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Short review

RIFM fragrance ingredient safety assessment, .α.-methylcyclohexylmethyl acetate, CAS Registry Number 13487-27-9

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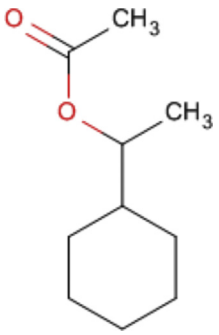

Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration.
AF - Assessment Factor.
BCF - Bioconcentration Factor.
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey

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(*continued*)

et al., 2015; Safford et al., 2015) 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.
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.
RIFM - Research Institute for Fragrance Materials.
RQ - Risk Quotient.
TTC - Threshold of Toxicological Concern.
UV/Vis Spectra - Ultra Violet/Visible spectra.
VCF - Volatile Compounds in Food.
VoU - Volume of Use.
vPvB - (very) Persistent, (very) Bioaccumulative.
WOE - Weight of Evidence.

RIFM's Expert Panel* 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 reviews 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 (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analogs d-cyclocitronellene acetate (CAS # 25225-10-9) and 1-cyclohexylethyl butyrate (CAS # 63449-88-7) show that this material is not genotoxic. Data from the suitable read across analog d-cyclocitronellene acetate (CAS # 25225-10-9) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was evaluated using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The developmental and reproductive toxicity endpoint was evaluated using 1-cyclohexylethyl butyrate (CAS # 63449-88-7), 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) as suitable read across analogs, which provided a MOE > 100. The repeated dose toxicity endpoint was evaluated using 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

(*continued*)

Genotoxicity: Not genotoxic.	(RIFM, 2008g; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 17 mg/kg/day.	(JECDB, 2013)
Developmental and Reproductive Toxicity: Developmental NOAEL = 1000 mg/kg/day and Reproductive NOAEL = 500 mg/kg/day.	(RIFM, 1978b)
Skin Sensitization: Not sensitizing.	(RIFM, 1981)
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: Screening Level: 2.93 (Biowin 3)	(EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 102.4 L/kg	(EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 96 h Algae EC50: 1.65 mg/l	(Episuite ver 4.1)
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: 1.65 mg/l	(Episuite ver 4.1)
RIFM PNEC is: 0.165 μg/L	

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe: <1

1. Identification

1. **Chemical Name:** .α.-methylcyclohexylmethyl acetate
2. **CAS Registry Number:** 13487-27-9
3. **Synonyms:** Cyclohexanemethanol, .α.-methyl-, acetate; Cyclohexylmethylcarbinyl acetate; .α.-methylcyclohexylmethyl acetate; アルキル (C = 1–4) カルボン酸シクロヘキシルエチル 中災防のウェブサイトではこれが検索されるが、構造から言って怪しい。; (1-methylcyclohexyl)methyl acetate
4. **Molecular Formula:** $C_{10}H_{18}O_2$
5. **Molecular Weight:** 170.52
6. **RIFM Number:** 5406

2. Physical data

1. **Boiling Point:** 207.63 °C [EPI Suite]
2. **Flash Point:** 162.00 °F TCC (72.20 °C)*
3. **Log K_{OW}:** 3.55 [EPI Suite]
4. **Melting Point**: −14.21 °C [EPI Suite]
5. **Water Solubility:** 56.85 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.165 mm Hg @ 20 °C [EPI Suite 4.0], 0.246 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** No data available

*http://www.thegoodscentscompany.com/data/rw1377631.html, retrieved 12/5/14.

