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Short Review

RIFM fragrance ingredient safety assessment, alpha-methyl-4-(1-methylethyl)-cyclohexanemethanol, CAS Registry Number 63767-86-2

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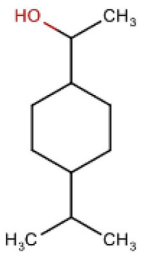


Abbreviation/Definition List:

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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 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 existing information supports the use of this material as described in this safety assessment.

α-Methyl-4-(1-methylethyl)-cyclohexanemethanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that α-methyl-4-(1-methylethyl)-cyclohexanemethanol is not genotoxic. Data on α-methyl-4-(1-methylethyl)-cyclohexanemethanol provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on read-across material 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol (CAS # 139504-68-0) provide a calculated MOE > 100 for the reproductive toxicity endpoint. Based on the existing data, α-methyl-4-(1-methylethyl)-cyclohexanemethanol does not present a concern for skin sensitization. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; α-methyl-4-(1-methylethyl)-cyclohexanemethanol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material, and the exposure to α-methyl-4-(1-methylethyl)-cyclohexanemethanol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; α-methyl-4-(1-methylethyl)-cyclohexanemethanol 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, 2015; RIFM, 1990b)
Repeated Dose Toxicity: NOAEL = 333.33 mg/kg/day. RIFM (1991)
Reproductive Toxicity: NOAEL = 500 mg/kg/day.
(ECHA REACH Dossier: 1-[(2-tert-Butylcyclohexyl)oxy]butan-2-ol; ECHA, 2012a)
Skin Sensitization: No safety concern for skin sensitization. RIFM (1989a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence:
Critical Measured Value: 36% (OECD 301C) RIFM (1989c)
Bioaccumulation:
Screening-level: 166 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 48-h *Daphnia magna* LC50: 1.966 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: 48-h *Daphnia magna* LC50: 1.966 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1966 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1

1. Identification

1. **Chemical Name:** α-Methyl-4-(1-methylethyl)-cyclohexanemethanol
2. **CAS Registry Number:** 63767-86-2
3. **Synonyms:** 1-(1-Hydroxyethyl)-4-(1-methylethyl)cyclohexane; 1-(1-Hydroxyethyl)-4-(1-methyl-ethyl)cyclohexane; 1-(4-Isopropylcyclohexyl)ethanol; Mugetanol; Mugetanol 600092; Cyclohexanemethanol, α-Methyl-4-(1-methylethyl)-; α-Methyl-4-(1-methylethyl)-cyclohexanemethanol
4. **Molecular Formula:** $C_{11}H_{22}O$
5. **Molecular Weight:** 170.29
6. **RIFM Number:** 7004
7. **Stereochemistry:** Isomer not specified. Three chiral centers and 9 total distereoisomers possible.

2. Physical data

1. **Boiling Point:** 231.8 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.87 (EPI Suite)
4. **Melting Point:** −1.89 °C (EPI Suite)
5. **Water Solubility:** 97.84 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00616 mm Hg @ 20 °C (EPI Suite v4.0), 0.0104 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.47% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00090 mg/kg/day or 0.066 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0076 mg/kg/day (RIFM, 2017)

*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 II, Intermediate* (Expert Judgment)

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was 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:** 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol (CAS # 139504-68-0)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

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

α-Methyl-4-(1-methylethyl)-cyclohexanemethanol 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Dossier available for "a mixture of diastereoisomers of 1-(1-hydroxyethyl)-4-(1-methylethyl)cyclohexane"; no dossier available for α-methyl-4-(1-methylethyl)-cyclohexanemethanol as of 01/17/19.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, α-methyl-4-(1-methylethyl)-cyclohexanemethanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment

α-Methyl-4-(1-methylethyl)-cyclohexanemethanol was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: < 80% relative cell density) without metabolic activation and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of α-methyl-4-(1-methylethyl)-cyclohexanemethanol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with α-methyl-4-(1-methylethyl)-cyclohexanemethanol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2015). Under the conditions of the study, α-methyl-4-(1-methylethyl)-cyclohexanemethanol was not mutagenic in the Ames test.

