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Short Review

RIFM fragrance ingredient safety assessment, cyclododecaneethanol, β-methyl-, CAS Registry Number 118562-73-5

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Local respiratory toxicity
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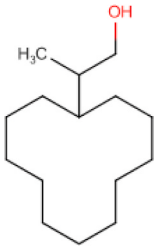
Version: 121018. This version replaces any previous versions.
Name: Cyclododecaneethanol, β-methyl-
CAS Registry Number: 118562-73-5



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

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe 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.

Cyclododecaneethanol, β-methyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3) show that cyclododecaneethanol, β-methyl- is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to cyclododecaneethanol, β-methyl- is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from cyclododecaneethanol, β-methyl- show that there are no safety concerns for cyclododecaneethanol, β-methyl-for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; cyclododecaneethanol, β-methyl- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cyclododecaneethanol, β-methyl- was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 1991; RIFM, 1989)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: No safety concerns at current, declared use levels.	(ECHA Dossier: 2-cyclododecylpropan-1-ol; ECHA, 2014)
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: 86.8% (OECD 301D)	(ECHA Dossier: 2-cyclododecylpropan-1-ol; ECHA, 2014)
Bioaccumulation:	
Screening-level: 8691 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-hour *Daphnia magna* LC50: 0.058 mg/L	(ECOSAR v1.11; 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-hour *Daphnia magna* LC50: 0.058 mg/L	(ECOSAR v1.11; US EPA, 2012b)
RIFM PNEC is: 0.0058 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1	

a. **Genotoxicity:** Tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

1. Identification

1. **Chemical Name:** Cyclododecaneethanol, β-methyl-
2. **CAS Registry Number:** 118562-73-5
3. **Synonyms:** 2-Cyclododecylpropanol;.β.-Methylcyclododecaneethanol; Cyclododecaneethanol,.β.-methyl-
4. **Molecular Formula:** $C_{15}H_{30}O$
5. **Molecular Weight:** 226.40
6. **RIFM Number:** 6326
7. **Stereochemistry:** Isomer not specified. Two chiral centers present and 4 total stereiosimers possible.

2. Physical data

1. **Boiling Point:** 336.8 °C (EPI Suite)
2. **Flash Point:** 165 °C (Globally Harmonized System)
3. **Log K_{OW}:** 5.8 (https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/7259/1 ECHA, 2014)
4. **Melting Point**: 35.07 °C (EPI Suite)
5. **Water Solubility:** 0.2554 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.01e-005 mm Hg @ 25 °C (EPI Suite), 0.00000469 mm Hg @ 20 °C (EPI Suite v4.0)
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):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.13% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0095 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0025 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 I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** Tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   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)

Cyclododecaneethanol, β-methyl- is not reported to occur 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

Available; accessed 10/03/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, cyclododecaneethanol, β-methyl- does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of cyclododecaneethanol, β-methyl-. Read-across can be made to tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3; see Section V). The mutagenic activity of tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations using the standard plate incorporation. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene in dimethyl sulfoxide (DMSO) at concentrations up to 1500 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, 1991). Under the conditions of the study, tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- was not mutagenic in the Ames test, and this can be extended to cyclododecaneethanol, β-methyl-.

The clastogenic activity of tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- 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 corn oil via intragastric gavage to groups of male and female CD-1 mice. A single dose of 698.4 mg/kg was administered to each animal. Mice 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 significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1989). Under the conditions of the study, tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to cyclododecaneethanol, β-methyl-.

Based on the available data, cyclododecaneethanol, β-methyl- does not present a concern for genotoxic potential.

Additional References: None.

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

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on cyclododecaneethanol, β-methyl- or on any read-across materials. The total systemic exposure to cyclododecaneethanol, β-methyl- is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on cyclododecaneethanol, β-methyl- or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to cyclododecaneethanol, β-methyl- (2.5 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/17/18.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on cyclododecaneethanol, β-methyl- or on any read-across materials. The total systemic exposure to cyclododecaneethanol, β-methyl- is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on cyclododecaneethanol, β-methyl- or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to cyclododecaneethanol, β-methyl- (2.5 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/01/18.

