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Short Review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, 1-Methyl-2-(1-methylpropyl)cyclohexyl acetate, CAS Registry Number 72183-75-6

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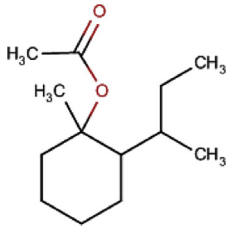

Abbreviation/Definition List

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

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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

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

1-methyl-2-(1-methylpropyl)cyclohexyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from 1-methyl-2-(1-methylpropyl)cyclohexyl acetate and the read-across analog 2,6-dimethyl-2-octyl acetate (CAS# 68480-08-0) show that 1-methyl-2-(1-methylpropyl)cyclohexyl acetate is not genotoxic. Data from 1-methyl-2-(1-methylpropyl)cyclohexyl acetate and the read-across analog 2-(1-methylpropyl)-1-vinylcyclohexyl acetate (CAS# 37172-02-4) show that 1-methyl-2-(1-methylpropyl)cyclohexyl acetate is not a concern for skin sensitization. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose and developmental and reproductive toxicity endpoints were completed using 3,3,5-trimethylcyclohexyl acetate (CAS# 67859-96-5) as a read-across analog, which provided an acceptable MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and data on 1-methyl-2-(1-methylpropyl)cyclohexyl acetate. The environmental endpoints were evaluated; 1-methyl-2-(1-methylpropyl)cyclohexyl acetate 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, 2000; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 50 mg/kg/day	(RIFM, 2016)
Developmental and Reproductive Toxicity: NOAEL = 500 mg/kg/day	(RIFM, 2016)
Skin Sensitization: Not a concern for skin sensitization	(RIFM, 1977e; RIFM, 1980; RIFM, 1977c)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB; RIFM, 1977a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 14% OECD 302C	(RIFM, 1998)
Bioaccumulation: Screening-level: 810 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h algae EC50: 0.23 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: 0.23 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.023 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1 **Chemical Name**: 1-Methyl-2-(1-methylpropyl)cyclohexyl acetate
2 **CAS Registry Number**: 72183-75-6
3 **Synonyms**: Cyclohexanol, 1-methyl-2-(1-methylpropyl)-, acetate; Metambrate; 1-Methyl-2-(1-methylpropyl)cyclohexyl acetate
4 **Molecular Formula**: $C_{13}H_{24}O_2$
5 **Molecular Weight**: 212.33
6 **RIFM Number**: 5969
7 **Stereochemistry:** Isomer not specified. Three stereocenters and 8 total stereoisomers possible.

2. Physical data

1 **Boiling Point**: 248.17 °C (EPI Suite)
2 **Flash Point:** 216.00 °F. TCC (102.40 °C)*
3 **. Log K_{OW}**: Log Pow = 5.5–5.6 (for the different isomers) (RIFM, 1997), 4.91 (EPI Suite)
4 **Melting Point**: 24.36 °C (EPI Suite)
5 **Water Solubility:** 2.404 mg/L (EPI Suite)
6 **Specific Gravity:** Not Available
7 **Vapor Pressure**: 0.03 mm Hg @ 25 °C (EPI Suite), 0.019 mm Hg @ 20 °C (EPI Suite v4.0)
8 **UV/Vis 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**: Not Available

*http://www.thegoodscentscompany.com/data/rw1055081.html#toorganoretrieved 8/18/2017.

3. Exposure

1 **Volume of Use (worldwide band)**: 0.1–1 metric ton per year (IFRA , 2015)
2 **95th Percentile Concentration in Hydroalcoholics**: 0.00091% (RIFM, 2015)
3 **Inhalation Exposure***: 0.00035 mg/kg/day or 0.025 mg/day (RIFM, 2015)
4 **Total Systemic Exposure****: 0.0028 mg/kg/day (RIFM, 2015)

*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 I, Low

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

2 **Analogs Selected**:
a **. Genotoxicity:** 2,6-Dimethyl-2-octyl acetate (CAS # 68480-08-0)
b **. Repeated Dose Toxicity:** 3,3,5-Trimethylcyclohexyl acetate (CAS # 67859-96-5)
c **. Developmental and Reproductive Toxicity:** 3,3,5-Trimethylcyclohexyl acetate (CAS # 67859-96-5)
d **. Skin Sensitization:** 2-(1-Methylpropyl)-1-vinylcyclohexyl acetate (CAS# 37172-02-4)
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)

