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RIFM fragrance ingredient safety assessment, 3a,7-methano-3ah-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate, CAS Registry Number 58096-47-2

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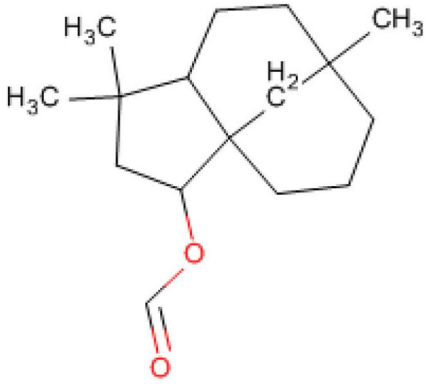
Version: 030918. This version replaces any previous versions.
Name: 3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate
CAS Registry Number: 58096-47-2



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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.

The material (3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate is not a safety concern at the current declared levels of use for the skin sensitization endpoint. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate. The environmental endpoints were evaluated; 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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, 2016b; RIFM, 2017)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: No safety concerns under the current, declared levels of use.	(RIFM, 2001)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB; RIFM, 1979)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.1 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 744 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h algae EC50: 0.297 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h algae EC50: 0.297 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0297 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1	

1. Identification

1. **Chemical Name:** 3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate
2. **CAS Registry Number:** 58096-47-2
3. **Synonyms:** decahydro-1,1,7-trimethyl-3a,7-methano-3aH-cyclopentacyclooct-3-yl formate; 1,1,7-Trimethyldecahydro-3a,7-methanocyclopenta [8]annulen-3-yl formate; 3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate
4. **Molecular Formula:** $C_{16}H_{26}O_2$
5. **Molecular Weight:** 250.38
6. **RIFM Number:** 6395
7. **Stereochemistry:** Isomer not specified. Four stereocenters and 16 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 292.22 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS)
3. **Log K_{ow}:** 4.86 (EPI Suite)
4. **Melting Point**: 83.25 °C (EPI Suite)
5. **Water Solubility:** 1.673 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000435 mm Hg @ 20 °C (EPI Suite 4.0), 0.000817 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.046% (RIFM, 2016a)
3. **Inhalation Exposure*:** 0.000018 mg/kg/day or 0.0014 mg/day (RIFM, 2016a)
4. **Total Systemic Exposure**:** 0.00056 mg/kg/day (RIFM, 2016a)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

*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:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (CAS # 113889-23-9)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** 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)

3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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

Pre-registered for 2010; no dossier available as of 2/15/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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, 2016b). Under the conditions of the study, 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate was not mutagenic in the Ames test.

The clastogenic activity of 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h 3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017). Under the conditions of the study, 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate does not present a genotoxic concern.

Additional References: None.

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

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate or any read-across materials. The total systemic exposure to 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate (0.56 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

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

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate or any read-across materials. The total systemic exposure to 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate (0.56 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

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

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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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 a guinea pig study, no reactions indicative of sensitization were observed with 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate (RIFM, 1975). Similarly, 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, 2002). Additionally, no reactions indicative of sensitization were observed with 20% 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate in petrolatum in a human repeated insult patch test (HRIPT) (RIFM, 1979). In an HRIPT from the read-across material, no reactions indicative of sensitization were observed in 112 subjects with 5% (1550 μg/cm2) butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester (RIFM, 2001).

Based on the weight of evidence from structural analysis, animal and human studies, as well as read-across material butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester, 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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: 09/10/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra and human study data, 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate in experimental models. UV absorption spectra indicate no significant absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In a photo-HRIPT, there was no evidence of phototoxicity or photoallergenicity with the application of 20% 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate (RIFM, 1979). Based on lack of absorbance and human study data, 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no significant absorbance in the range of 290–400 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: 08/23/17.

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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate. Based on the Creme RIFM Model, the inhalation exposure is 0.0014 mg/day. This exposure is 336 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: 08/31/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers of screening level 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate 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) identified 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WOE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current VoU (2015), 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate presents a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data:

3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate has been pre-registered for REACH with no additional information 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.235			1,000,000	0.001235	
ECOSARAcute Endpoints **(Tier 2)** ***Ver 1.11***	0.719	1.099	0.297	10,000	0.0297	Esters
ECOSARAcute Endpoints **(Tier 2)** ***Ver 1.11***	0.558	0.413	0.915			Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.8	4.8
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 0.0297 µg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material 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 to this article can be found online at https://doi.org/10.1016/j.fct.2018.10.018.

Appendix

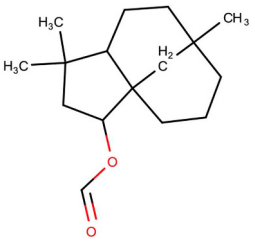
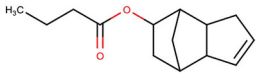
Read-across Justification

Methods

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

(OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (EPI Suite, 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	3a,7-Methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate	Butanoic acid, 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl ester
CAS No.	58096-47-2	113889-23-9
Structure		
Similarity (Tanimoto Score)		0.74
Read-across Endpoint		• Skin sensitization
Molecular Formula	$C_{16}H_{26}O_2$	$C_{14}H_{20}O_2$
Molecular Weight	250.38	220.31
Melting Point (°C, EPI Suite)	83.25	55.60
Boiling Point (°C, EPI Suite)	292.22	283.56
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.109	0.323
Log Kow (KOWWIN v1.68 in EPI Suite)	4.86	3.83
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.673	18.41
J_{max} (mg/cm^2/h, SAM)	0.212	9.472
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.10E + 002	3.02E + 001
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• SN2 reaction
Protein Binding (OECD)	• Acylation	• Acylation
Protein Binding Potency	• Not possible to classify	• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• SN2 reaction
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 3a,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate (CAS # 58096-47-2). 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) was identified as a read-across material 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,7-methano-3aH-cyclopentacycloocten-3-ol, decahydro-1,1,7-trimethyl-, formate (CAS # 58096-47-2) for the skin sensitization endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.

- ○ The target substance and the read-across analog share a cyclic alcohol fragment.
- ○ The key difference between the target substance and the read-across analog is that the target substance has formyl moiety as an acid fragment and the read-across analog has propyl moiety as an acid fragment. This structural difference is toxicologically insignificant.
  o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic 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 have several protein binding alerts, such as Acylation, and the read across analog has an additional alert for SN2 reaction. The data described in the skin sensitization section above show that the read-across analog does not pose a concern for skin sensitization under the current, declared levels of use. Therefore, the alert will be superseded by the availability of the data.
- ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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. Simple 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 sulphonate or sulphamate? No, Class III (High Class).

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