10.1.4. Skin sensitization

Based on existing data, cyclododecaneethanol, β-methyl- does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, cyclododecaneethanol, β-methyl- is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD toolbox v4.2). In a guinea pig maximization test, no reactions indicative of sensitization were observed with 100% cyclododecaneethanol, β-methyl- (ECHA, 2014).

Based on weight of evidence (WoE) from structural analysis and animal studies, cyclododecaneethanol, β-methyl- 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: 11/08/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cyclododecaneethanol, β-methyl- 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 cyclododecaneethanol, β-methyl- 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, cyclododecaneethanol, β-methyl- 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: 07/17/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for cyclododecaneethanol, β-methyl- 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 cyclododecaneethanol, β-methyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.0095 mg/day. This exposure is 147.4 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: 10/23/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of cyclododecaneethanol, β-methyl- 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, cyclododecaneethanol, β-methyl- 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 cyclododecaneethanol, β-methyl- as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value $<$ 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value $<$ 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$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.

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), cyclododecaneethanol, β-methyl- presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. No data available.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.3. Other available data. Cyclododecaneethanol, β-methyl- has been registered under REACH, and the following data is available (ECHA, 2014):

The ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. Under the conditions of the study, biodegradation of 86.8% was observed after 28 days.

A 96-hour fish (Rainbow trout) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions, and the LC50 (based on the geometric mean concentration) was reported to be 0.21 mg/L.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 under static conditions. The 48-hour EC50 was reported to be 0.0778 mg/L.

An algae growth inhibition study was conducted according to the OECD 201 method. The 72-hour EC50 was reported to be greater than 0.19 mg/L.

10.2.2. 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)**	0.1506			1,000,000	0.0001506	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.072	0.058	0.184	10,000	0.0058	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.8	5.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 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 0.0058 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: 11/19/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/30/20.

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.2020.111485.

Appendix

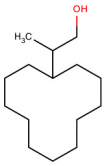
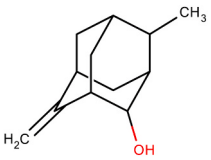
Read-across justification

Methods

The read-across analog was 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 Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).

- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite 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	Cyclododecaneethanol, β-methyl-	Tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene-
CAS No.	118562-73-5	122760-84-3
Structure		
Similarity (Tanimoto Score)		0.41
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{15}H_{30}O$	$C_{12}H_{18}O$
Molecular Weight	226.40	178.27
Melting Point (°C, EPI Suite)	27.26	50.74
Boiling Point (°C, EPI Suite)	322.93	258.98
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.00391	0.14
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.98	3.23
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.799	318.6
J_{max} (μg/cm^2/h, SAM)	1.15	126.37
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.35	3.23
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-Carcinogen (low reliability)	• 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
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 cyclododecaneethanol, β-methyl- (CAS # 118562-73-5). 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, tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Tricyclo[3.3.1.1.(3.7)]decan-2-ol, 4-methyl-8-methylene- (CAS # 122760-84-3) was used as a read-across analog for the target material cyclododecaneethanol, β-methyl- (CAS # 118562-73-5) for the genotoxicity endpoint.

  - o The target substance and the read-across analog share similar structural features and belong to a class of macrocyclic alcohols.
  - o The target substance and the read-across analog both have a macrocyclic hydrocarbon fragment with a single alcohol group.
  - o The key difference between the target substance and the read-across analog is that the read-across structure contains 3 fused rings with a vinyl group, whereas the target material is a 12-carbon saturated macrocyclic ring with a branched aliphatic primary alcohol. Despite the significant differences in the hydrocarbon structure, the read-across analog captures the most important features of the target, including the large hydrocarbon and single alcohol group without other structure alerts. These structural differences, although substantial are toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. 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} for the target substance corresponds to skin absorption $\leq 40\%$, and J_{max} for the read-across analog corresponds to skin absorption $\leq 80\%$]. 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.

- o According to the OECD QSAR Toolbox v4.2, 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 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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