1-Methyl-2-(1-methylpropyl)cyclohexyl 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 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 2013; no dossier available as of 03/15/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1-methyl-2-(1-methylpropyl) cyclohexyl acetate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 1-Methyl-2-(1-methylpropyl)cyclohexyl acetate was tested using the BlueScreen assay and found not to be genotoxic with or without S9 metabolic activation (RIFM, 2013). The mutagenic activity of 1-methyl-2-(1-methylpropyl)cyclohexyl acetate 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 1-methyl-2-(1-methylpropyl)cyclohexyl acetate 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,

2000). Under the conditions of the study, 1-methyl-2-(1-methylpropyl) cyclohexyl acetate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 1-methyl-2-(1-methylpropyl)cyclohexyl acetate. The clastogenic activity of read-across material 2,6-dimethyl-2-octyl acetate (CAS # 68480-08-0) was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2,6-dimethyl-2-octyl acetate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation for 4 and 24 h 2,6-Dimethyl-2-octyl acetate 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, 2,6-dimethyl-2-octyl acetate was considered negative for clastogenicity in the *in vitro* micronucleus assay, and this can be extended to 1-methyl-2-(1-methylpropyl)cyclohexyl acetate.

Based on the available data, 1-methyl-2-(1-methylpropyl)cyclohexyl acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/02/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 1-methyl-2-(1-methylpropyl)cyclohexyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1-methyl-2-(1-methylpropyl)cyclohexyl acetate. Read-across material, 3,3,5-trimethylcyclohexyl acetate (CAS # 67859-96-5; see Section V) has sufficient repeated dose toxicity data. An OECD/GLP 422 oral gavage combined repeated dose toxicity and reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered via gavage with test material, 3,3,5-trimethylcyclohexyl acetate at doses of 0, 50, 150, or 500 mg/kg/day in corn oil. Additional groups of 6 rats/sex/dose were assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups. Males were dosed once daily for a total of 6 weeks (2 weeks each before, during, and post mating) while females were dosed once daily for 2 weeks prior to mating, throughout gestation, and for 5 days after delivery. Male and female recovery groups were dosed for 6 weeks. Two high-dose dams of the main group were found dead on PPD 3 and 5 with observed clinical signs of soiled perineal region and staining around the mouth and/or hematuria. Gross pathology of the 2 dams revealed small thymus (2/2) and spleen (1/2), enlargement of adrenals (1/2), and black focus in the forestomach (1/2), while histopathology revealed marked thymic lymphoid atrophy (2/2) and mild splenic lymphoid atrophy (2/2) in these 2 dams. Furthermore, mild adrenal cortical hypertrophy (1/2) and mild erosion/ulceration of stomach (1/2) were observed. These test material-related findings are frequently observed in rats under poor conditions. There were no other treatment-related adverse effects observed in clinical signs, body weights, food consumption, sensory function, motor activity, urinalysis, hematology, and clinical chemistry parameters among male and female animals of all treatment groups. Thus, the NOAEL for systemic toxicity was considered to be 150 mg/kg/day, based on the mortality of the dams at the highest dose group (RIFM, 2016).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 150/3 or 50 mg/kg/day.

Therefore, the 1-methyl-2-(1-methylpropyl)cyclohexyl acetate MOE for the repeated toxicity endpoint can be calculated by dividing the 3,3,5-trimethylcyclohexyl acetate NOAEL in mg/kg/day by the total systemic exposure to 1-methyl-2-(1-methylpropyl)cyclohexyl acetate, 50/0.0028 or 17857.

In addition, the total systemic exposure to 1-methyl-2-(1-methylpropyl)cyclohexyl acetate (2.8 μg/kg/day) is below the TTC (30 μg/kg bw/day) (Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/10/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 1-methyl-2-(1-methylpropyl)cyclohexyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 1-methyl-2-(1-methylpropyl)cyclohexyl acetate. Read-across material, 3,3,5-trimethylcyclohexyl acetate (CAS # 67859-96-5; see Section V) has sufficient developmental and reproductive toxicity data. An OECD/GLP 422 oral gavage combined repeated dose toxicity and reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered via gavage with test material, 3,3,5-trimethylcyclohexyl acetate at doses of 0, 50, 150, or 500 mg/kg/day in corn oil. Additional groups of 6 rats/sex/dose were assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups. Males were dosed once daily for a total of 6 weeks (2 weeks each before, during, and post mating), while females were dosed once daily for 2 weeks prior to mating, throughout gestation, and for 5 days after delivery. Male and female recovery groups were dosed for 6 weeks. In addition to the systemic toxicity parameters, effects on fertility and the development of the pups were also evaluated. There were no treatment-related adverse effects observed in the mating period, mating index, gestation period, male and female fertility indices, gestation index, pre- and post-implantation loss rates, live birth index, mean litter size, external examination of pups, body weights of pups, sex ratio of pups, and viability index of PNDs 0 and 4 up to the highest dose tested. Thus, the NOAEL for developmental and reproductive toxicity was considered to be 500 mg/kg/day, the highest dose tested (RIFM, 2016).