2.1. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.40% (RIFM, 2014a)
3. **Inhalation Exposure*:** 0.00092 mg/kg/day or 0.068 mg/day (RIFM, 2014a)
4. **Total Systemic Exposure **:** 0.0090 mg/kg/day (RIFM, 2014a)

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

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

3. Derivation of systemic absorption

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

4. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogues Selected:
   a. **Genotoxicity:** *d*-cyclocitronellene acetate (CAS # 25225-10-9); 1-cyclohexylethyl butyrate (CAS # 63449-88-7)
   b. **Repeated Dose Toxicity:** 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5); *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5)
   c. **Developmental and Reproductive Toxicity:** 1-cyclohexylethyl butyrate (CAS # 63449-88-7); 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5); *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5)
   d. **Skin Sensitization:** d-cyclocitronellene acetate (CAS # 25225-10-9)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

5. Metabolism

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

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

The material, .α.-methylcyclohexylmethyl, acetate 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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

7. IFRA standard

None.

8. REACH Dossier

Pre-Registered for 2010; no dossier available as of 03/02/2017.

9. Summary

9.1. Human health endpoint summaries

9.1.1. Genotoxicity

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

9.1.1.1. Risk assessment. The material .α.-methylcyclohexylmethyl acetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013a). There are no studies assessing the mutagenicity of .α.-methylcyclohexylmethyl acetate. Read across material d-cyclocitronellene acetate (CAS # 25225-10-9; see Section 5) was assessed for mutagenic activity in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA were evaluated at concentrations up to 313 μl/plate of d-cyclocitronellene acetate in DMSO (dimethyl sulfoxide) in the presence and absence of metabolic activation. No increase in the frequency of revertant colonies was observed in the any of the strains at any concentration (RIFM, 2008g). Under the conditions of the study, d-cyclocitronellene acetate is not mutagenic in bacteria and this can be extended to α-methylcyclohexylmethyl acetate.

There are no studies assessing the clastogenicity of .α.-methylcyclohexylmethyl acetate. The clastogenicity of read across material 1-cyclohexylethyl butyrate (CAS # 63449-88-7; see Section 5) was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral lymphocytes were treated with 1-cyclohexylethyl butyrate in DMSO at concentrations up to 300 μg/ml in the presence and absence of metabolic activation (S9). No statistically significant increases in the frequency of cells with micronuclei were observed (RIFM, 2015). Under the conditions of the study, 1-cyclohexylethyl butyrate was considered not clastogenic and this

can be extended to .α.-methylcyclohexylmethyl acetate. Also, both parent and read across materials did not give any structural alerts for genotoxicity using Derek as an *in silico* prediction tool (Derek Nexus v5.0.2) and also OASIS by using TIMES *in vitro* and *in vivo* simulators for Ames and micronucleus test (OASIS v2.27.19.13 from OECD, 2012).

Based on the available data, .α.-methylcyclohexylmethyl acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/30/13.

9.1.2. Repeated dose toxicity

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

9.1.2.1. Risk assessment. There are no repeated dose toxicity data on .α.-methylcyclohexylmethyl acetate. Read across material 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5) was administered to a group of twelve rats/sex/group at 0, 50, 150, or 500 mg/kg/day in a corn oil vehicle daily for 14-days before mating, through the mating period, until the day of necropsy for males (day of study 42) and through gestation and four days of lactation for the females (day of study 41–46). Additional non-mating satellite groups of 10 female rats/dose were administered 0 or 500 mg/kg/day for 42 days. From these groups, 5 rats/sex/dose from the mating groups were gavaged with 0 or 500 mg/kg/day and five and three of the non-mating satellite female rats were gavaged with 0 and 500 mg/kg/day, respectively; the rats were gavaged for the 42 days described above then maintained for a further 14-day treatment-free recovery period. The NOAEL was determined to be 50 mg/kg/day, based on centrilobular hepatocyte hypertrophy (JECDB, 2013).

