guideline. The inoculated medium (100 mL) and 15.2 mg/L 3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-5-yl methyl ether were added to vessels which were sealed and were incubated for 28 days. After 28 days, biodegradation was 0.3%.

RIFM, 1996**:** A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. Mineral salts medium (100 mL) inoculated with activated sludge plant secondary effluent and 10 mg/L of 3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-5-yl methyl ether were added to multiple vessels. The vessels were sealed and incubated 28 days. After 28 days the biodegradation rate was 0.3%.

RIFM, 1993**:** The inherent biodegradability of the test material was evaluated using a modified sealed vessel test according to the OECD 301B method. Mineral salts medium (100 mL) inoculated with secondary effluent and the test material (10 mg/L) were added to multiple vessels. The vessels were sealed and incubated for 56 days. Under conditions of the study no biodegradation was observed.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} used	2.54	2.54
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	< **1**	< **1**

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

The RIFM PNEC is 0.07499 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 11/29/17.

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. The links listed above were active as of 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.04.024.

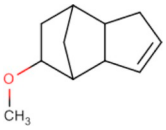
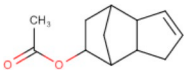
Appendix

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 (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 v4.2 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2012).

	Target Material	Read-across Material
Principal Name	3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene	Acetoxydihydrodicyclopentadiene (mixture of isomers)
CAS No.	53018-24-9	54830-99-8
Structure		
Similarity (Tanimoto Score)		0.73
Read-across Endpoint		• Repeated dose • Reproductive
Molecular Formula	$C_{11}H_{16}O$	$C_{12}H_{16}O_2$
Molecular Weight	164.24	192.25
Melting Point (°C, EPI Suite)	7.01	44.07
Boiling Point (°C, EPI Suite)	209.47	253.97
Vapor Pressure (Pa @ 25°C, EPI Suite)	43.8	1.94
Log Kow (KOWWIN v1.68 in EPI Suite)	2.54	2.98
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	442.4	137.4
J_{max} (mg/cm^2/h, SAM)	49.222	22.988
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.32E-004	1.34E-003
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive 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 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene (CAS # 53018-24-9). Hence, *in silico*

evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–-chemical properties, and expert judgment, acetoxydihydrodicyclopentadiene (mixture of isomers) (CAS # 54830-99-8) was identified as 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 3a,4,5,6,7,7a-hexahydro-5-methoxy-4,7-methano-1H-indene (CAS # 53018-24-9 mixture of isomers) for the repeated dose and reproductive toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic bicyclic ethers and esters, respectively.
  - o The target substance and the read-across analog share a common unsaturated bicyclic structure.
  - o The key structural difference between the target substance and the read-across analog is that the target is a methyl ether, whereas the read-across analog is an acetate ester. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the near identity of these bicyclic unsaturated structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target and read-across analog have toxicant alert by CAESAR model. According to these predictions, the read-across analog has comparable reactivity to the target substance. The data described in the repeated dose and reproductive section above shows that based on the current existing data, the read-across analog does not pose a concern for repeated dose and reproductive endpoints. Therefore, the predictions are superseded by data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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