The clastogenic activity of α-methyl-4-(1-methylethyl)-cyclohexanemethanol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in arachis oil via oral administration to groups of male and female NMRI mice. Doses of 1250, 2500, and 5000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1990b). Under the conditions of the study, α-methyl-4-(1-methylethyl)-cyclohexanemethanol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, α-methyl-4-(1-methylethyl)-cyclohexanemethanol does not present a concern for genotoxic potential.

Additional References: RIFM, 1988.

Literature Search and Risk Assessment Completed On: 01/01/18.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment

There are sufficient repeated dose toxicity data on α-methyl-4-(1-methylethyl)-cyclohexanemethanol. In an OECD 407 and GLP-compliant toxicity study 6 SPF Wistar rats/sex/dose were administered the test material by oral gavage at doses of 0 (vehicle: 1,2-propandiol), 10, 100, and 1000 mg/kg/day, once daily for a period of 30 days. No mortality was reported at any dose level. No treatment-related alterations were reported for any of the tested parameters. However, at all doses, male rat kidneys showed α-2u-globulin nephropathy-related histopathological changes which were confirmed by Heidenhain staining. Since this effect is not relevant to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990), the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day for both sexes based on the absence of adverse effects up to the highest tested dose (RIFM, 1991).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day 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 1000/3 or 333.333 mg/kg/day.

Therefore, the α-methyl-4-(1-methylethyl)-cyclohexanemethanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the α-methyl-4-(1-methylethyl)-cyclohexanemethanol NOAEL in mg/kg/day by the total systemic exposure to α-methyl-4-(1-methylethyl)-cyclohexanemethanol, 333.33/0.0076 or 43860.

In addition, the total systemic exposure to α-methyl-4-(1-methylethyl)-cyclohexanemethanol (7.6 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/04/19.

10.1.3. Reproductive toxicity

The MOE for α-methyl-4-(1-methylethyl)-cyclohexanemethanol is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment

There are insufficient reproductive toxicity data on α-methyl-4-(1-methylethyl)-cyclohexanemethanol. Read-across material 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol (CAS # 139504-68-0; see Section V) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint.

In an OECD 415/GLP 1-generation reproductive toxicity study, groups of 24 Wistar rats/sex/dose were administered 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol via oral gavage at doses of 0, 20, 100, or 500 mg/kg/day in a 0.5% sodium carboxy methylcellulose/Tween 80 vehicle. Males were treated for at least 10 weeks prior to pairing, and treatment continued until termination (at least 18 weeks of treatment). Females were treated for at least 2 weeks prior to pairing and then throughout mating, gestation, and lactation until weaning (day 21 of lactation). In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. There were no treatment-related adverse effects on fertility or on the survival, growth, or development of offspring up to the highest dose tested. The NOAEL for reproductive toxicity was considered to be 500 mg/kg/day (ECHA, 2012a).

Therefore, the α-methyl-4-(1-methylethyl)-cyclohexanemethanol MOE for the reproductive toxicity endpoint can be calculated by dividing the 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol NOAEL in mg/kg/day by the total systemic exposure to α-methyl-4-(1-methylethyl)-cyclohexanemethanol, 500/0.0076 or 65789.

In addition, the total systemic exposure to α-methyl-4-(1-methylethyl)-cyclohexanemethanol (7.6 μg/kg bw/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive endpoint of a Cramer Class II material at the current level of use.

Additional References: RIFM, 1991.

Literature Search and Risk Assessment Completed On: 01/02/19.

10.1.4. Skin sensitization

Based on the existing data, α-methyl-4-(1-methylethyl)-cyclohexanemethanol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment

Based on the existing data, α-methyl-4-(1-methylethyl)-cyclohexanemethanol is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 3.1.0; OECD Toolbox v4.2). In guinea pigs, maximization tests did not present reactions indicative of sensitization (RIFM, 1989a).

Based on weight of evidence (WoE) from structural analysis and animal studies, α-methyl-4-(1-methylethyl)-cyclohexanemethanol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/07/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, α-methyl-4-(1-methylethyl)-cyclohexanemethanol 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 α-methyl-4-(1-methylethyl)-cyclohexanemethanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, α-methyl-4-(1-methylethyl)-cyclohexanemethanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for α-methyl-4-(1-methylethyl)-cyclohexanemethanol 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 α-methyl-4-(1-methylethyl)-cyclohexanemethanol. Based on the Creme RIFM Model, the inhalation exposure is 0.066 mg/day. This exposure is 7.12 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/11/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of α-methyl-4-(1-methylethyl)-cyclohexanemethanol 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, α-methyl-4-(1-methylethyl)-cyclohexanemethanol 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) did not identify α-methyl-4-(1-methylethyl)-cyclohexanemethanol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012b). 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), α-methyl-4-(1-methylethyl)-cyclohexanemethanol presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies

10.2.2.1.1. Biodegradation. **RIFM, 1989c:** The biodegradability of the test material was evaluated according to the modified screening test following OECD 301C guidelines. After 28 days, biodegradation of 36% was observed.