Additionally, read across material *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5; see Section 5) was administered to groups of twelve males and twelve females, selected to achieve dose levels of 0, 75, 200 and 500 mg/kg/day. The measured intake was 0, 56, 168, and 505 mg/kg/day in males and 0, 52, 151, and 437 in females. Male animals received the test material in the diet daily during a 10-week premating period and during mating up to the day of euthanasia; females received the test material in the diet daily during a 10-week premating period, during mating, gestation and lactation, and up to the day of euthanasia (approximately day 4 of lactation). The test was conducted according to the OECD 422 dietary combined repeated dose toxicity study and reproduction/developmental toxicity screening and a NOAEL of 437 mg/kg/day for repeated dose toxicity was determined, the highest dosage tested (RIFM, 2012b). The most conservative NOAEL of 50 mg/kg/day was selected for this safety assessment.

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study. The safety factor has been approved by RIFM's Independent Expert Panel*.

The derived NOAEL for the repeated dose toxicity after applying the safety factor of 3 is 50/3 or 17 mg/kg/day.

Therefore, the .α.-methylcyclohexylmethyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-*tert*-butylcyclohexyl acetate NOAEL in mg/kg/day by the total systemic exposure for .α.-methylcyclohexylmethyl acetate, 17/0.0090 or 1889.

In addition, the total systemic exposure for .α.-methylcyclohexylmethyl acetate (9 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: RIFM, 2008d; Belsito et al., 2008; RIFM, 1978a; RIFM, 2000; ECHA REACH Dossier: reaction mass of (1S,1′R)-[1-(3′,3′-dimethyl-1′-cyclohexyl) ethoxycarbonyl] methyl propanoate, (1R,1′R)-[1-(3′,3′-dimethyl-1′-cyclohexyl) ethoxycarbonyl] methyl propanoate and (1R*,2′R*)-(2,6,6-trimethyl-1-cycloheptyloxycarbonyl) methyl propanoate; RIFM, 1990; RIFM, 2008c; RIFM, 2008e; RIFM, 2014b; RIFM, 2012a; RIFM, 2007; RIFM, 2008f; RIFM, 2008a; RIFM, 2008b; RIFM, 2013b.

Literature Search and Risk Assessment Completed on: 06/08/16.

9.1.3. Developmental and reproductive toxicity

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

9.1.3.1. Risk assessment. There are no developmental toxicity data on .α.-methylcyclohexylmethyl acetate. Read across material 1-cyclohexylethyl butyrate (CAS # 63449-88-7; see Section 5) has a gavage developmental toxicity study conducted in rats which concluded a NOAEL of 1000 mg/kg/day, based on fetal body weights (RIFM, 1978b). There were no teratogenic effects observed even at dosages that caused maternal toxicity. **Therefore, the .α.-methylcyclohexylmethyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the 1-cyclohexylethyl butyrate NOAEL in mg/kg/day by the total systemic exposure for .α.-methylcyclohexylmethyl acetate, 1000/0.0090 or 111111.**

There are no reproductive toxicity data on .α.-methylcyclohexylmethyl acetate. Read across material 1-cyclohexylethyl butyrate (CAS # 63449-88-7) has a gavage developmental toxicity study conducted in rats which concluded a NOAEL for maternal toxicity of 300 mg/kg/day, based on maternal body weights and clinical signs (RIFM, 1978b). There are no male reproductive data on 1-cyclohexylethyl butyrate. Read across material 2-*tert*-butylcyclohexyl acetate (CAS # 88-41-5; see Section 5) has a gavage combined repeated dose toxicity study and reproduction/developmental toxicity screening test conducted in rats which determined the NOAEL for fertility to be 500 mg/kg/day, the highest dosage tested (JECDB, 2013). Additionally, read across material *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5; see Section 5) has an OECD 422 dietary combined repeated dose toxicity study and reproduction/developmental toxicity screening test in rats which concluded a NOAEL of 437 mg/kg/day for reproductive toxicity, the highest dosage tested (RIFM, 2012b). The NOAEL of 500 mg/kg/day was selected for the reproductive toxicity endpoint. **Therefore, the .α.-methylcyclohexylmethyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the 1-cyclohexylethyl butyrate NOAEL in mg/kg/day by the total systemic exposure for .α.-methylcyclohexylmethyl acetate, 500/0.0090 or 55555.**

In addition, the total systemic exposure for .α.-methylcyclohexylmethyl acetate (9 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoints.