Therefore, the 1-methyl-2-(1-methylpropyl)cyclohexyl acetate MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the 3,3,5-trimethylcyclohexyl acetate NOAEL in mg/kg/day by the total systemic exposure to 1-methyl-2-(1-methylpropyl)cyclohexyl acetate, 500/0.0028 or 178571.

In addition, the total systemic exposure to 1-methyl-2-(1-methylpropyl)cyclohexyl acetate (2.8 μg/kg/day) is below the TTC (30 μg/kg bw/day) (Kroes et al., 2007) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/10/17.

10.1.4. Skin sensitization

Based on the existing data and read-across analog 2-(1-methylpropyl)-1-vinylcyclohexyl acetate (CAS# 37172-02-4), 1-methyl-2-(1-methylpropyl)cyclohexyl acetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for 1-methyl-2-(1-methylpropyl)cyclohexyl acetate. Based on the existing data and read-across analog 2-(1-methylpropyl)-1-vinylcyclohexyl acetate (CAS # 37172-02-4; see Section V), 1-methyl-

2-(1-methylpropyl)cyclohexyl acetate does not present a concern for skin sensitization. The chemical structures of these materials indicate that 1-methyl-2-(1-methylpropyl)cyclohexyl acetate is not predicted to be reactive to skin proteins directly (Toxtree 2.6.13; OECD toolbox v3.4). The read-across analog 2-(1-methylpropyl)-1-vinylcyclohexyl acetate is predicted to be reactive to skin proteins (Toxtree 2.6.13). In guinea pigs, maximization tests and an open epicutaneous test (OET) with 1-methyl-2-(1-methylpropyl)cyclohexyl acetate did not present reactions indicative of sensitization (RIFM, 1980; RIFM, 1977f). Additionally, a guinea pig Buehler test and an OET with read-across analog 2-(1-methylpropyl)-1-vinylcyclohexyl acetate also did not present reactions indicative of sensitization (RIFM, 1976; RIFM, 1977b). In a confirmatory human repeat insult patch test (HRIPT) with 4% 1-methyl-2-(1-methylpropyl)cyclohexyl acetate, no reactions indicative of sensitization were observed in any of the 52 volunteers (RIFM, 1977e). In another confirmatory HRIPT with 2% read-across material 2-(1-methylpropyl)-1-vinylcyclohexyl acetate, no reactions indicative of sensitization was observed in any of the 54 volunteers (RIFM, 1977c). Based on weight of evidence from structural analysis, animal and human studies, and read-across analog 2-(1-methylpropyl)-1-vinylcyclohexyl acetate, 1-methyl-2-(1-methylpropyl)cyclohexyl acetate does not present a concern for skin sensitization.

Additional References: RIFM, 1977a.

Literature Search and Risk Assessment Completed On: 08/15/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and existing data, 1-methyl-2-(1-methylpropyl)cyclohexyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Phototoxicity of 1-methyl-2-(1-methylpropyl)cyclohexyl acetate at 100% was evaluated *in vivo* in guinea pigs. There were no reactions (RIFM, 1977d). Based on lack of absorbance and the *in vivo* study, 1-methyl-2-(1-methylpropyl)cyclohexyl acetate would not be expected to 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: 07/18/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1-methyl-2-(1-methylpropyl)cyclohexyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 1-methyl-2-(1-methylpropyl)cyclohexyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.025 mg/day. This exposure is 56 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: None.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1-methyl-2-(1-methylpropyl) cyclohexyl acetate 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, 1-methyl-2-(1-methylpropyl)cyclohexyl 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 EPI Suite v4.11 (US EPA, 2012a) identified 1-methyl-2-(1-methylpropyl)cyclohexyl acetate 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 the current Volume of Use (2015), 1-methyl-2-(1-methylpropyl)cyclohexyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 1998: The inherent biodegradability of the test material was evaluated by the Manometric respirometry test according to the OECD 302C method. On day 35, 7% biodegradation was observed, and 14% was observed on day 41.

RIFM, 1995: The ready biodegradability of the test material was evaluated by the Manometric respirometry test according to OECD 301F guidelines. The nominal concentration of the test material was 100 mg/L. By day 28, only 3% of the test material underwent biodegradation.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 1 -Methyl-2-(1-methylpropyl)cyclohexyl

acetate 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.2113			1,000,000	0.000211 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.564	0.859	0.23	10,000	0.0.23	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.422	0.313	0.71			Neutral Organics SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.6	5.6
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 available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.023 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environmental at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/2/17.

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
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.06.042.