RIFM, 1996: The ready biodegradability of the test material was evaluated using a Manometric Respirometry Test according to the OECD 301F guidelines. Biodegradation of 1% was observed after 28 days.

10.2.2.1.2. Ecotoxicity. **RIFM, 1990a:** An acute fish (*Brachydanio rerio*) toxicity study was conducted according to the OECD 203 method under

semi-static conditions. Under the conditions of this study, the 96-h LC50 was reported to be 7.8 mg/L.

RIFM, 1989b: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The EC50 48-h LC50 was calculated to be 24.7 mg/L.

10.2.2.1.3. Other available data. α-Methyl-4-(1-methylethyl)-cyclohexanemethanol has been registered under REACH with no additional data at this time.

10.2.3. Risk assessment refinement. Since α-methyl-4-(1-methylethyl)-cyclohexanemethanol has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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)**	6.229			1000000	0.006229	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.913	1.966	2.993	10000	0.1966	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.8	3.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	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 0.1966 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 VoU.

Literature Search and Risk Assessment Completed On: 01/03/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/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:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.111001.

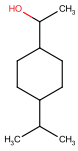
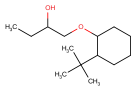
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	α-Methyl-4-(1-methylethyl)-cyclohexane-methanol	1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol
CAS No.	63767-86-2	139504-68-0
Structure		
Similarity (Tanimoto Score)		0.48
Read-across Endpoint		• Reproductive Toxicity
Molecular Formula	$C_{11}H_{22}O$	$C_{14}H_{28}O_2$
Molecular Weight	170.2	228.37
Melting Point (°C, EPI Suite)	−1.89	52.67
Boiling Point (°C, EPI Suite)	231.80	292.87
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.38	0.0158
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.87	4.05
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	97.84	34.85
J_{max} (μg/cm^2/h, SAM)	52.12	9.80
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.05E+000	4.22E-002
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)	• Non-Toxicant (moderate reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on α-methyl-4-(1-methylethyl)-cyclohexanemethanol (CAS # 63767-86-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 1-(2-*tert*-butyl cyclohexyloxy)-2-butanol (CAS # 139504-68-0) was identified as read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 1-(2-*tert*-Butyl cyclohexyloxy)-2-butanol (CAS # 139504-68-0) was used as a read-across analog for the target material α-methyl-4-(1-methylethyl)-cyclohexanemethanol (CAS # 63767-86-2) for the reproductive toxicity endpoint.

- ○ The target material and the read-across analog are structurally similar and belong to a class of saturated alkyl secondary alcohols bearing a cycle.
- ○ The target material and the read-across analog share an alkyl straight chain secondary alcohol with a cyclohexyl saturated ring.
- ○ The key differences between the target substance and the read-across analog are that the read-across analog has an ether group, the read-across analog has a tert-butyl substitution in the 2 position in the cyclohexyl ring, in contrast to the isopropyl group in the 6 position in the cyclohexane ring in the target material. The length of the alkyl saturated straight chain bearing the secondary alcohol group is different for both materials—a 2-carbon chain for the target material and a 4-carbon chain for the read-across analog. These structural differences are toxicologically insignificant.
- ○ Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- ○ Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq 80\%$ and J_{max} for the read-across analog corresponds to skin absorption $\leq 40\%$. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- ○ The target material has a toxicant alert from the CAESAR model. The data for the read-across analog confirm that the MOE is adequate at the current level of use. Therefore, based on the structure similarity and the data for the read-across analog, the predictions are superseded by data.
- ○ The target material 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

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? NO
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? NO
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? NO
Q19. Open chain? NO
Q23. Aromatic? NO
Q24. Monocarbocyclic with simple substituents? Yes
Q18. One of the list? (see Cramer et al., 1978 for detailed explanation on list of categories)? Yes Class II (Class moderate)

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