Additional References: RIFM, 2008d; Belsito et al., 2008; RIFM, 1978a; RIFM, 2000; ECHA REACH Dossier: reaction mass of (1S,1′R)-

[1-(3′,3′-dimethyl-1′-cyclohexyl) ethoxycarbonyl] methyl propanoate, (1R,1′R)-[1-(3′,3′-dimethyl-1′-cyclohexyl) ethoxycarbonyl] methyl propanoate and (1R*,2′R*)-(2,6,6-trimethyl-1-cycloheptyloxycarbonyl) methyl propanoate; RIFM, 1990; RIFM, 2008c; RIFM, 2008e; RIFM, 2014b; RIFM, 2012a; RIFM, 2007; RIFM, 2008f; RIFM, 2008a; RIFM, 2008b; RIFM, 2013b.

Literature Search and Risk Assessment Completed on: 06/08/16.

9.1.4. Skin sensitization

Based on the available data and read across to d-cyclocitronellene acetate (CAS # 25225-10-9), .α.-methyl-cyclohexylmethyl acetate does not present a concern for skin sensitization.

9.1.4.1. Risk assessment. Based on the available data and read across to d-cyclocitronellene acetate (CAS # 25225-10-9), .α.-methylcyclohexylmethyl acetate does not present a concern for skin sensitization. The material, d-cyclocitronellene acetate and .α.-methylcyclohexylmethyl acetate are not predicted to be reactive to skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD Toolbox v3.1). In a guinea pig maximization test and human confirmatory studies, no results indicative of a sensitization potential were reported with read across material d-cyclocitronellene acetate (RIFM, 1981; RIFM, 1982; RIFM, 1977d; RIFM, 1977e; RIFM, 1977b; RIFM, 1977c). Similarly, no sensitization reactions were reported in a human repeated insult patch test conducted with 100% .α.-methylcyclohexylmethyl acetate (RIFM, 1977a).

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/30/13.

9.1.5. Phototoxicity/Photoallergenicity

Based on UV/Vis absorption spectra, .α.-methylcyclohexylmethyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

9.1.5.1. Risk assessment. There are no phototoxicity studies available for .α.-methylcyclohexylmethyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, .α.-methylcyclohexylmethyl acetate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/26/16.

9.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, .α.-methylcyclohexylmethyl acetate, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

9.1.6.1. Risk assessment. There are no inhalation data available on .α.-methylcyclohexylmethyl acetate. Based on the Creme RIFM model, the inhalation exposure is 0.068 mg/day. This exposure is 20.6 times lower than the Cramer Class I TTC value of 1.4 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: RIFM, 1977a.

Literature Search and Risk Assessment Completed on: 6/1/2016.

10. Environmental endpoint summary

10.1. Screening-level assessment

A screening level risk assessment of α.-methylcyclohexylmethyl acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, α.-methylcyclohexylmethyl acetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify α.-methylcyclohexylmethyl acetate as persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2. Risk assessment

Based on current Volume of Use (2011), α.-methylcyclohexylmethyl acetate presents a risk to the aquatic compartment in the screening level assessment.

10.3. Key studies

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data: The material α.- methylcyclohexylmethyl acetate has been pre-registered for REACH with no additional data.

10.4. 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)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	11.39 mg/L			1,000,000	0.011 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.83 mg/L	4.98 mg/L	1.65 mg/L	10,000	0.165 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	5.65 mg/L	3.71 mg/L	4.99 mg/L			Neutral Organic

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.55	3.55
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.165 µg/L. The revised PEC/PNECs for EU and NA is <1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 07/30/13.

11. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab%3dww&ei%3dKMSoUpiQK-arsQS324GwBg%26ved%3d0CBQQ1S4

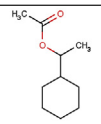
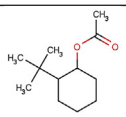
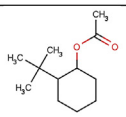
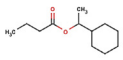
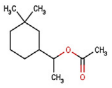
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Tanimoto values were calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010)

	Target Material	Read Across Material			
Principal Name	.α.-methylcyclohexylmethyl acetate	2-tert-butylcyclohexyl acetate	cis-2-tert-butylcyclohexyl acetate	1-cyclohexylethyl butyrate	d-cyclocitronellene acetate
CAS No.	13487-27-9	88-41-5	20298-69-5	63449-88-7	25225-10-9
Structure					
3D Structure	http://www.thegoodscentscompany.com/opl/13487-27-9.html	http://www.thegoodscentscompany.com/opl/88-41-5.html	http://www.thegoodscentscompany.com/opl/20298-69-5.html	http://www.thegoodscentscompany.com/opl/63449-88-7.html	http://www.thegoodscentscompany.com/opl/25225-10-9.html
Read-across endpoint		•Repeated Dose •Developmental/ Reproductive	•Repeated Dose •Developmental/ Reproductive	•Developmental/ Reproductive • Genotoxicity	•Genotoxicity •Skin sensitization
Molecular Formula	$C_{10}H_{18}O_2$	$C_{12}H_{22}O_2$	$C_{12}H_{22}O_2$	$C_{12}H_{22}O_2$	$C_{12}H_{22}O_2$
Molecular Weight	170.25	198.31	198.31	198.31	198.31
	Target Material	**Read Across Material**			
Melting Point (°C, EPISUITE)	-14.21	10.93	10.93	7.96	13.46
Boiling Point (°C, EPISUITE)	207.63	232.5	232.55	244.94	230.13
Vapor Pressure (Pa @ 25°C, EPISUITE)	32.8	7.106	7.106	4.746	10.36
Log Kow (KOWWIN v1.68 in EPISUITE)	3.55	4.42	4.42	4.53	4.42
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	56.85	7.462	7.462	5.997	7.462
J_{max} (mg/cm^2/h, SAM)	57.55224224	17.07952394	17.07952394	21.45262384	13.38676759

	Target Material	Read Across Material			
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	56.924385	100.321883	100.321883	100.321883	100.321883
Similarity (Tanimoto score)[1]		75%	75%	75%	76%
Genotoxicity					
DNA binding (OASIS v1.1)	•Schiff base formers •Schiff base formers >> Direct acting Schiff base formers •Schiff base formers >> Direct acting Schiff base formers >> Specific Acetate Esters •SN1			•No alert found	•Schiff base formers •Schiff base formers >> Direct acting Schiff base formers •Schiff base formers >> Direct acting Schiff base formers >> Specific Acetate Esters •SN1
	Target Material	**Read Across Material**			
	•SN1 >> Carbenium ion formation •SN1 >> Carbenium ion formation >> Specific Acetate Esters •SN2 •SN2 >> Acylating agents •SN2 >> Acylating agents >> Specific Acetate Esters •SN2 >> SN2 at sp3-carbon atom •SN2 >> SN2 at sp3-carbon atom >> Specific Acetate Esters				•SN1 >> Carbenium ion formation •SN1 >> Carbenium ion formation >> Specific Acetate Esters •SN2 •SN2 >> Acylating agents •SN2 >> Acylating agents >> Specific Acetate Esters •SN2 >> SN2 at sp3-carbon atom •SN2 >> SN2 at sp3-carbon atom >> Specific Acetate Esters
DNA binding (OECD)	•No alert found			•No alert found	•No alert found