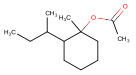
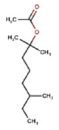
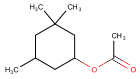
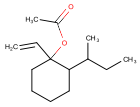
Appendix

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 (US EPA, 2012a,b).
- 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	1-Methyl-2-(1-methylpropyl) cyclohexyl acetate	2,6-Dimethyl-2-octyl acetate	3,3,5-Trimethylcyclohexyl acetate	2-(1-Methylpropyl)-1-vinylcyclohexyl acetate
CAS No.	72183-75-6	68480-08-0	67859-96-5	37172-02-4
Structure				
Similarity (Tanimoto Score)			0.81	0.80
Read-across Endpoint		• Genotoxicity	• Skin Sensitization • Repeated dose toxicity	• Developmental and Reproductive toxicity
Molecular Formula	$C_{13}H_{24}O_2$	$C_{12}H_{24}O_2$	$C_{11}H_{20}O_2$	$C_{14}H_{24}O_2$
Molecular Weight	212.34	200.32	184.28	224.35
Melting Point (°C, EPI Suite)	24.36	−2.29	9.43	33.76
Boiling Point (°C, EPI Suite)	248.17	218.36	217.21	264.06
Vapor Pressure (Pa @ 25°C, EPI Suite)	4	19	20.2	1.43
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.91	4.61	3.93[1]	5.27
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.404	5.056	23[2]	1.034
J_{max} (mg/cm^2/h, SAM)	22.182	19.095	1.608	5.440
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.33E+002	2.25E-003	7.56E+001	1.32E+002
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• Schiff base formation • Nucleophilic attack • Acylation	• Schiff base formation • Nucleophilic attack • Acylation		
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found		
Carcinogenicity (ISS)	•Non-carcinogen (low reliability)	•Non-carcinogen (low reliability)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found		
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found		
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Reproductive and Developmental Toxicity				
ER Binding (OECD QSAR Toolbox v3.4)	• Non binder, without OH or NH2		• Non binder, without OH or NH2	
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (moderate reliability)		• Non-toxicant (low reliability)	
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found			• No alert found
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			• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found			• Alert for Acyl transfer agent
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 1-methyl-2-(1-methylpropyl)cyclohexyl acetate (CAS # 72183-75-6). 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, 2,6-dimethyl-2-octyl acetate (CAS # 68480-08-0), 3,3,5-trimethylcyclohexyl acetate (CAS # 67859-96-5), and 2-(1-methylpropyl)-1-vinylcyclohexyl acetate (CAS # 37172-02-4) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 2,6-Dimethyl-2-octyl acetate (CAS # 68480-08-0) was used as a read-across analog for the target material 1-methyl-2-(1-methylpropyl)cyclohexyl acetate (CAS # 72183-75-6) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a tertiary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a cyclohexan ring on the acid portion of the ester while the read-across does not. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the tertiary alcohol fragment. 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 substance and the read-across analog have a Schiff base formation alert for DNA binding by OASIS. The data described in the genotoxicity section above shows that the read-across analog does not pose a concern for genotoxicity endpoint. Therefore, the alert will be superseded by the availability of the 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.
- 3,3,5-Trimethylcyclohexyl acetate (CAS # 67859-96-5) was used as a read-across analog for the target material 1-methyl-2-(1-methylpropyl) cyclohexyl acetate (CAS # 72183-75-6) for the repeated dose and developmental and reproductive toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a cyclic alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a tertiary alcohol fragment and the read-across analog has a secondary alcohol fragment. This structural difference is toxicologically insignificant.
  - o 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.
  - 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 Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target substance and $\leq 40\%$ for the read-across analog. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - 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 substance is predicted to be a toxicant by the CAESAR model for developmental toxicity. The read-across analog does not have any alert. The data described in the developmental toxicity section above shows that the margin of exposure of the read-across analog is adequate at the current level of use. Based on structural similarity and data availability for the target and the read-across analog, the alert for the target substance can be superseded by data availability on the read-across analog.
  - 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.
- 2-(1-Methylpropyl)-1-vinylcyclohexyl acetate (CAS # 37172-02-4) was used as a read-across analog for the target material 1-methyl-2-(1-methylpropyl)cyclohexyl acetate (CAS # 72183-75-6 for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a cyclic tertiary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a saturated alcohol fragment and the read-across analog has an unsaturated alcohol fragment. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a cyclic tertiary alcohol fragment. 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 Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target substance and $\leq 40\%$ for the read-across analog. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - 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 substance and the read-across analog have an acylation alert for protein binding by OECD. The *in silico* alerts are consistent with data described in the skin sensitization section above. Also, the data described in the skin sensitization section shows that the read-across analog does not pose a concern for skin sensitization endpoint.
  - 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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