	Target Material	Read Across Material			
Carcinogenicity (genotox and non-genotox) alerts (ISS)	•No alert found			•No alert found	•No alert found
DNA alerts for Ames, MN, CA (OASIS v1.1)	•No alert found			•No alert found	•No alert found
***In vitro* mutagenicity (Ames test) alerts (ISS)**	•No alert found			•No alert found	•No alert found
***In vivo* mutagenicity (Micronucleus) alerts (ISS)**	•H-acceptor-path 3-H-acceptor			•No alert found	•H-acceptor-path 3-H-acceptor
Oncologic classification (OECD)	•Not classified			•Not classified	•Not classified
Repeated Dose Toxicity					
Repeated dose	Not categorized	Not categorized	Not categorized		
	Target Material	**Read Across Material**			
(HESS)					
Developmental and Reproductive Toxicity					
ER binding (OECD)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group	
Developmental toxicity model (CAESAR v2.1.6)	Non-Toxicant (low reliability)	Toxicant (moderate reliability)	Toxicant (moderate reliability)	Non-Toxicant (moderate reliability)	
Skin Sensitization					
Protein binding (OASIS v1.1)	•No alert found				•No alert found
Protein binding (OECD)	•No alert found				•No alert found
Protein binding potency (OECD)	•Not possible to classify according to these rules (GSH)				•Not possible to classify according to these rules (GSH)
	Target Material	**Read Across Material**			
Protein binding alerts for skin sensitization (OASIS v1.1)	•No alert found				•No alert found
Skin sensitization model (CAESAR v2.1.6)	Sensitizer (good reliability)				Sensitizer (good reliability)
Metabolism					
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data 2	See supplemental data 3	See supplemental data 4	See supplemental data 5

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

Summary

There are insufficient toxicity data on .α.-methylcyclohexylmethyl acetate (CAS # 13487-27-9). Hence, *in silico* evaluation was conducted to determine suitable read across materials. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read across materials were identified as proper read across for their respective toxicity endpoints.

Conclusion/Rationale

- 2-*tert*-Butylcyclohexyl acetate (CAS # 88-41-5) and *cis*-2-*tert*-butylcyclohexyl acetate (CAS # 20298-69-5) were used as read across analogs for the target material, .α.-methylcyclohexylmethyl acetate (CAS # 13487-27-9) based on:
  - The target and analogs belong to the generic class of esters, specifically: esters/alkyl cyclic alcohol, simple acid ester/secondary alcohol metabolite/saturated.
  - They have the same carboxylic acid and a similar alcohol part.
  - The key difference is in the alcohol part of the molecule. The target has a cyclohexanemethanol with an α-methyl group, while the analogs have a cyclohexanol with a butyl group. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts; therefore, the toxicity profiles are expected to be similar.
  - The target and analogs show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- The materials 1-cyclohexylethyl butyrate (CAS # 63449-88-7) was used as read-across analog for the target material .α.-methylcyclohexylmethyl acetate (CAS # 13487-27-9) based on:
  - The target and analog belong to the generic class of esters, specifically: esters/alkyl cyclic alcohol, simple acid ester/secondary alcohol metabolite/saturated.
  - They have similar carboxylic acid and the same alcohol part.
  - The key difference is in the carboxylic acid part of the molecule. The target is an acetate, while the analog is a butyrate. The differences between structures do not essentially change the physicochemical properties, nor raise any additional structural alerts; therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog show similar alerts for protein binding.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- The material d-cyclocitronellene acetate (CAS # 25225-10-9) was used as a read across analog for the target .α.-methylcyclohexylmethyl acetate (CAS # 13487-27-9) based on:
  - The target and analog belong to the generic class of esters, specifically: esters/alkyl cyclic alcohol, simple; acid ester/secondary alcohol metabolite/saturated.
  - They have the same carboxylic acid part and a similar alcohol part.
  - The key difference is in the alcohol part. The analog has an additional dimethyl group on the cyclohexanol portion of the molecule. The differences between structures do not essentially change the physicochemical properties, nor raise any additional structural alerts; therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog show similar alerts for protein binding.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.05.064.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.05.064.

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